Plant-Caused Skin Disorders

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FOREWORD

It is estimated that 10,000–50,000 plant species of the world's total flora are able to be used in the diet. Today, only about 5000 species are used directly in the human diet, while three basic edible plants—maize, wheat, and rice—satisfy as much as 60% of human energy and protein needs (Anon., 1999). There are more than 1000 species known in the world today that can be used as vegetables in the diet in a fresh, dry, cooked, processed, or preserved state. About 150 species are grown in the world, and about 30–50 species of vegetables are widely used (Lopez, 1994).

Of the 5,000 plant species used in the diet, only 57 species are staple crops that feed all of humanity. There are eight species of plants belonging to cereals, seven legumes, seven oil-producing species, three tuber species, and two sugar-producing species. In addition to these plants, there are 15 vegetable and 15 fruit species of great importance for the population’s nutrition. These cultivated plants provide the necessary proteins, carbohydrates, fats, vitamins, minerals, and bioactive substances for the normal development and functioning of the human body and all of the heterotrophic species in the animal kingdom.

According to Chinese traditional medicine, there are about 5000 medicinal plants, while today's folk medicine relies on about 400 medicinal plants (Petrovska, 2012). Even today, about 80% of the population in developed countries rely on medicines derived from plant extracts; thus, even in highly technologically advanced countries, such as the US, about 25% of prescriptions are for medicines with active ingredients obtained by plant extraction or processing.

Biochemical analyses show that plants produce very different compounds, including those that have toxic and dermatological effects on humans and domestic animals. Plants that are characterised by the synthesis and accumulation of large amounts of these substances are considered to be toxic and dermatologically active. At the same time, these plants are not necessarily harmful. Many of them are known to be excellent medicinal plants, and some of them are decorative and edible plants that are fairly regularly used in the diet. However, on this occasion, our attention in this monograph is focused on plants that cause dermatoses, which can have undesirable and sometimes fatal consequences for humans and domestic animals. Our goal was to point out some of their traits and their importance, outline the basic properties of the major groups of compounds that cause dermatoses and, especially, to focus on introducing certain species of plants, as well as their dermatosis-inducing constituents and specific effects on humans and animals.

In recent years, science has developed new methods and techniques that are of great importance for the isolation, identification, and characterization of the various organic compounds found in plants and other living organisms. Thus, in many plants, very complex organic compounds have recently been discovered and there is still little known about their function. Without a knowledge of the structure of their compounds, it is almost impossible discuss their physiological functions, including their toxicity or their pharmacological activity outside the organism in which they were formed.

When preparing this monograph, the authors had in mind a long-known and well-tried system of giving theoretical explanations for many phenomena and processes occurring in the process of biosynthesis and metabolism of toxic compounds in plants in addition to basic phenomena. However, due to the volume of the material and the basic purpose of this monograph, not all of the theoretical explanations have been given for the many biosynthesis or transformation processes of the numerous compounds included in the composition of a large number of plants which exhibit dermatological properties and which are very difficult to separate from their medicinal effects and use in traditional medicine. Very often it is the same plant or its constituent, but it will have different effects in living organisms at different doses. This is most likely to cause misunderstanding among a wide readership: how can one and the same plant or its constituent can have a dual effect? This is best explained by the famous words of Paracelsus: "Sola dosis sola facit venenum", meaning "the dose makes the poison".

This monograph has two parts. The first part covers the basic concepts of phytodermatoses and the groups of compounds in plants that have this type of physiological effect on humans and animals. The most common form of phytodermatosis is contact dermatitis, and the most common dermatological symptom is eczema. In order to better understand phytodermatoses, the skin reactions caused by contact with plants can be classified as follows:

- Allergic contact dermatitis
- Irritant contact dermatitis
- Contact urticaria
- Phytophotodermatitis

Dermatoses are caused by certain plant constituents that are often classified into groups, such as alkaloids, glycosides, glucosinolates, saponins, phenols, and other compounds.

The second part of the monograph describes 68 plants species that cause dermatoses in humans, especially in those who are engaged in their production, cultivation, planting, pruning, arranging, and selling. These plants are classified into 25 families. Each plant’s morphological description, habitat, ecological indices, distribution, variability, and main constituents with toxic and dermatological effects have been provided. Most of the plants covered in this monograph belong to the following families: Apiaceae (12), Ranunculaceae (7), Araceae (6), and Asteraceae (6 species), which make up 45,59% of all the plants covered in this monograph. A colour photograph is provided for each plant to help with their identification. These plants are most commonly found in our region and there are some constituents in their organs or other parts that exhibit dermatological activity at certain stages of their growth and development. It would be repetitive if the function, biosynthesis, and action of these constituents were explained again in this section. This is why this part of the monograph covers the constituents, their distribution, symptoms of dermatological activity, and similar properties, given that many properties are explained in more detail in the first part of the monograph.

Not only have chemists succeeded in gaining knowledge of some natural products and their materials, as well as synthesizing them in an artificial environment (first in the laboratory and then in the industry as a true "replacement" of natural materials), but they have also managed to produce more complex substances and synthetic products than nature has provided. In chemical laboratories, various substances are synthesized and technological processes for production are tested under very complex and diverse conditions; this includes the natural constituents of the plants that are the subject of this monograph. However, because of their complex structure, steroisomerism, and other properties, the question remains to what degree these two groups are identical.

And finally, of course, the civilizations, societies, and peoples that lived before us did not know as much as we do today. However, we cannot be flattered because we do not know much about their level of understanding. It is enough to mention the achievements of the ancient peoples of Tibet, India, and China, as well as their knowledge of self-hypnosis, telepathy, and telaesthesia, which are only now being studied in the West. Even with the help of modern technology, we probably do not know how much these ancient peoples knew about plants and their uses for various purposes, particularly in terms of medicine.

INTRODUCTION

The world of plants is extraordinarily rich and diverse; it includes over 270.000 known species on Earth today, and it is assumed that there are further undiscovered plant species, which are currently unknown to botanists. The flora of Europe is particularly diverse and distinctive. In Europe, due to its geographical position, climatic, edaphic, and geomorphological conditions, there are eleven vegetation zones with a large number of endemic plant species (Janjic, 2008). The flora is more or less widespread everywhere. Plains, hills, and highlands, as well as areas by the sea, rivers, and lakes, are characterised by typical vegetation. Plants are found in rivers, lakes, seas, and other bodies of water. It is diverse, rich, and extremely interesting. Of this number, only a few hundred are of particular practical importance. The enormous abundance of plants is not yet sufficiently known or exploited.

In recent years, there has been an increasing interest in sources of plant food found in nature. Since substantial amounts of food from nature decay or remain unused, one should not ignore the fact that considerable savings in the national economy could be achieved by both harvesting and industrially processing some of these plants. However, natural reserves of food will be useful to anyone at risk of getting lost or who finds themselves helpless in nature. The awareness that they will be able to survive in any situation, wherever they are, will give them the security and confidence they need. It is understandable that the reserves of food found in nature are essential in cases of severe natural disasters, war, famine, and scarcity of other foods.

There are many plants in nature with certain characteristics. The use of medicinal herbs is widespread in traditional medicine, since many of them have been used since ancient times. It will be sufficient to only mention some of these herbs, such as marsh-mallow (*Althaea officinalis*), yarrow (*Achillea millefolium*), hoary plantain (*Plantago media*), sage (*Salvia officinalis*), thyme (*Thumus serpyllum*), and valerian (*Valeriana officinalis*), to be reminded of their role in treating people during difficult times and wars. These and other herbs are also often used as treatments in peacetime, because it has been observed that the massive and frequent use of synthetic preparations has certain effects on the body.

However, many plants, even herbs, exhibit toxic and dermatological effects on humans and animals under certain conditions. Therefore, the name, “poisonous plant”, is conditional and relative, since most of these plants are used in traditional medicine, and the substances that cause their toxicity are included in the composition of galenic preparations in small, precisely defined quantities to form the active components of specific physiological and therapeutic effects. When ingested in large quantities, these substances are highly toxic (Janjic, 1987; Janjic *et al*. 2008). The importance of this is illustrated by the example of aconitine alkaloid, which belongs to the group of the most potent herbal poisons; its lethal dose for humans is 4 to 6 mg. Therefore, it is of particular importance to know which wild plants are poisonous.

For a plant to have practical use, it is necessary to know its chemical composition among other things. Knowing the chemical composition and quality of individual plants is an important field of research, as it creates conditions for their wider use, which is not only important for wartime conditions but also for general economic progress.

The body of plants is composed of 21 elements: 16 of which (H, O, C, N, P, S, Na, K, Mg, Ca, Cl, Mn, Fe, Co, Cu, and Zn) are part of the composition of all living organisms, and five (B, Al, V, Mo, and J) of some species. It has been found that 29 organic molecules (glucose, ribose, fats, phosphatides, 20 amino acids, and 5 nucleotides), which exist as either monomers or polymers, form a huge number of the different compounds found in plants.

In addition to proteins, carbohydrates, and fats, the composition of plants, includes many other compounds whose role within the plant itself, as well as its physiological effect on other living organisms, is not fully known. First of all, these include organic acids, numerous phenolic compounds, essential oils, glycosides, resins, and alkaloids, as well as a number of other natural compounds. They all participate in the transfer of matter and exert specific and very important different functions. For example, some organic acids do not accumulate in significant amounts and, as a rule, after being formed, they are immediately consumed for other synthetic reactions. Other compounds tend to accumulate, such as alkaloids, essential oils, and saponins, and then are used to exert some physiological effect on living organisms outside the body of the plant.

The formation of primary and secondary metabolites in plants is a dynamic process that changes during their ontogenetic development; this also depends on many environmental factors. During ontogenesis, the plant goes through a phase of vegetative development, involving flowering and fruiting. Each cell and organ reaches a certain size, exhibits certain functions, and then dies. Ontogenesis is characterised by certain transfer of substances: carbohydrates, fats, and proteins (as well as enzymes and coenzymes, such as vitamins). This process includes changes in the dynamics of the synthesis of alkaloids, glycosides, terpenes, phenolic and compounds, etc.

It should be noted that there are specificities in the formation of some secondary metabolites that depend on the systematic affiliation of some plants. It is generally known that there are groups of plants that accumulate essential oils and alkaloids, etc. Furthermore, an uneven distribution of toxic compounds in plants is common. As a rule, the highest percentages of, for example, cardiac glycosides are found in leaves and essential oils in fruits. Likewise, different stages (different phenophases) in the development of one and the same plant are characterised by considerable differences in the number of toxic compounds. Therefore, a plant can be poisonous and dermatologically active only at a certain stage or only some of its organs or parts can be poisonous. Not only the quantity but also the qualitative composition of toxic compounds depends on the stage of plant development. The qualitative composition of toxic compounds may also be different for different organs in the same plant.

Even in species in which the whole plant is poisonous, the number of toxic compounds in different organs usually varies. Thus, for example, in the white hellebore (*Veratrum album*), all parts of the plant are poisonous, but different amounts of these substances are found in different organs: 2.5% in the root, 1.3% in the rhizome, and about 0.5% in the stem. As a rule, the highest percentage of toxic compounds is found in the leaves of the plant during its flowering stage, in the fruiting stage in seeds and fruits, and at the end of the growing season in underground organs, roots, rhizomes, and bulbs. It is not unusual that some plants' young shoots and spring leaves are edible, even delicious, but which become inedible, bitter, and even poisonous in the later stages of development. This effect can be found in the following species: asparagus (*Asparagus acutifolius*), black bryony (*Tamus communis*), rough bindweed (*Smilax aspera*), butcher's-broom (*Ruscus aculeatus*), old man's beard (*Clematis vitalba*), pokeweed (*Phytolacca americiana*), and common milkweed (*Asclepias syriaca*). The content of toxic compounds usually increases during the growing season and most often reaches a maximum during flowering.

Poisonous and skin irritant plants grow together with other plants; therefore, one must be careful when picking wild plants for food. Children are especially attracted by shiny red berries (similar to currants), and there are some deadly poisonous berries among them. These include the fruits of the February daphne (*Daphne mezereum*) and fly honeysuckle (*Lonicera xylosteum*). There have been reports of alder buckthorn (*Rhamnus frangula*) collectively poisoning children on school trips. Children are also attracted to the red berries of wild arum

(*Arum maculatum*) and lily-of-the-valley (*Convallaria majalis*), which are highly toxic. Deadly nightshade (*Atropa belladonna*) berries are also deadly poisonous.

For this reason, it is essential to know what these poisonous plants look like, their phenology, the degree of toxicity, and their physiological effects with symptoms of poisoning, as well as their frequency in different areas.

Depending on the conditions, the soil composition, and the degree of sensitivity of their botanical composition, certain poisonous plants can be found in the following areas:

- On wet meadows: hedge hyssop (*Gratiola officinalis*), creeping buttercup (*Ranunculus repens*), and common soapwort (*Saponaria officinalis*).
- In hilly and humid conditions: autumn crocus (*Colchicum autumnale*) and white hellebore (*Veratrum album*).
- In dry and warm areas: cypress spurge (*Euphorbia cyparissias*), pheasant's eye (*Adonis vernalis*), and yellow foxglove (*Digitalis ambiqua*).
- On slopes: royal knight's-spur (*Delphinium consolida*), corn-cockle (*Agrostema githago*), and charlock mustard (*Sinapsis arvensis*).
- In forest vegetation: fragrant hellebore (*Helloborus odorus*) and deadly nightshade (*Atropa belladonna*).
- In rural habitats: jimson weed (*Datura stramonium*), birthwort (*Aristolochia clematitis*), black henbane (*Hyosciamus niger*), and others.

Accidental poisoning almost always occurs after the ingestion of a plant’s attractive parts. Many researchers around the world have found that accidental poisoning, especially when it comes to children, is caused by ingesting the fruits of plants with a beautiful appearance, colour, shine, and shape. Berries are the fruits of plants containing fleshy and more or less succulent tissue with multiple seeds inside their outer layer. The berry is a juicy fruit with two parts of the fruit layer: an exocarp (in the form of a thin outer layer) and a mesocarp with an endocarp (the largest, fleshy part of the fruit).

It often happens that children, who are looking for blueberries or other fruits in the forest, find similar and very poisonous fruits, such as deadly nightshade (*Atropa belladonna*), Eurasian baneberry (*Actaea spicata*), herb-paris (*Paris quadrifolia*), or fly honeysuckle (*Lonicera xylosteum*). Many berries of poisonous plants are shiny and succulent, and similar in shape and colour to edible berries; they also often grow in the same habitats. Therefore, the most common victims of berry poisoning are preschool children and, less often older boys eager to prove themselves to their peers. Children are especially attracted to shiny red berries similar to currants, and there are some deadly poisonous ones among them. These include the berries of February daphne (*Daphne mezerum*) and fly honeysuckle *(Lonicera xylosteum*). There have been several cases of poisoning on school trips from fly honeysuckle berries.

Children are also attracted by the red berries of wild arum (*Arum maculatum*) and lily-of-the-valley (*Convallaria majalis*), which are deadly poisonous. The berries of bittersweet nightshade (*Solanum dulcamara*) are very poisonous and they resemble the edible red berries of European barberry (*Berberis vulgaris*) in colour and shape. Black bryony (*Tamus communis*) and white bryony (*Bryonica dioica*) climb up shrubs and trees that have edible fruits (e.g. rowans: *Sorbus aucuparia*); their beautiful red berries cause confusion, which can explain the rare cases of poisoning from this plant. There are also dark berries (blueberries: *Juniperus communis*) among edible berries, so one should take special care that children do not confuse them with the deadly poisonous berries of deadly nightshade (*Atropa belladonna*), herb-paris (*Paris quadrifolia*), Eurasian baneberry (*Actea spicata*), and blackberry nightshade (*Solanum nigrum*). There was also a case of the mass poisoning of French soldiers on manoeuvres by nightshade berries. It is not only wild species that are dangerous for children, but also berries from ornamental shrubs, which they come into contact with in playgrounds, parks, gardens, and urban areas. Ornamental shrubs with poisonous berries include guelder rose (*Viburnum* *opulis*), common holly (*Ilex aquifolium*), common yew (*Taxus baccata*), common snowberry (*Symphoricarpos albus*), common ivy (*Hedera helix*), and common spindle (*Euonymus europaea*). Fortunately, most poisonous berries have a sharp, bitter, or repulsive taste, but those that do not have this can be particularly dangerous (e.g., deadly nightshade, wild arum, and black bryony).

In the 1980s in Europe, particularly in Germany, Switzerland, and Austria, it was believed that herbs could only have a therapeutic effect and could not cause unwanted side effects and poisoning, despite the problems resulting from the intentional and unintentional consumption of poisonous plants (Sperl et al. 1995; Rasenack et al. 2003). Due to the dangers that may arise, the Federal Ministry of Health (BGA in Berlin) in Germany has drastically restricted the production and sale of plant products containing unsaturated compounds of necines to reduce the risk to public health caused by pharmaceuticals.

The number of toxic compounds in plants of the same species also depends on external conditions. Trace elements, such as magnesium, iron, manganese, nitrogen, sulphur, and phosphorus, have a great influence on the content of toxic compounds in plants. The number of alkaloids is known to increase in many alkaloid plants if fertilized extensively with nitrogen fertilizers, because alkaloids are derivatives of nitrogen. In addition to fertilizers, soil properties affect the percentage of toxic compounds in plants (e.g., humus content and irrigation). On the basis of comparative studies of the quantitative presence of alkaloids in deadly nightshade (*Atropa belladona*) in two habitats that differed in microclimatic conditions (insolation, temperature, and humidity), it has been shown that the plants that grew under the conditions of intense light, less precipitation, and higher temperature had about twice as many alkaloids. As a rule, most other poisonous plants in southern, sunny, warm, and dry areas contain more toxic compounds than plants that are widespread in northern, cool, and less sunny areas.

There are basically three groups of plants that have adverse effects on humans, as well as animals. The first group includes plants whose pollen has effect on the human body, by causing allergies (pollinosis), especially in people sensitive to it. The second group are plants which, when ingested, have toxic effects due to their constituents. Finally, in nature, there are plants that cause dermatoses when they come into contact with the human body. This third group of plants is the subject of this monograph. We have written a book, *Ragweed*, on allergenic plants, which particularly focused on ragweed as it is the most allergenic plant; this text was published by the Weed Science Society of Serbia (*Herbološko društvo Srbije*) (Janjić and Vrbničanin, 2007). The monograph, *Poisonous Plants and their Poisonous Constituents* was published by the Academy of Sciences and Arts of Republika Srpska (Janjić and Lazić 2016), and we are now preparing this monograph, *Plant Caused Skin Disorders*, which will be published by Cambridge Scholars Publishing (Janjić, 2020).

PART ONE

DERMATOSES AND THE PLANT CONSTITUENTS THAT CAUSE THEM

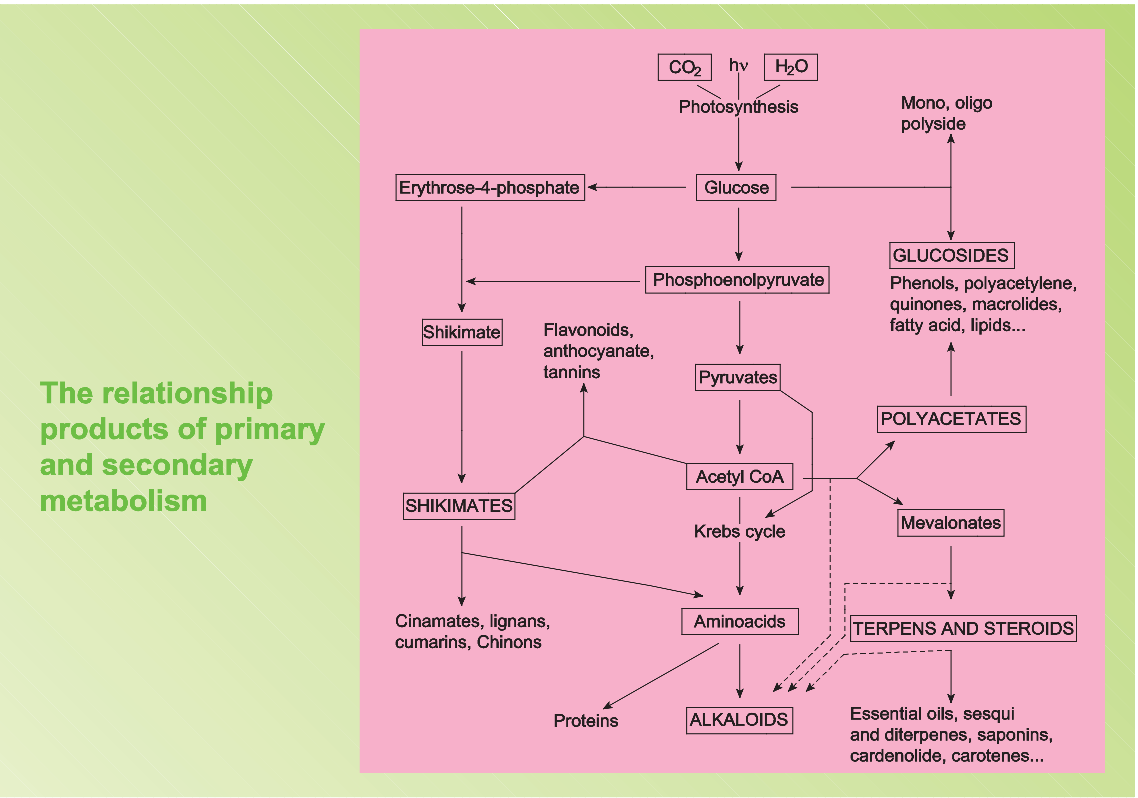
VASKRSIJA JANJIC AND VESNA GAJANIN

PRIMARY AND SECONDARY METABOLISM OF PLANTS: PRIMARY AND SECONDARY METABOLITES

Primary metabolism in plant cells includes the photosynthesis and the transformation of the resulting products. In these processes, the basic building compounds are formed, transformed, and broken down, which provides energy for the growth, development, and functioning of all of an organism's cells. The mechanism of all of the primary metabolism processes is the same in all plants. The main characteristic of the cells of plants and other living organisms is the very close interconnections between certain processes of matter and their energy transfer. In living organisms, there is a uniformity of metabolism that occurs as a result of the high integration between the metabolism of proteins, carbohydrates, lipids, minerals, and other substances (Plaxton *et.al.* 2006). Without the close connection between the catabolism and anabolism reactions, one could not imagine the maintenance, growth, development, and function of cells and the organism as a whole. Central to the metabolism are proteins, which are characterised by the exceptional richness and diversity of their chemical properties and functions, as well as a wide range of simple and complex compounds that are part of the cellular protoplasm. There are numerous examples which refer to the uniformity of metabolism in the major groups of organic compounds (Kruger *et al.* 1999). For example, amino acids may be subject to oxidative deamination, as they can be separated into keto acids and NH_3, which, by amination with other keto acids formed during the oxidation of sugar, breakdown products and produce new amino acids that are part of new proteins. However, the keto acids formed by deamination can be subject to oxidative decarboxylation, which forms CO_2.

The basic characteristics of plants' secondary metabolites are that they have low-molecular weight compounds which have no energy significance, they are very chemically diverse, and they perform certain biological and pharmacological activity. Secondary metabolism processes only partly occur using the same mechanism in different plants. There are certain specificities in the formation of secondary metabolites in different plant species, or in the same plant species, but in different tissues (Hussein and El-Anssary, 2018). These specificities are due to the presence of different enzymes in these plants or their organs and tissues, which contributes to changes in their basic biosynthetic pathway or its branches; this leads to the synthesis of different metabolites. The enzymes that cause the individual stages of certain secondary metabolic processes have only been partially identified and are still not fully understood.

Secondary metabolic pathways in plants are extremely complex and usually incorporate a number of different interconnected mechanisms. The enzymes involved in these mechanisms are mainly influenced by external factors. The pathways that regulate these enzymes represent a fascinating area of scientific research since many products from the secondary plant metabolism are of great importance, especially for the pharmaceutical and food industries. According to the chemical classification, secondary plant metabolites include organic acids (aliphatic, aromatic, and heteroaromatic), phenolic compounds (phenolic glycosides, phenolic acids, lignans, coumarins, hormones, xanthones, quinones, and tannins), terpenes (monoterpenes, sesquiterpenes, diterpenes, triterpenes, gibberellins, carotenoids, and polyterpenes), iridoids, volatile oils, steroid compounds, saponins, alkaloids, compounds containing sulphur, and other groups of secondary biomolecules (Pagare *et al*. 2015).



Scheme 1-1: Relationship between primary and secondary metabolism products

For a long time, the real function of secondary metabolites in the body of plants was unknown. It is now known that secondary metabolism compounds are inactive forms and that they are depots for harmful products. They are components of some enzyme systems (coenzymes); they have hormonal activity and a protective effect for the plants in which they are found; and they regulate relations to other plants (allelopathic effect). The role of secondary metabolites is the adaptation of a particular plant species to the function of various environmental factors. The function of secondary metabolites is not yet fully understood, and it is being extensively studied today.

THE MAIN CONSTITUENTS OF PLANTS THAT CAUSE DERMATOSES

Thousands of plant species and many of their constituents cause dermatoses in humans. Most reactions caused by plant chemical irritants come from seven basic irritant groups: calcium oxalate, protoanemonin, isothiocyanates, diterpene esters, bromelain, and alkaloids. They are dissolved or suspended in sap from a plant's stem, leaves, flowers, fruits, and roots.

Calcium salts of oxalate are insoluble in water and are in the form of crystals called raphides, which have a specific shape. Due to their sharp structure, they cause mechanical damage to the skin when they come into contact with it. Raphides longer than 180 µm are considered to have the strongest effects (Sakai *et al*. 1984). They are classified as chemical irritants because they enable the penetration of other chemical compounds, including proteases, saponins, alkaloids, and bromelain. *Dieffenbachia*, a very common and interesting decorative indoor plant, contains calcium oxalate in its leaves and flowers, which very often causes severe effects on the hands (Ippen *et al*. 1986). Then, saponins, glycosides, cyanogenic proteolytic enzymes, and alkaloids go through the damaged skin, which probably contributes to the formation of blisters on the skin. If the content is transferred from the hands to the eyes, then pain is felt, as calcium oxalate penetrates the cornea (Ippen *et al*. 1986). Other plants of the *Araceae* family, such as *Philodendron* spp., can cause similar symptoms due to the presence of calcium oxalate (Barabe *et al*. 2004).

The saps of tulips and other plants of the *Liliaceae* family contain the well-characterised Tulipalin A. The combined effects of irritants and allergens lead to the specific symptoms of a disease called "tulip fingers" (Bruynzeel, 1997). The hands become chapped and hyperkeratosis forms due to the effects of this irritant. This dermatosis is probably most common in florists (Lovell, 1993). Their stem contains plenty of calcium oxalate in the form of raphides. Following contact with their mucus and sap, which are found in its hollow stem, the so-called "daffodil itch" occurs, usually on the fingers and forearms (Bruynzeel, 1997; Julian and Bowers, 1997). Hyacinths and sentry plants also contain large amounts of calcium oxalate. Thus, for example, one drop of the sentry plant sap extracted from a leaf (0.03 mL) contains about 100 calcium oxalate raphides longer than 500 μm (Salinas *at al.* 2001). Raphides are also present in other plants. For example, the dry matter of some cacti, such as *Cephalocereus senilis*, contains about 85% calcium oxalate.

Protoanemonin is an irritant chemical compound that can be found in many plants of the *Ranunculaceae* family. It usually causes conjunctivitis and irritation to the nasal airways. Longer contact causes erythema, oedema, blisters, ulceration, and residual hyperpigmentation (Rudzki and Dajek, 1975). It is often confused with phytophotodermatitis (Lovell 1993, McGovern and Barkley, 1998). These phenomena are caused only by fresh macerated leaves, as protoanemonin is hydrolysed to anemonin, which does not cause skin irritation. *Ranunculus illyricus* has a particularly high content of protoanemonin; this plant grows as a weed and is used in medicine in South America and the Middle East (Polat *et al.* 2007; Oztas *et al.* 2006). In addition to the genus *Ranunculus*, this compound can be found in some genera of decorative plants, such as *Anemone*, *Clematis*, and *Helleborus*. The genus *Pulsatilla*, which includes the European species *Pulsatilla vulgaris* and the American prairie species *Pulsatilla patens* is particularly significant (Lovell, 1993). In this family, *Ceratocephalus falcatus*, an increasingly common weed species in the Middle East, is also known for this phenomenon; it also causes second-degree blisters (Karaca *et al.* 2005; Metin *et al*. 2005).

Isothiocyanates are major irritant compounds found in many species of plants of the *Brassicaceae* family. Glucosides (glucosinolates), which are precursors in the synthesis of isothiocyanates, are found in all parts of these plants, but particularly in their seeds. Irritants are formed under the influence of the myrosinase enzyme and released after damage to the plant. This reaction produces isothiocyanate, which reacts with the proteins in human skin and mucous membranes (Spoerke and Smolinske, 1990; Crosby, 2004). The spicy taste of these plants comes from isothiocyanate (Marks and De Leo, 2002). The symptoms appear in the form of erythema and urticaria. In addition to plants belonging to the *Brassicaceae* family, isothiocyanates and similar compounds can also be found in the following families: *Resedaceae*, *Caricaceae*, *Euphorbiaceae*, *Tropaeolaceae*, *Phytolaccaceae*, *Plantaginaceae*, and *Capparaceae* (Spoerke and Smolinske, 1990).

Phorbol, ingenol, and daphnane are also irritant chemical compounds, which are collectively referred to as diterpene esters. They are the most irritant compounds among all of the plant irritants (Crosby, 2004). They are most prevalent in the *Euphorbiaceae* family, which is a very large as it is comprised of more than 8,000 species in 300 genera (Webster, 1986). It is believed that diterpene ester is the primary substance found in the sap of these plants. In fact, almost 90% of species of the *Euphorbiaceae* family have irritant effects (Kinghorn, 1979; Kinghorn and Evans, 1975). In addition to their irritant effect, diterpene esters also play a role in tumourigenesis, through the activation of the cellular protein kinase C (Ono *et al.* 1989). Since the esters in their sap are irritants, the plants of this family are the most irritant plants. The skin and eyes are especially sensitive to these irritants. As a result of their toxic effects, pain, erythema, oedema, conjunctivitis, and even blindness might occur (Lowell, 1993; Asilian and Faghihi, 2004). If the leaves or fruits are ingested, bloody diarrhoea and vomiting will occur. *Euphorbia pulcherrima* is known as a decorative plant from this family, as well as for its low content of these irritant substances. Other plants of the *Euphorbia* genus, such as *Euphorbia maculata*, *Euphorbia peplus*, and *Euphorbia marginata*, are weeds known for causing irritation (Crosby, 2004; Marks and DeLeo, 2002). *Hippomane mancinella*, a woody species growing in Central America, and the southern region of Florida, is perhaps the most famous member of the *Euphorbia* family. This plant produces fragrant fruits which, when ingested, cause pain in the mouth and mucosal oedema, followed by vomiting and haemorrhagic diarrhoea (Morton and Miami, 1971). Every part of the stem can cause irritation to the skin on the hands, face, and genitals (Gunjan et al. 2009). Even when it is dried, it can still cause irritation. *Euphorbia tricualli*, a more widespread plant with a greater sap production, is known to cause dermatitis and even temporary blindness (Crosby, 2004). The majority of plants from the genus *Euphorbia* grow as shrubs in the USA. *Croton texensis*, which also belongs to this genus, causes blisters on the skin due to phorbol esters found in the leaves, stems, and fruits. There are about 45 species of the *Croton* genus in the USA, some of which are decorative (Crosby, 2004; Hausen and Schulz, 1977).

Bromelain is isolated from the fruit of *Ananas comosus* (the *Bromeliceae* family). This enzyme contains proteases, phosphatases, and peroxidases. Since it has distinct enzymatic activity, bromelain is used in the food and meat industry (Raison-Peyron *et al.* 2003). The proteolytic activity of bromelain causes skin irritation and also affects the dermal blood vessels (McGovern and Barkley, 1998). Due to bromelain's activity, workers who cut pineapple often lose their fingerprints. Many other plant constituents can cause dermatoses in humans, and they are described in more detail in this monograph.

Since ancient times, plants have been known to cause hyperpigmentation of the skin. As early as 2,000 BC, the ancient Egyptians used the plant *Ammi majus* (*Apiaceae*, *Umbeliferae*), which grows in the valley of the Nile, for sun exposure. Even today, Egyptian merchants and herbalists sell a yellowish-brown powder called "Aatrillal", which is prepared from the *Ammi majus* seeds to treat leukoderma. Indian medicine uses hot extracts from the *Psoralea corylifolia*'s leaves, seeds, and roots, which is known as "bevachee" in southern Africa. In India it is used for "white leprosy", which is also known as "vitiligo", while the Chinese recommend the leaves of *Angelica archangelicum* for the same purpose. The name for these extracted compounds is psoralenes; these are isolated from the plant *Psorela corylifolia (*Pathak, 1986; Pathak and Fitzpatrick, 1992).

Dermatitis caused by parsley (*Pastinaca sativa*) and/or garden angelica (*Angelica archangelicum*) was identified in the USA and England as early as 1897 (Mabberley, 1987; Stowers, 1897). Unfortunately, at the time, the authors were unaware that their reaction occurred in the presence of UVA. In 1916, Freund observed hyperpigmentation resulting from bergamot oil (Freund, 1916). This author also did not know that the presence of UVL was required to cause changes to the skin. Oppenheim (1932) found that the exposure to UVL was required to induce the reaction and that blisters appeared 24–48 hours later (Oppenheim, 1932). Kuske (1938) showed that plant furocoumarins cause photosensitisation. Jensen and Hansen found that UVL of a wavelength between 320 and 380 nm caused the maximum reactions (Jensen and Hansen, 1939). Klaber coined the term phytophotodermatitis in 1942, to emphasise that it takes a plant and light to cause the reaction (Klaber, 1942). Finally, an Egyptian professor at the Cairo Faculty of Medicine, Department of Dermatology, noticed that some plants were used in traditional medicine, which started the development of modern phytotherapy (PUVA) for vitiligo and psoriasis. In 1940, El Moftyhe used crystalline methoxsalen (8-MOP, xanthotoxin) and then treated vitiligo exposed to the sun.

Vitiligo or leukoderma is an acquired chronic skin disease that occurs in the form of smooth, white spots on different parts of the body. It is one of the most common diseases in the group of hypopigmentation disorders. The exact cause of the disease is complex and it has not yet been understood. In 30% of cases the disease is hereditary. It is assumed that melanocytes (cells that produce the skin pigment melanin) are destroyed for unknown reasons. Other contributing factors include repeated sunburn, trauma, and emotional stress; vitiligo is also increasingly regarded as an autoimmune disease. This disease is not contagious and occurs in all age groups and in both sexes. The incidence of the disease is about 1–2%.

Psoriasis has been successfully treated with PUVA since 1974 at Harvard Medical School's Department of Dermatology. PUVA is an acronym: P stands for psoralen, U for ultra, V for violet, and A for the part of the solar spectrum between 320 and 400 nanometres wavelength. Today, PUVA is used in the treatment of many diseases, including palmoplantar pustulosis, fungal mycoses, and atopic dermatitis (Pathak and Fitzpatrick 1992). Psoralens are chemicals found in certain plants. They have the ability to absorb ultraviolet light in the UVL part of the solar spectrum. When the light energy is absorbed, psoralen interacts with DNA causing the inhibition of cell division, which is its default mode of action.

There are a great many plants in the world that have toxic and irritant effects on humans and animals. Of course, it would be almost impossible to cover them in one book. Table 1-1 lists plants that commonly cause various dermatoses in humans, which are present throughout the world.

Table 1-1: Plants that cause dermatosis in the world (cited and adapted from Muenscher, 1960; Tampion, 1977; Janjić and Lazić, 2016).

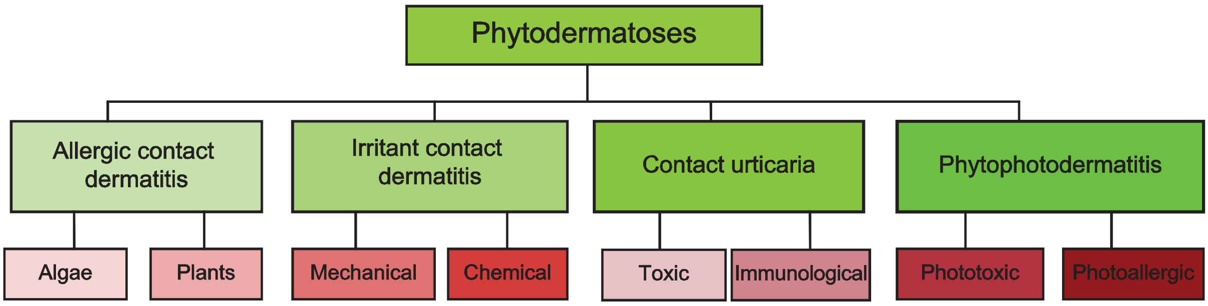
Species name	**Part of the plant**	**Species name**	**Part of the plant**
Ailanthus altissima (Mill.) Swingle	Flower, leaf	*Hedera helix* L.	Leaf
Anacardium occidentale L.	Sap	*Heleborus niger* L.	Leaf
Anagallis arvensis L.	Leaf	*Heracleum lanatum* Michx	Leaf
Anthemis arvenssis L.	Leaf, flower	*Hippomane mancinella* L.	Milky sap
Anthemis cotula L.	Leaf, flower	*Humulus lupulus* L.	Leaf
Aralia spinose L.	Seed	*Hypericum perforatum* L.	Leaf
Arctium lappa L.	Leaf	*Iris versicolor* L.	Rhizomes
Arisaema triphyllum L.	Leaf, root	*Iris spp.*	Rhizomes
Asarum canadense L.	Leaf	*Iva xanthifolia* L.	Leaf
Asimina triloba (L.) Dunal	Fruit	*Jatroha stimulosa* Michx.	Leaf, stem
Asparagus officinalis L.	Young stem	*Juniperus virginiana* L.	Fruit
Borago officinalis L.	Leaf	*Juniperus spp.*	Fruit

Buxus sempervirens L.	Leaf	*Laportea Canadensis* (L.) Wedd	Leaf, stem
Cannabis sativa L.	Leaf, flower	*Leonnurus cardiac* L.	Leaf
Catalpa speciosa (Warder) Warder ex Engelm	Flower	*Lycopersicon esculentum* (L.) H. Karst	Leaf, stem, fruit
Caulophyllum thalictroides (L.) Michx.	Root	*Maclura pomifera* (Raf.) Schneid	Milky sap, thorns
Chelidonium majus L.	Sap	*Mentzelia spp.*	Leaf
Chimaphila umbellata (L.) Barton	Leaf, stem	*Metopium toxiferum* (L.) Krug & Urb.	Leaf, bark
Clematis virginiana L.	Leaf, stem	*Nerium oleander* L.	Leaf
Colchicum autumnale L.	Leaf	*Pastinaca sativa* L.	Leaf, hairs, stem
Conium maculatum (L.,1753)	Leaf	*Phaecelia spp.*	Leaf
Convallaria majalis L.	Leaf	*Podophyllum peltatum* L.	Root
Cypripedium reginae Walter	Hairs, leaf, stem	*Polygonum spp.*	Leaf
Cypripedium parviflorum Salisb.	Hairs, leaf, stem	*Primula spp.*	Leaf
Daphne mezerum L.	Bark	*Ptelea trifoliate* L.	Leaf
Datura stramonium L.	Leaf, flower, fruit	*Ranunculus spp.*	Leaf
Daucus carota L.	Leaf	*Rheum rhaponticum* L.	Leaf
Delphinium ajacis L.	Leaf, seed	*Rus verniciflua* Stokers (RVS)	Leaf, bark, fruit, lacquer
Dictamnus albus L.	Seeds, leaf	*Rumex spp.*	Leaf
Dirca palustris L.	Bark	*Ruta graveolens* L.	Leaf
Echium vulgare L.	Leaf, stem	*Sanguinaria canadensis* L.	Stem, root sap
Encelia californica Nutt	Leaf	*Sedum acre* L.	Sap
Erigeron Canadensis (L.) Cronquist	Leaf	*Taxus spp.*	Tree
Euphorbia marginata Pursh	Milky sap	*Toxidendron radicans* (L.) Kuntze	Leaf, bark, fruit
Euphorbia spp.	Milky sap	*Toxidendron vernis* (L.) Kuntze	Leaf, bark, fruit
Fagopyrum esculentum Moench	Leaf	*Trifolium hybridum* L.	Leaf
Gelsemium sempervirens (L.) J. St-Hil.	Leaf, stem	*Urtica spp.*	Leaf, stem
Ginkgo biloba L.	Fruit	*Veratrum viride* Aiton	Leaf

TYPES OF PLANT-INDUCED DERMATOSES

Many plants cause dermatoses in humans and pose a problem for dermatologists and allergists (McGovern and Barkley, 1998). Even today, the frequency of plant-induced dermatoses is still not known. It is estimated that around 334 million people, that is, 3.5% of the world's population, are diagnosed with dermatoses every year (Anon., 2015). Dermatitis most commonly occurs in early childhood. About 20% of children in the UK and 10% in the USA suffer from different types of dermatoses (McAleer *et al*. 2012). Out of more than 500,000 species of plants in the world, it is estimated that around 10,000 can cause dermatoses in humans (McGovern, 2007). Phytodermatoses are plant-induced dermatoses. They are mainly caused by direct contact with a plant, but they can also occur due to sun exposure (Reis, 2010). Dermatoses that occur without direct contact with a plant can be caused by certain perfumes, creams, and other cosmetic products. Some cosmetic products contain substances, such as eugenol, isoeugenol, cinnamaldehyde, rosin, and turpentine, which originate from plants and are found in many cosmetic products (Figures 1-1 and 1-2). Lichens, which are not considered to be plants but are, instead, organisms formed by a symbiosis between fungi and algae, produce usnic acids, which are commonly used in cosmetics for sun protection (Quirino and Barros, 1995; Rademaker, 2000). In order to better understand phytodermatoses, skin reactions caused by contact with plants can be classified as follows:

- Allergic contact dermatitis
- Irritant contact dermatitis
- Contact urticaria
- Phytophotodermatitis



Scheme 1-2: Types of phytodermatosis in humans

Plants from the *Asteraceae* (Compositae) family most commonly cause dermatoses in humans, especially those who work with them frequently (farmers, gardeners, florists, etc.) (Stoner and Rasmussen, 1983; Mitchell and Rook, 1979; Hausen, 1973). There are about 150 plant species in this family that cause dermatoses in humans. Dermatoses caused by these plants occur throughout the world, but they are more frequent in areas with warmer climates (Stoner and Rasmussen, 1983; Mitchell and Rook, 1979; Lonkar *et al*. 1974; Pasricha and Fox, 1987; Burry *et al*. 1973; Menz and Winkelman, 1987; Tiwari *et al*. 1979). Due to the vast expanse and geographical variability, different genera from this family are present in various parts of the world. For example, the *Ambrosia* genus (e.g. *Ambrosia psilostachya*) is present in the USA, the *Chrisanteme* genus in Europe, and the *Arctotheca calendula* genus in Australia (Stoner and Rasmussen, 1983; Mitchell and Rook, 1979). In India, *Parthenium hysterophorus* from the *Asteraceae* (*Compositae*) family commonly causes contact dermatitis (Lonkar *et al*. 1974; Pasricha and Fox, 1987; Tiwari *et al*. 1979), while only 4 species, according to some studies, cause dermatoses in humans in northern India (Sharma and Kaur, 1990).

Figure 1-1: Allergic reaction and clearly restricted erythema: the patient applied sunscreen lotion (Vesna Gajanin, 2019)

Figure 1-2: Clearly restricted erythematous plaque: allergic reaction to deodorant with essential oils (Vesna Gajanin, 2019)

There are about 500 varieties of chrysanthemums in the *Asteraceae* (*Compositae*) family. They are the most common cause of dermatoses in florists. This family is one of the largest families and it includes about 20,000 species of plants. These are mainly herbaceous plants. Many of these species are weeds, and only some are vegetables or ornamental plants. Allergens, which are found in plants of this family, belong to sesquiterpene lactones. Over 100 identified sesquiterpene lactones are potentially allergenic (Salopoic *et al.* 2013). A problem may arise when it comes to determining which lactone is allergenic. Unfortunately, general tests cannot be used here, but instead they must be done with the actual plant to which the patient has been exposed. Diffuse redness and thickening of the skin occur, which resembles photodermatitis.

Table 1-2: Overview of families and genera that cause dermatoses in humans

Family	**Genus**	**Type of allergy**	**Substance that causes dermatosis**
Amaryllidaceae	*Alsmeria*	Allergic contact dermatitis	Tulipanin (methylene lactone)
	Narcissus	Irritant and contact dermal dermatitis	Alkaloids
Anacardiaceae	*Anacardium*, *Mangifera*, *Rhus*, *Semecarpus*, *Toxicodendron*	Allergic contact dermatitis	Phenol derivatives, urushiol
Apiaceae	*Anthurium*, *Arum*, *Caladium*, *Dieffenbacchia*, *Epipremnum*, *Philodendron*	Irritant dermatitis (Epipremnum = allergic contact dermatitis)	Calcium oxalate crystals
Araliaceae	*Hedera*	Allergic contact dermatitis	Falcarinol
Aspleniaceae	*Rahmora*	Allergic contact dermatitis	
Asteraceae	*Achillea*, *Ambrosia*, *Cichorium*, *Chrysanthemum*, *Cynara*, *Helenium*, *Lactuca*, *Leuchanthemum*, *Matricaria*, *Parthenium*, *Rudbeckia*, *Solidago*, *Tageted*, *Taraxacum*, *Xanthium*	Allergic contact dermatitis	Sesquiterpene lactones
Boraginaceae		Mechanical dermatitis, irritant dermatitis	Irritant hairs
Bromeliaceae		Irritant dermatitis	Acid derivatives, proteolytic enzymes
Cactaceae	*Opuntia*	Mechanical dermatitis, irritant dermatitis	Hairs
Capparidaceae	*Boscia*, *Bucholzia*, *Capparis*, *Cleoma*, *Crateva*, *Gynandropsis*, *Maerva*, *Polinasia*	Irritant dermatitis	Sulphur glycosides
Cladoniaceae	*Cladonia*	Allergic contact dermatitis	Usnic acid

Crassulaceae	*Sedum, Sempervivum*	Irritant dermatitis	Acid derivatives
Brassicaceae	*375 Rodova Brassica*	Irritant dermatitis	Glucosinolates
Cucurbitaceae	*Echballium*	Irritant dermatitis	
Davalliaceae	*Nephrolepsis*	Allergic contact dermatitis	
Euphorbiaceae (Podfam. Crotonoideae, Euphorbiodeae	*Aleurite*, *Codiaeum*, *Euphorbia*, *Hippomane*, *Hura*, *Synadenium*	Allergic contact dermatitis	Tetracyclic diterpene derivatives
Fabaceae	*Myroxolon*	Allergic contact dermatitis	Aldehyde, alcohol derivatives
Frullaniaceae	*Frunalia*	Allergic contact dermatitis	Sesquiterpene lactones (frullanolide)
Ginkgoceae	*Ginkgo*	Allergic contact dermatitis	Phenolic acids
Hydrophyllaceae	*Phacelia*, *Wigendia*	Allergic contact dermatitis	Quinone derivatives
Lauraceae	*Cinnamomum*, *Lauris*	Allergic contact dermatitis	Proteolytic enzymes
Lilliaceae	*Allium*, *Erythronium*, *Tulipa*, *Aloeas*	Allergic contact and irritant dermatitis	Sulphur derivatives, alkaloids
Magnoliaceae	*Liriodendron*, *Magnolia*, *Michelia*	Allergic contact dermatitis	Sesquiterpene lactones
Moraceae	*Ficus*	Phytophotodermatitis	Furocoumarins (psoralen, bergapten)
Orchidaceae	*Coleus*, *Cymbdium*, *Cypripedium*	Allergic contact dermatitis	Quinone derivatives
Papaveraceae		Irritant dermatitis	Alkaloids
Paremliaceae	*Parmelia*	Allergic contact dermatitis	Usnic acid
Polygonaceae	*40 genera*, *Rumex genus*	Irritant dermatitis	Calcium oxalate crystals
Primulaceae	*Anagalis*	Irritant dermatitis	Proteolytic enzymes
	Primula	Erythema multiforme, Allergic contact dermatitis	Quinone derivatives, primin allergen in trichomes
Protaceae	*Grevillea*	Allergic contact dermatitis	Phenols
Ranunculaceae	*Anemona*, *Caltha*, *Clematis*, *Ranunculus*	Irritant dermatitis	Lactone derivatives
Resedacea	*Reseda*	Irritant dermatitis	Thioglycoside derivatives

Rosaceae	*Reseda*	Mechanical irritation	Thorn
Rutaceae	*Citrus*	Irritant dermatitis, Allergic contact dermatitis, Phytophotodermatitis	Aldehydes, alcohols
	Dictamus, *Ruta*	Phytophotodermatitis	Acid derivatives
Solanaceae	*Capsicum*	Irritant dermatitis	Capsaicin
Thymelaeaceae	*Daphne, Thymelaea*	Irritant dermatitis	Terpene derivatives
Urticaceae	*Parietaria*, *Urtica*	Urticaria	
Usneaceae	*Evernia*, *Usnea*	Allergic contact dermatitis	Usnic acid

ALLERGIC CONTACT DERMATITIS (ACD)
(*Dermatitis allergica e contaactu*)

Allergic contact dermatitis is an inflammatory dermatosis that results from the skin’s inadequate response to environmental allergens. According to the current classification, this dermatosis develops due to the delayed allergic reaction of type IV (according to the classification by Gell and Coombs, Descotes and Choquet-Kastylevsky, 2001), during which antigen and antigen-presenting cells (Langerhans cells) react in the small blood vessels of the dermis. Clinical symptoms occur between 24 and 72 hours after contact. According to their course, allergic reactions can be acute, subacute, subchronic, and chronic. The severity of an allergic reaction depends on the potential and the concentration of the contact allergen substance, damage to the skin's protective barrier (acidic pH of the skin and the protective lipid layer on the surface of the skin), and the length of exposure to the allergen.

There are three types of allergic contact dermatitis:

- Basic contact dermatitis
- Allergic dermatitis of the *Tulipa* type
- Contact dermatitis to allergens in the air

Basic contact dermatitis (an acute form of contact allergic dermatitis) is accompanied by severe itching of the skin. The clinical signs describe four stages:

- Erythematous: clearly limited redness and swelling of the skin (erythema and oedema) (Figures 1-3 and 1-4)
- Vesicular: emergence of blisters (vesicles or bullae) (Figures 1-5 A and B, 1-6)
- Wetting stage: emergence of bare, wet areas on the skin (erosion) due to a blister bursting
- Drying, changing, and healing

Figure 1-3 (left): Clearly restricted erythematous plaques at the area of contact with the allergen (Vesna Gajanin, 2020)

Figure 1-4 (right): Volar side of forearm: oedema and clearly limited erythematous plaques (Vesna Gajanin, 2020)

Figure 1-5: A) single erythematous papules, plaques, and bullae; B) erythematous plaques with vesicles and bullae on the surface (Vesna Gajanin, 2019)

Figure 1-6: Bullous: an acute form of allergic contact dermatitis (Vesna Gajanin, 2019)

Chronic allergic contact dermatitis occurs after prolonged exposure to allergens. It is characterised by skin writing, dry thickened skin with lichenoid papules, rhagades (cracks on the skin), and scabs. These changes result from scratching due to the intense itching (Figures 1-3 and 1-4).

A diagnosis of ACD is made on the basis of medical history and clinical presentation, and it is confirmed by laboratory patch tests. Patch tests are performed on clean back skin using allergens in petroleum jelly. Readings are performed after 24, 48, and 96 hours. Positive reactions are read in stages, from the occurrence of mild erythema and skin oedema at the site of application, through the occurrence of a moderate number of erythematous papules and vesicles, to the occurrence of a large number of papules and vesicles, and intense erosion and wetting (Lipozenčić, 2008; Karadaglić 2016).

Differential diagnosis. *impetigo*, *lichen simplex chronicus*, atopic dermatitis, nummular eczema, scabies, psoriasis, seborrheic dermatitis, and insect bites.

Treatment. The most important part of treatment is to avoid allergens. For changes on the skin, depending on the form (dry forms, i.e., non-wetting forms), a topical corticosteroid and antibiotic ointments and creams may be applied, or saline and silver nitrate pledgets if there are bare and wet areas on the skin. For severe allergic reactions, systemic corticosteroid and antibiotic therapy is administered, with the application of antihistamines (Lipozenčić, 2008). Phototherapy, azathioprine, and cyclosporine are also applicable in the third line of treatment (Ferri, 2011).

In addition to the above forms of allergic contact dermatitis, *Tulipa* allergic dermatitis can also occur, as well as contact dermatitis caused by allergens from the air. Allergic dermatitis of the *Tulipa* type occurs frequently in people who grow plants from the *Liliaceae* and *Alstroemeriaceae* families, and it is manifested by painful changes on fingers (Saint-Mezard, 2004). The following stages are described for allergic dermatitis of the *Tulipa* type:

- Hyperkeratosis
- Inflammatory granuloma
- Same symptoms as those following contact with the *Tulipa* bulb

Contact dermatitis of the *Tulipa* type occurs in about 30% of workers who cultivate these plants. Also, there is a difference in the allergic reactions caused by tulips grown in India compared to those grown in Europe. Since a manual process is used to grow these plants, it is necessary to use protective gloves because allergic changes can appear on both hands, the thumb, forefinger, and the thenar. The intensity of allergic changes on the skin depends on the stage of plant growth. The most severe lesions on the skin appear during the processing of the bulb (Hassan *et al.* 2017).

People who work in the field are usually exposed to contact dermatitis due to the presence of allergens in the air (Avalos and Maibach, 2000). Without treatment, this dermatitis lasts two to three weeks and sometimes longer depending on the degree of exposure. Out of the plants that are widespread in our country, chrysanthemums, tulips, lilies, and primroses are probably the most common causes of allergic contact dermatitis. The *Anacardiaceae* family includes *Toxicodendron vernicifluum* that cause specific allergic skin reactions called urushiol. This name derives from urushiol sap, which contains a mixture of catechol (1,2-dihydroxybenzene) and resorcinol (1,3-dihydroxybenzene). Catechols and their side chains are immunologically inactive, but the presence of long chains increases their allergenicity and irritancy (Schempp *et al*. 2002). Poison ivy and poison oak commonly cause allergic dermatitis in North America (Fisher, 1996). Severe reactions, such as multiform erythema, occur after contact dermatitis from *Toxidendron* sp., *Melaleuica alternifolia*, or *Parthenium histerophorus.* In plants from the *Asteraceae* family, the major allergen is sesquiterpene lactone (LSK), which is found in leaves, stems, and flowers. Alpha methylene groups linked to the lactone ring increase its allergenicity. Today, there are over 1,350 LSKs, some of which are described in more detail in this monograph. The major allergen in plants of the *Primulaceae* family *(Primula obconica*) is primin, which is found in glandular hairs. Today, there are Primula obconica varieties without primin in the European market.

Allergic contact dermatitis occurs, especially in the tropics, when working with technical wood. According to the clinical presentation, it resembles photodermatitis (Saint-Mezard, 2004). Allergens are found in the middle of the trunk, but rarely in the sap. Sometimes allergies can occur when processing wood to make musical instruments, jewellery, carvings, and furniture, etc. The major allergens belong to benzo, naphtha, furano, and phenanthrene quinones.

Aeroallergens are one of the most common causes of allergic diseases; they include pollen, dust mites, house dust, animal hairs, and products of animal origin. Allergy-causing pollen mainly comes from grass, weeds, and trees. The analysis of the allergic diseases found patients treated at the Clinical Centre of Banja Luka from 2001 to 2010 revealed that the most commonly diagnosed allergy symptoms were rhinitis (40.8%), dermatitis (27.6%), various allergy diagnoses (16.1%), and asthma (15.5%) (Balaban and Gajanin, 2012). Many people, especially in rural areas, resort to the use of plants to treat some diseases (e.g. arthritis) in the form of compresses on painful areas. An example is allergic contact dermatitis due to *Ranunculus arvensis* (An *et al*. 2019). Contact dermatitis due to allergens in the air has the following stages:

- Photodermatosis lichenified, which is when the skin is thickened and leathery
- Symptoms similar to those resulting from plant pollen from the *Asteraceae (Compositae)* family

Table 1-3: Plants that cause contact dermatitis

Botanical name	**Botanical name**
Amaryllidaceae	
Narcis sp. L.	
Anacardiaceae	
Anacardium occidentale L. *Comocladia sp.* (e.g. *Comocladia dodonaea* (L.) Urban) *Cotinus coggygria* Scop. *Mangifera indica* L. *Metopium toxiferum* (L.) Krug & Urban *Schinus terebinthifolius* Raddi	Toxicodendron diversilobum (Torr. & A. Gray) Greene *Toxicodendron pubescens* P. Mill. *Rhus toxicodendron* L. *Rhus quercifolia* (Michx.) Steudel) *Toxicodendron radicans* (L.) Kuntze *Toxicodendron rydbergii* (Small) *Toxicodendron vernix* (L.) Kuntze
Annonaceae	
Asimina triloba (L.) Dunal	
Apocynaceae	
Allamanda cathartica L.	*Nerium oleander* L.
Apiaceae (Umbelliferae)	
Ammi majus L. *Anthriscus sylvestris* (L.) Hofmann *Daucus carota L. var. carota* *Daucus carota var. sativus* Hoffm.	*Heracleum lanatum* Michx. *Heracleum mantegazzianum* Sommier & Levier *Heracleum sphondylium* L. *Pastinaca sativa* L.
Araceae	
Alocasia sp. (e.g. *Alocasia macrorrhiza* (L.) G. Don) *Anthurium andreanum* Linden *Arum italicum* Mill. *Arum maculatum* L. *Caladium bicolor* (Ait.) Venten. *Calla palustris* L.	*Colocasia sp.* Schott (e.g. *Colocasia esculenta* (L.) *Dieffenbachia sp. Schott* *Epipremnum aureum* (Linden & André) Bunt. *Raphidophora aurea* (Linden & André) Birdsey; Krause) *Philodendron scandens* C. Koch & H. Sello *Philodendron selloum* C. Koch
Araliaceae	
Hedera canariensis Willd.	*Hedera helix* L.
Aristolochiaceae	
Aristolochia elegans M.T. Mast *Aristolochia gigantea* Mart. & Zucc. Hook.	*Aristolochia grandiflora* Swartz
Asclepiadaceae	
Calotropis gigantea (L.) Ait.	*Calotropis procera* (Ait.) Ait.
Bignoniaceae	
Campsis radicans (L.) Seem.	
Bromeliaceae	
Ananas comosus (L.) Merrill	
Chenopodiaceae	
Sarcobatus vermiculatus (Hook.) Torr.	

Commelinaceae	
Rhoeo spathacea (Swartz) Stearn	*Setcreasea pallida Rose cv*. "Purple Heart"
Asteraceae (Compositae)	
Ambrosia sp. L. *Artemisia sp*. L. *Aster sp*. L. *Chrysanthemum sp*. L. *Erigeron sp*. L. *Franseria acanthicarpa* (Hook.) Coville *Gaillardia sp*. Foug. *Helenium autumnale* L. *Helenium microcephalum* DC. *Iva sp*. L. *Lactuca sativa* L.	*Oxytenia acerosa* Nutt. *Achillea millefolium* L. *Anthemis cotula* L. *Parthenium argentatum* Gray *Parthenium hysterophorus* L. *Rudbeckia hirta* L. *Soliva pterosperma* (Juss.) Less. *Tanacetum vulgare* L. *Tagetes minuta* L. *Xanthium sp*. L.
Convolvulaceae	
Dichondra repens J. R. & G. Forst.	
Cornaceae	
Cornus sanguinea L.	
Euphorbiaceae	
Hura crepitans L. *Euphorbia cotinifolia* L. *Euphorbia gymnonota* Urb. *Euphorbia lactea* Haw. *Euphorbia lathyris* L. *Euphorbia marginata* Pursh *Euphorbia milii* Ch. des Moulins *Euphorbia myrsinites* L. *Euphorbia tirucalli* L.	*Excoecaria agallocha* L. *var. orthostichalus* Muell. Arg. *Grimmeodendron eglandulosum* (A. Rich.) Urb. *Hippomane mancinella* L. *Pedilanthus tithymaloides* (L.) Poit. *Sapium hippomane* G.F.W. Mey. *Sapium laurocerasus* Desf. *Stillingia sylvatica* Gard. *Synadenium grantii* Hook. f.
Fumariaceae	
Dicentra spectabilis (L.) Lem.	
Ginkgoaceae	
Ginkgo biloba L.	
Poaceae (Gramineae)	
Oryza sativa L. *Panicum glutinosum* Sw.	*Secale cereale* L.
Hydrophyllaceae	
Phacelia campanularia Gray *Phacelia crenulata* Torr. ex S. Wats. *Phacelia minor* (Harv.) Thell. ex F. Zimm. *Whitlavia grandiflora* Harv. *Phacelia parryi* Torr.	*Phacelia viscida* (Benth. ex Lindl.) Torr. *Phacelia imbricata* Greene *Phacelia malvifolia* Cham. *Wigandia caracasana* H.B.K. *Wigandia urens* (Ruiz & Pav.) H.B.K.
Juglandaceae	
Juglans nigra L.	
Fabaceae (Leguminosae)	
Prosopis glandulosa Torr. *Lupinus hirsutissimus* Benth. *Mucuna deeringiana* (Bort) Merrill	*Mucuna pruriens* DC. *Mucuna urens* (L.) DC.

Liliaceae	
Allium cepa L. *Allium sativum* L.	*Hyacinthus sp.* Tourn. ex L. *Tulipa sp.* L.
Loranthaceae	
Phoradendron serotinum (Raf.) M.C. Johnst.	
Magnoliaceae	
Magnolia grandiflora L.	
Moraceae	
Maclura pomifera (Raf.) C.K. Schneid. *Ficus carica* L.	*Ficus pumila* L.
Myrtaceae	
Eucalyptus globulus Labill.	
Orchidaceae	
Cypripedium sp. L.	
Palmae (Arecaceae)	
Caryota mitis Lour.	
Pinaceae	
Abies balsamea (L.) Mill.	
Primulaceae	
Primula farinosa L.	*Primula obconica* Hance
Proteaceae	
Grevillea banksii R. Br.	*Grevillea robusta* A. Cunn.
Ranunculaceae	
Caltha palustris L. *Clematis sp.* L. *(e.g.Clematis virginiana* L.*)* *Ricinus communis* L.	*Clematis sp.* L. (e.g. *Clematis virginiana* L.) *Pulsatilla patens* *Ranunculus sp.* L. (e.g. *Ranunculus acris* L.)
Rosaceae	
Agrimonia sp. Tourn. ex L. *Rosa odorata* (Andr.) Sweet	*Agrimonia eupatoria* L.
Rutaceae	
Citrus aurantiifolia (Christm.) *Dictamnus albus* L.	*Pelea anisata* H. Mann *Ruta graveolens* L.
Saxifragaceae	
Hydrangea sp. L.	
Solanaceae	
Lycopersicon esculentum Mill. *Solanum carolinense* L.	*Solanum tuberosum* L.
Thymelaeaceae	
Daphne mezereum L.	*Dirca* palustris L.
Ulmaceae	
Ulmus glabra Huds.	*Ulmus procera* Salisb.
Urticaceae	
Laportea aestuans (L.) Chew *L. canadensis* (L.) Weddell *Urera baccifera* (L.) Weddell	*Urtica dioica* L. *Urtica urens* L.

Vitaceae	
Parthenocissus quinquefolia (L.) Planch.	*Parthenocissus triscuspidata* (Siebold & Zucc.) Planch.
Zygophyllaceae	
Larrea tridentata (Sesse & Moc. ex DC.) Coville	

Table 1-4: Plants that cause allergic contact dermatitis (Gambillara *et al*. 2010)

Name of the plant	**Compound**
Parthenium hysterophorus L.	Sesquiterpene lactones
Primelia, Evenia, Cladonia i Uselia	Usnic acid, atranorin
Frullania sp. Raddi	Sesquiterpene lactones
Chrysanthemum sp. L.	Sesquiterpene lactones
Alstromeria sp. L.	Tuliposide A
Pinus sp. L.	Colophony (resin)
Toxidendron sp. Mill.	Urushiol, pentadecyl catechol
Primula obconica Hance	Triterpenoids, Primin
Primula praenitens Ker Gawl.	
Ambrosia sp.	Sesquiterpene lactones
Tulipa sp. L.	Tuliposide A
Toluifera pereirae (Royle) Baill.	Balsam
Daucus carota L.	Furocumarines
Petroselinum crispum (Mill) Fuss	
Apium graveolens L.	
Helianthus annuus L.	Sesquiterpene lactones
Dahlia sp. Cav.	
Cynara scolimus L.	
Arnica montana L.	
Matricaria chamomilla (L.) Rydb.	
Cichorium sp. L.	
Chrisanthemum sp. L.	
Narcissus sp. L.	Isoquinoline alkaloids
Allium cepa L.	Diallyl sulphide, allicin, tulip (A and B), 6-tuliposide A
Allium sativum L.	
Tulipa sp. L.	
Hyacinthus sp. Tourn. ex L.	
Orchis sp. Tourn. ex L.	Benzoquinones
Vanilla sp. Plum. Ex. Mill.	

NON-ALLERGIC CONTACT DERMATITIS (CD)
(Irritant contact dermatitis)

Non-allergic contact dermatitis is the inflammation caused by damage to the outer, protective layer of the skin due to the effect of mechanical or chemical factors. Non-allergic contact dermatitis basically has no immune mechanism. Acute and chronic forms of non-allergic contact dermatitis have been described according to the course of the disease. Irritation can be caused by the following methods:

- Mechanical
- Chemical

Acute non-allergic contact dermatitis. Changes in the acute form of non-allergic contact dermatitis can be observed in parts of the body that are exposed to irritants. According to the course of the disease, the following stages take place:

- Erythematous
- Vesicular
- Erosive with wetting
- Scab formation
- Increased desquamation (flaking)

Chronic non-allergic contact dermatitis. Changes in chronic non-allergic contact dermatitis occur with prolonged exposure to certain irritants. It is clinically manifested by thickening, desquamation, and even cracks in the skin (rhagades). A diagnosis of non-allergic contact dermatitis is made on the basis of medical history and clinical presentation.

Treatment primarily involves avoiding irritants and, when it comes to already present changes, corticosteroid and antibiotic topical pads, creams, and ointments can be applied. With more severe changes, it is necessary to administer systemic antihistamines and corticosteroids. Constant skin care by applying nutrient and neutral ointments and creams is also necessary (Karadaglić, 2016; Glodsmith *et al.* 2012)

Alstromeria species are popular cut flowers that are often found in florists. Due to frequent contact, florists often have dermatoses caused by these types of flowers. Their fingers become cracked and red, and these symptoms can spread to the forearms and face. Sometimes there is a loss of skin pigmentation. *Tulipa* are popular spring flowers that have a limited duration. In the USA, about 56% of workers are sensitive to the effects of these types of flowers. *Primula* is a houseplant with beautiful flowers and a long blooming season. It is estimated that over 50% of positive reactions occur following a patch test. Characteristic symptoms appear on the fingers, hands, face, and neck. Primulin is included in the standard patch test kit. Daffodils may cause itching and rashes on the face, hands, and forearms. Phytophotodermatosis-inducing plants contain furocoumarins or related compounds. The two prerequisites for this type of dermatosis are contact with a plant that contains furocoumarines and the presence of an ultraviolet light of a wavelength greater than 320 nm. This dermatitis is usually seasonal. At the start, there will be erythema and blisters on the skin, and then hyperpigmentation, which can last for months. Contact urticaria usually occurs within 15 minutes of contact with such plants. Allergic contact dermatitis causes the most problems (Kimber *et. al*. 2002). Numerous plants, their parts, and their products can cause dermatoses. Symptoms often depend on a number of factors, including human sensitivity, length of contact, and the conditions of the plants and the plant products.

IRRITANT DERMATITIS

Irritant dermatitis or inflammation of the skin basically has no immune mechanism. Irritation can be one of the following:

- Mechanical
- Chemical

Mechanical irritation is caused by damage to the skin from thorns, as well as the trichomes and glochids found on the leaves, stems, and fruits of some plants. These parts are anatomically sharp and easily pierce the skin causing skin lesions. Chemical irritation is caused by the presence of various chemical compounds in plants or their parts, including acids, glycosides, proteolytic enzymes, and crystalline compounds, which cause corrosive burns, blisters, and sting wounds on contact with the skin. The intensity of damage depends on the following:

- Irritant concentration
- Contact time
- Skin integrity and thickness

Lesions can be found on the areas of contact. There are two types of irritant dermatitis:

- Acute dermatitis, with a collective skin reaction and symptoms that occur a few hours after contact with even minimal amounts of irritant
- Chronic or cumulative dermatitis resulting from repeated contact with an irritant

Irritant contact dermatitis occurs in the form of stains, spots, papules, and lupus, which are restricted to the parts that were in direct contact with an irritant. The lesions are painful and itchy (Modi *et al*. 2009; McGovern, 2007).

Mechanical irritations

In some plants, under the influence of external factors, the leaves take on special functions and undergo metamorphosis. Such leaves partially or completely transform into thorns. The leaves of succulent plants transform into thorns, thereby reducing leaf transpiration and the photosynthetic area. Since these are autotrophic plants, the function of the leaves is performed by the stems. These plants are from the following genera: *Agave*, *Rubus*, *Citrus*, *Rosa*, *Cactus*, *Pseudocactus*, and others. There are several genera in the *Cactaceae* family, including *Opuntia*, *Cereus*, *Cephalocereus*, and *Acanthocereus*, that have metamorphosed leaves which have turned into thorns (Rietschel and Fowler, 2008). Many other plants also have similar outgrowths in their structure that can cause skin damage when working with them without protective clothing. By damaging the skin, these outgrowths can cause inflammatory reactions in humans. In addition, they not only cause irritant dermatitis but can also cause infections through various pathogens (*Clostidium tetani*, *Staphilococcus aureus*, *Sporothrik schenckii*, etc.).

Some plants have their own defence mechanisms in the form of thorns, serrated leaves, and spikes that can directly injure the skin. This causes mechanical irritation (Dermatitis by Physical Trauma). Skin lesions are most commonly caused by thorns, trichomes, and glochids, which are found on the leaves, stems, and fruits of some plants. These are the parts of the plant that are anatomically sharp and which can easily pierce the skin, thereby causing skin lesions (Reis, 2010).

Table 1-5: Plants that cause irritations with crystal needles

Species name
Alocasia macrorrhiza (L.) G. Don
Anthurium andreanum Linden
Arum maculatum L.
Arum italicum Mill.
Caltha palustris L.
Dieffenbachia sp.
Parthenocissus triscuspidata (Siebold & Zucc.) Planch.
Parthenocissus quinquefolia (L.) Planch.
Philodendron scandens (C. Koch & H. Sello) ssp. *oxycardium* (Schott) Bunt.
Philodendron selloum C. Koch
Scindapsus aureus (Linden, André Engl., & K. Krause)

Table 1-6: Plants as external irritants (causing irritations with needles and hairs)

Botanical name	**Botanical name**
Cactaceae	***Fabaceae (Leguminosae)***
Opuntia sp. Mill *(e.g. O. microdasys (Lehm.) Pfeiff.)*	*Lupinus hirsutissimus* Benth.
Cannabaceae	*Mucuna pruriens* DC.
Humulus lupulus L.	*Dolichos pruriens* L.
Cornaceae	*Mucuna urens* (L.) DC.
Cornus sanguinea L.	*Mucuna deeringiana* (Bort) Merrill
Euphorbiaceae	***Malpighiaceae***
Acidoton urens Sw.	*Malpighia polytricha* A. Juss.
Cnidoscolus chayamansa McVaugh	*Malpighia urens* L.
Cnidoscolus stimulosus (Michx.) Engelm.	***Sterculiaceae***
Cnidoscolus texanus (Muell. Arg.) Small	*Sterculia apetala* (Jacq.) Karst.
Cnidoscolusurens (L.) Arth.	***Urticaceae***
Dalechampia scandens L.	*Laportea aestuans* (L.) Chew
Platygyne hexandra (Jacq.) Muell. Arg.	*Laportea canadensis* (L.) Weddell
Tragia volubilis L.	*Fleurya aestuans* (L.) Gaud.)
Hydrophyllaceae	*Urtica dioica* L.
Phacelia imbricata Greene	*Urtica urens* L.
Phacelia malvifolia Cham.	
Wigandia caracasana H. B. K.	
Wigandia urens (Ruiz & Pav.) H. B. K.	

Chemical irritations

Chemical irritants can penetrate the skin without causing mechanical damage. They can cause painful skin irritation and even permanent damage. Contact with the eyes may cause temporary blindness. Also, when burning plants, there is a possibility of irritants penetrating from the smoke, which causes irritant dermatitis (http://contactpoisonousplants.org). Chemical irritation is caused by the presence of various chemical compounds in plants or their individual parts, such as acids, glycosides, proteolytic enzymes, and crystalline compounds, which cause corrosive burns, blisters, and sting wounds on contact with the skin. The intensity of the damage depends on the following:

- Irritant concentration
- Contact time
- Skin integrity and thickness (McGovern, 2007).

Plants that cause this type of dermatosis primarily affect the skin with their pharmacologically active ingredients. These include the well-known plants, *Urticaria dioica* and *Urticaria urens*, which have hairs on them that sting and burn uncovered areas of the skin when working with them. When penetrating the skin, they break and release their contents, which consists of histamine, serotonin, acetylcholine, and other substances (Reis, 2010). Plants with this morphology also grow in other parts of the world, such as *Cnidosculos urens*, *Fleuria aestuans*, *Loasa rupestris*, *Cnidosculos phillacantus*, *Dalechampia scandens*, *Nectandra nitidula*, and *Mucuna urens*. Chemical irritant dermatitis can be caused by many substances found in plants, such as formic, acetic, oxalic, malic, citric acid, glycosides, glycosyl flavones, phenols, proteolytic enzymes (papin, bromelain), crystalline compounds (calcium oxalate crystals), diallyl disulphide, and allicin, etc. (Wilkeni and Schempp, 2005). These substances are mainly found in vegetable juice or in some plant parts and organs.

Calcium oxalate is a very common irritant present in plants, especially in those from the *Araceae* family (*Dieffenbachia picta*). This substance is released from their leaves and causes oedema, blisters, and vesicles upon contact with the skin. The swelling and pain disappear in 4–12 days. Calcium oxalate can also increase the toxicity of other plant constituents, such as bromelain and the proteolytic enzymes found in pineapple. Daffodils, tulips, hyacinths, spurge, and other plants also contain calcium oxalate. Due to the content of glycoside flavonoids and triterpene phenols in its milky sap, spurge is very poisonous and can cause bullous dermatitis, and even temporary blindness if it comes into contact with the eyes (Wilkeni and Schempp, 2005). Ranunculin is transformed into protoanemonin; this is then rapidly polymerized into anemonin, which is not an irritant (Karimian-Teherani *et al*. 2008). Therefore, only freshly cut plants cause irritations. Capsaicin causes the expansion of blood vessels, a burning sensation, irritation, and erythema without blisters. The symptoms can last for days.

Table 1-7: Plants that cause irritation with milky sap or latex

Botanical name	**Botanical name**
Agavaceae	***Euphorbiaceae***
Agave sp. L. *(e.g. Agave americana L.)*	*Excoecaria agallocha* L.
Apocynaceae	*Grimmeodendron eglandulosum* (A. Rich.) Urb.
*Acokanthera oblongifolia (*Hochst.) Codd	*Hippomane mancinella* L.
Plumeria sp. L.	*Pedilanthus tithymaloides* (L.) Poit.
Asclepiadaceae	*Sapium hippomane* G.F.W. Mey.
Calotropis gigantea (L.) Ait. f.	*Sapium laurocerasus* Desf.
Calotropis procera (Ait.) Ait. f.	*Stillingia sylvatica* Gard.
Euphorbiaceae	*Synadenium grantii* Hook. f.
Euphorbia cotinifolia L.	***Ranunculaceae***
Euphorbia gymnonota Urb.	*Caltha palustris* L.
Euphorbia lactea Haw.	*Clematis sp.* (e.g. *Clematis virginiana* L.)
Euphorbia lathyris L.	*Pulsatilla patens* Mill. (=*Anemone patens* L.)
Euphorbia marginata Pursh	*Ranunculus sp.* (e.g. *Ranunculus acris* L.)
Euphorbia milii Ch. des Moulins	***Thymelaeaceae***
Euphorbia myrsinites L.	*Daphne mezereum* L.
Euphorbia tirucalli L.	*Dirca palustris* L.

Table 1-8: Main constituents of plants causing irritant dermatitis (Gambillara *et al*., 2010)

Family	**Latin name**	**Irritant**	**Localization**
Agavacae	*Agave americana* L.	Calcium oxalate, saponins	Milky sap
Alliaceae	*Allium sativum* L.	Thiocyanates	Bulb
Amarylidaceae	*Narcissus spp.*	Calcium oxalate	Flowers, leaves, bulb
Anacariaceae	*Anacardium accidentale* L.	Oil	Fruit mesocarp
Brassicaceae	*Brassica nigra* L.	Glucosinolates	Leaves, root, fruits
	Raphanus sativum L.		
Bromellaceae	*Ananas comosus* (L.) Merr.	Bromelain	Flowers, fruits
Euphorbiaceae	*Codiaeum variegatum* (L.) A. Juss.	Phorbol esters	Sap, flowers, leaves, and fruits
	Euphorbia esula L.		
	Hippomante mancinella L.		
Liliaceae	*Hyaccinthus orietallis* L.	Calcium oxalate	Bulb
Polygonaceae	*Rheum rhaponticum* L.		Leaves
Ranunculaceae	*Aquielegia spp.*	Protoanemonin	Freshly cut plant, whole plant
	Caltha spp.		
	Ranunculus spp.		
Solanaceae	*Solanum annuum* C. V. Morton	Capsaicin	Fruit placenta

Plants from the *Urticaceae*, *Loasaceae*, *Boraginaceae* (subfamily *Hidrophilloidea*e), and *Euphorbiaceae* families have hairs (Lookadoo *et al.* 1991). Several unrelated plant families have hairs, and their structure is generally similar. The base of a hair supports an elongated cell with a brittle tip. When the tip of a hair is broken, the pressure injects its contents into the skin. Hairs or trichomes grow on the leaves and stems of many plants. Some plants have glandular hairs. Glandular hairs have tissues that produce secondary metabolism secretions. These constituents are either food or insect repellents (Huttunen et al. 2008). Some glandular hairs can cause irritation just through contact. Their general structure is similar in all of the families that have them, except for *Tragia* and *Dalechampia*. The multicellular base of a hair is usually 1–8 mm long, with a tapered tip so that it can easily penetrate the skin. A hair has a fine tube with calcium carbonate at the base and silicon dioxide at the very tip. One hair of *Urtica thunbergiana* has about 4 nanolitres (4 x 10^{-6} ml) of liquid. The concentration of toxins in the liquid in the hairs of *Urtica thunbergiana* is as follows: histamine 0.53%, tartaric acid 1.44 %, and oxalic acid 0.12 % (Kuo-Huang and Huang, 2006).

The effects caused by the hairs of plants from the *Urtica* genus, especially some subspecies of *Urtica dioica*, are due to a number of constituents, including histamine, acetoholine, serotonin, and formic acid. Histamine is a neurotransmitter that causes pain and itching when it gets into the skin.

Many plants that burn the skin belong to the *Urtica* genus. The *Urtica* genus has 24–39 species. They are a cosmopolitan species, as well as mostly herbaceous and perennial. They originate from Europe, Africa, Asia, and North America. The *Urticaceae* family includes other species that have hairs, but which do not belong to the *Urtica* genus, including *Dendrocnide excels*, *Dendrocnide moroides*, *Girardinia diversifolia*, *Laportea canadensis*, *Urera baccifera*, and *Urera tenax*. Some other plants of other families have hairs on their organs, including Euphorbiaceae (Cnidoscolus stimulosus, Cnidoscolus urens, Croton ciliato-glandulosus, Dalechampia *spp.*, Jatropha urens, and Tragia *spp.*), Fabaceae (Mucuna pruriens), *Loasaceae* (Caiophora *spp.*, Loasa *spp.*, and Cevallia *spp*), and Solanaceae (Solanum carolinense).

Figure 1-7: Hairs of *Urtica dioica* L. (photo, Vaskrsija Janjic)

Figure 1-8: Thorns of *Datura stramonium* L. (photo, Vaskrsija Janjic)

Figure 1-9: Milky sap of *Chelidonium majus* L. (photo, Vaskrsija Janjic)

Table 1-9: Combined effect of plants that cause dermatoses in humans

Effect	Latin name
Allergic contact dermatitis + irritant dermatitis	*Anthemis arvensis* L.
	Capsicum annuum L.
	Codiacum variegatum var. pictum L.
	Cymbopogon nardus (L.) Will. Watson
	Eucalyptus globulus Labill
	Euphorbia pulcherrima Willde. ex Klotzsch.
	Ginkgo biloba L.
	Hedera helix L.
	Illicium verum Hook. f.
	Jasminum officinale L.
	Lavandula angustifolia Miller
	Lavandula latifolia (L.f.) Medikus
	Narcissus poeticus L.
	Narcissus jonquilla L.
	Narcissus pseudonarcissus L.
	Pelargonium sp.
	Leucanthemum vulgare L.
	Poinsettia pulcherrima J. Graham
	Semecarpus anacardium L.
	Sesamum indicum L.
	Smodingium argutum E. Mey
	Tagetes minuta L.
	Tulipa sp.
	Zingiber officinalis Rosc.
Allergic contact dermatitis + phytophotodermatitis	*Citrus* sp.
Allergic contact dermatitis + urticaria	*Lactica sativa* L.
Urticaria	*Parietaria officinalis* L.
	Urtica dioica L.
Allergic contact dermatitis + erythema polymorph	*Primula obconica* Hance
	Primula sinensi (Lindl.)
	Primula veris L.
Irritant dermatitis + urticaria	*Ricinus communis* L.
	Salsola kali L.

PHYTOPHOTODERMATOSES

Phytophotodermatoses occur as a result of abnormal or excessive reactions when the skin is exposed to the sun after contact with certain plants. This is due to the presence of furocoumarins, such as bergapten, psoralens, and xanthotoxins. Toxic effects occur after contact with these plant substances and exposure to ultraviolet rays. The radiation wavelength is equal to or greater than 320 nm. There are two types of skin photosensitivity:

- Phototoxic reactions
- Photoallergic reactions

Phototoxic reactions are non-immunological reactions. They correlate with the physiology of the skin; they are localised on the area that was in contact with the plant, and then exposed to light. Reduced skin sensitivity to ultraviolet radiation is due to the phototoxic substances found in certain plants, such as furocoumarins, psoralen, and methoxypsoralen (bergapten isolated from *Citrus bergami* or cantotoxin isolated from *Fragaria kanthokiloides*). Ultraviolet light induces psoralen, which then forms covalent bonds with pyrimidines. That leads to the formation of free radicals that are responsible for the epidermis lesions.

Lesions are strictly localised on the areas of the skin exposed to the sun. Reactions on can appear between a few hours and 72 hours in the form of erythema (redness), and smaller and bigger blisters (vesicles and bullae) (Figure 1-10). The shape of erythematous lesions on the skin depends on the imprint of the plant that caused the phototoxic reaction (Figure 1-14). In severe skin reactions, the vesicles and bullae will burst and leave bare areas of the skin (Junior *et al*. 2016). When the skin lesions disappear, the residual hyperpigmentation will still remain (James, 2011). Lesions in the form of stains can appear on the neck, arms, and face of people wearing perfume containing 5-MOP (xanthotoxin or bergamot) (Berloque dermatitis) (Figure 1-12).

Figure 1-10: Erythematous plaques, papules, and vesicles (Vesna Gajanin, 2019)

Figure 1-11: Bizarrely shaped erythematous plaques, erythematous papules, and vesicles (Vesna Gajanin, 2019)

There are many contact allergic reactions that occur on the skin when using cosmetic products. In recent years, most cosmetic products involve the use of organic or herbal preparations, such as organic or plant hair dyes and even tattoo materials. Figures 1-12 and 1-13 show allergic contact dermatitis caused by henna hair dye and tattoo.

Rosa mosqueta oil is known for its antioxidant effects and it is widely used in the treatment of postoperative wounds; it is also able to reduce wrinkles (Figure 1-14). However, it has been found that it can cause an allergic reaction (Ibernón *et al*. 2018). Bergamot, argan, and other essential oils can also cause allergic contact dermatitis (Foti *et al*. 2014; Lauriola and Corazza, 2016).

Figure 1-12: Allergic reaction after dying: erythematous plaque and flakes (Vesna Gajanin, 2020)

Figure 1-13: Erythematous plaque in the shape of a tattoo (henna tattoo) (Vesna Gajanin, 2019)

Figure 1-14: Erythematous plaques and oedema at the area of contact with a cream based on herbal preparations (Vesna Gajanin, 2019)

Photoallergic reactions are type IV immunoallergic reactions (Gell and Combs), which are delayed in a small number of individuals. Photoallergens are activated by light; they combine with skin proteins, and thus become complete allergens, triggering an immune response (Lipozenčić, 2008). Reactions are polymorphic in nature and appear as welts and eczema on the skin, usually occurring about 48 hours after exposure. Photoallergic reactions are very rare, since they depend not only on the photosensitizer concentration but also on the radiation dose. These include lesions on the skin, which has not been exposed to the sun. With each subsequent exposure to the sun, the condition worsens as the threshold decreases and the intensity of the reaction increases. Photoallergic reactions are caused by *Heracleum giganteum* plants (Karimian-Teherani *et al*. 2008) and plants of the *Asteraceae* family, such as chrysanthemums and pyrethrum (McGovern, 2007).

The diagnosis of phytophotodermatitis is made on the basis of medical history and clinical presentation. Differential diagnoses include inflammatory dermatoses (cellulitis, erysipelas, herpes zoster) and a reaction to medication (erythema fixum). Treatment is based on avoiding phototoxic substances and, if there are lesions on the skin, cold compresses, emollient agents, and topical corticosteroid creams are applied (Karadaglić, 2016).

Plants from the *Apiaceae* family are the main causes of phytophotodermatitis, while representatives of the *Heracleum* genus are the main causes of dermatoses in Europe and North America (Karimian-Teherani *et al.* 2008). Furocoumarins, and especially psoralen, are substances used for plant protection to suppress the growth of certain types of fungi that act as parasites on some plants. Plants treated with psoralen against some fungi, such as *Sclerotinia sclerotium*, contain increased amounts of psoralen; therefore, people who work with these plants or consume them may be more exposed to their effects.

Table 1-10: Plants that cause phytophotodermatosis in humans

Family	**Name of the species**
Apiaceae (Umbelliferae)	*Apium graveolens* L.
	Angelica archangelica L.
	Anethum graveolens L.
	Anthriscus sylvestris (L.) Hofmann
	Foeniculum vulgare Mill
	Daucus carota L. *var. carota*
	Daucus carota var. sativus Hoffm.
	Heracleum sphondylium L.
	Pastinaca sativa L.
	Petroselinum crispum (Mill.) Nym
Asteraceae (Compositae)	*Achillea millefolium* L.
	Anthemis cotula L.
Hypericaceae	*Hypericum perforatum* L
Moraceae	*Ficus carica* L.
Rosaceae	*Agrimonia eupatoria* L.
Rutaceae	*Citrus bergamia* Risso
	Citrus lemon (L.) Osbeck
	Citrus medica L.
	Citrus x aurantiifolia (Christm) Swingle
	Dictamnus albus L.
	Ruta graveolens L.

The main plant families that cause phytophotodermatoses are *Apiaceae* (*Umbeliferae*), *Fabaceae* (*Papilonacae*), *Moraceae*, and *Rutaceae*. Bergapten (5-MOP) and xanthotoxin (8-MOP) are the most common linear furocoumarins found in these plants that cause phytophotodermatoses. Angular furocoumarins, such as pimpinelin, angelicin, and sphondin, have lower occurrences of phytophotodermatoses.

Apiaceae is a family of plants that most commonly causes phytophotodermatoses. The plants from this family are very easy to spot in nature because of their distinctive flowers. Their fruits are small, round, or cylindrical. Some species are difficult to identify because the plants are similar to each other. *Ammi majus* is a major source of xanthotoxin (8-MOP) in the world. It is widespread in Egypt in the valley of the Nile, in Europe, India, Russia, the USA, and South America (Pathak, 1986). Furocoumarins are particularly found in the root and leaves of these plants. The root of *Angelica gigas* is used in medicine as a diuretic, and to treat anaemia and haemorrhoids. People who work with this plant often have phytophotodermatitis.

Heracleum sphondylium is a major cause of phytophotodermatosis in Europe and North America (Pathak, 1986). This plant grows rapidly. Its black seeds and leaf extracts are the best photosensitizers. The stems of *Heracleum mantegassianum* and *Heracleum laciniatum* are used as trumpet mouthpieces in Norway, which causes some perioral problems in children (Lovell, 1993). The flowers, fruits, leaves, and root of *Heracleum laciniatum* are more phototoxic than the stem (Kavli *et al*. 1983). The *Heracleum* species contain both 5-MOP and 8-MOP. It is believed that a concentration of 0.1 g of linear furocoumarines in 100 g of dry matter of the plant can cause phototoxic reactions.

Table 1-11: Concentration of 5-MOP and 8-MOP in some plants from the *Apiaceae* (*Umbelliferae*) family (g/100 g of dry matter) (Alehaideb *et al.* 2017)

Plant species	**5-MOP (Begapten)**	**8-MOP (Xanthotoxin)**
Ammi majus L.	0.11	0.36
Pastinaca sativa L.	0.02–0.30	0.03–0.35
Heracleum laciniatum Hornem.	0.4–0.5	
Heracleum nipponicum (Kitag.) H. Ohba	0.01	
Apium graveolens L.	0.02	0.06

The *Rutaceae* family includes tropical and subtropical plants that are widely distributed in the world and known to cause phytophotodermatoses. Many species of this family are shrubs. These are major phytotoxic plants in the USA, especially in Florida. *Citrus aurantifolia* and *Citrus sinensis* species are known to cause dermatoses even after contact with the skin of the fruit (Volden *et al*. 1983). *Ruta graveolens* is a shrub that grows in the Mediterranean region, with a long medical tradition as a remedy for urticaria, warts, and erysipelas. It has a bitter and surprising taste. It is probably the most common cause of phytotoxicity in English gardens. It contains 5-MOP, 8-MOP, and angelicins (Lovell, 1993). Other plants that cause dermatoses include *Dictamnus albus*, *Cneoridium dumosum*, and *Pelea anisate*, which grow in different parts of the world. It is even mentioned in the Bible that *Ficus carica* plants from the *Moraceae* family, which originatefrom the Middle East, were used to eliminate warts and treat skin infections. Psoralen and bergapten are mainly found in juice from the leaves and young plants. No furocoumarin has been found in unripe and ripe fruits (Zaynoun *et al.* 1984).

Table 1-1: Significant plants of the *Apiaceae* (*Umbeliferae*) and Rutaceae families that cause phytotoxic reactions

Family Apiaceae		
Ammi majus L.	*Heracleum lanatum* Michx	*Heracleum mantegazzianum* Sommer & Levier
Angelica archangelica L.	*Daucus carota* L.	*Heracleum sphondylium* L.
Angelica sylvestris L.	*Foeniculum vulgare* Mill.	*Pastinaca sativa* L.
Anthriscus sylvestris (L.) Hoffm.	*Heracleum laciniatum* Hornem.	*Petroselinum crispum* (Mill.) Fuss
Apium graveolens L.		

Family Rutaceae		
Citrus x aurantiifolia (Christm.) Swingle	*Citrus limon* (L.) Osbeck	*Phebalium squamulosum* Vent.
Citrus x aurantium L.	*Citrus x paradisii* Macfad.	*Pelea anisata* H. Mann
Citrus bergamia Risso	*Dictamnus albus* L.	*Ruta graveolens* L.
Citrus limetta Risso		

The main source of psoralen for the treatment of vitiligo in India is *Psoralea corilifolia*, which belongs to the *Fabaceae* family. The *Psoralea* genus is known for its phytotoxic constituents. The seeds of the plants from this genus have been used since 1400 BC for the treatment of vitiligo (Pathak, M., 1986). This genus also includes *Myroxylon balsamum* and *Myroxylon pereirae*, whose balm is extracted in Peru (Mabberley, 1987; Lovell, 1993). Other families, such as *Asteraceae*, *Ranunculaceae*, *Brassicaceae, Convolvullaceae*, *Hypericaceae*, and *Ananaccardiceae*, contain furocoumarins and other photosensitive chemicals but do not cause clinical phytophotodermatoses (Pathak, 1986).

URTICARIA

Many plants can cause urticaria or eczema after contact with the skin via an IgE mediated mechanism. This type of dermatitis (protein contact dermatitis) is often restricted to areas of skin that have come in contact with plants, but respiratory and digestive symptoms (contact urticaria syndrome) can also occur. People with atopy are predisposed to contact urticaria. Pruritus, erythema, oedema, and sometimes vesicles appear 30 minutes after contact. The list of plants, fruits, herbs, and trees that can cause urticaria is very long (Lukacs et al. 2016). However, there needs to be frequent and continuous use for it to occur. The best example would be celery (*Apium graveolens*). In general, this form of dermatitis affects food industry workers, cooks, gardeners, and florists (Reis, 2010).

Urticaria is a transient eruption of papules and plaques in the form of welts. It is most often caused by an immunological and, less often, a non-immunological process. In addition to the skin, the gastrointestinal, respiratory, and cardiovascular systems can also be affected. Pathogenically, urticaria can occur after a direct IgE-mediated reaction with subsequent mast cell degranulation or with direct mast cell degranulation, without an immune mechanism (Bulur and Gokalp, 2017). Mast cells and basophils are thought to be the first link in the development of urticaria. A cascade of mediators, such as histamine, heparin, and proteases, are released, which affects the blood vessels, airways, intestine mucosa, and the like.

Urticaria is manifested by the sudden onset of erythema and oedema in the form of papules and plaques of various shapes and sizes (Figures 1-13, 1-14, and 1-15). Erythema is more visible on the periphery of the change, while the whitish colour in the centre comes from the oedema's pressure on the capillaries. Changes on the skin disappear in 3–4 hours, and sometimes after 24 hours. Erythema is less pronounced than oedema in angioedema. Itching is urticaria's dominant symptom.

The respiratory system may also be affected, which can be accompanied by shortness of breath; it can also have an impact on the GI system via nausea and vomiting symptoms. If the cardiovascular system is affected, that can cause a drop in blood pressure and a state of shock. Urticaria can be caused by physical factors (heat, cold, and radiation etc.) and non-physical factors, such as food, inhalants, drugs, parasites, and insect bites, while contact urticaria is described as a special form of urticaria.

Figure 1-15: Erythematous plaques in the form of welts (Vesna Gajanin, 2019)

Contact urticaria

Contact urticaria is an acute skin condition that occurs after contact with plants containing compounds that can cause this phenomenon (Lahti, 1986). The urticaria mechanism is an immunological or non-immunological response to released histamine. As a result of the effects of substances released from the mast cells that participate in the allergic reaction and lymphokines, biologically active substances are produced by stimulated lymphocytes and then tissue damage occurs, which is described as an allergic inflammation. Acute urticaria (hives) is a skin disease where welts (skin lesions that correspond to those that appear on contact with nettles) appear on the skin. The welts are raised, reddish or pale in colour; they can be various sizes and shapes. The outbreak of welts is usually accompanied by severe itching. Welts disappear as fast as they appear, usually within 24 hours. Mast cells play a key role in the formation of urticaria; they are found in the subcutaneous tissue, from which histamine and other mediators of inflammation are released, as well as prostaglandins and leukotrienes, etc. Urticaria can occur daily or intermittently (with a shorter or longer period without the outbreak of welts) for a period up to 6 weeks, at which point it becomes acute urticaria. The outbreak of welts for a period longer than 6 weeks is classified as chronic urticaria. Urticaria is caused by a type I allergic reaction, which means that it is initiated by the antigen binding to the antibody. The antigen-binding antibody is usually bound to the surface of inflammatory cells, such as mast cells and basophils containing active chemical substances (histamine, serotonin, and bradykinin). Chemically active substances generally cause the expansion of the capillaries, which in turn causes erythrocytes leakage from the capillaries (redness) and plasma leakage through the capillaries. According to the reaction that takes place in the body, skin lesions occur 20 minutes to a few hours after the intake of allergens.

Welts appear at the point of contact with plant toxins (e.g. nettle), marine animal toxins (jellyfish, sea anemone), insect toxins, and drugs, etc. Welts are restricted to the point of contact. In immunologically-induced contact urticaria, there needs to be prior contact with the allergen in order to develop skin hypersensitivity, whereas in non-immunologically induced contact urticaria, even the first contact leads to the formation of urticaria. Immunological contact urticaria is rare and generally occurs if certain foods are eaten (Schaub and Bircher, 2003). It most commonly occurs when vegetables, fruits, and nuts, etc. are used in the diet. This form of urticaria can be caused by the following vegetables: carrots, celery, potatoes, chicory, tomatoes, apples, and bananas. Urticaria is generally restricted to the skin, with a risk of a systemic reaction (anaphylactic shock). The dermatological literature describes "contact urticaria syndrome" (contact urticaria syndrome) in detail; this condition not only affects the skin, but also the mucous membranes (Aalto Korte, 2017). The following manifestations of the disease are also possible: swelling of the tongue, oedema of the larynx, bronchial asthma attack, symptoms of the gastrointestinal tract (vomiting, diarrhoea), and swelling of the joints.

Urticaria can also be caused by non-immunological factors: the mechanism of idiosyncrasy or by the direct non-immunological release of inflammatory mediators from mast cells. Non-immunological urticaria is also caused by plants belonging to the *Urticaceae* family. There are hairs on their leaves, stems, and petioles that release irritant substances, such as histamine, acetylcholine, and serotonin. Symptoms appear 3–5 minutes after contact; this causes erythema and itching that can last several hours. Some plants from the *Urticaceae* (*Dendrocnide*) family, which are mainly found in Australia, can cause very severe urticaria, which can sometimes be fatal to animals.

Diagnosis. The diagnosis of urticaria is made on the basis of medical history, clinical presentation, and laboratory and allergy tests. Differential diagnosis: erythema multiforme, erythema marginatum, erythema infectiosum, urticarial vasculitis, herpes gestationis, multiple insect bites, and bullous pemphigoid.

Treatment of urticaria. First line: eliminating or avoiding substances that cause urticaria; oral antihistamines. Second line: corticosteroids (e.g. Prednisone 20 mg); H_1 and H_2 blockers (cimetidine, ranitidine, etc.). Third line: Doxepin (tricyclic antidepressant 25–75 mg); lower doses of immunosuppressants (e.g. Cyclosporine 2.5–3 mg/kg/day) (Ferri 2011)

Table 1-13: Plants that cause contact urticaria

Name of the plant	**Compound**
Capsicum sp. L.	Capsaicin
Mucuna prunens (L.) DC.	Mucanian
Urtica dioica L.	Histamine and other mediators

Table 1-14: Major contact allergens in technical wood (Hausen, 1973; Sandennann and Barghoom, 1956; Wagenfiihr, 1984; WagenIunr and Scheiber, 1985; Tišler and Lipušček, 2001).

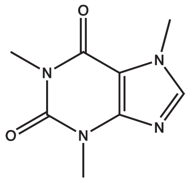
Latin name	Allergen
Acacia melanoxylon R. Br.	Malacidin, acamelin, benzoquinones
Khaya ivorensis A. Chev.	Anthothecol
Calocedrus decurrens (Torr.) Florin	Thymoquinone
Distemonanthus benthamianus Baill.	Oxyanine A and B
Mansonia altissima A. Chev.	Mansonon A
Dalbergia spp.	Dalbergion
Brya ebenus (L.) DC.	Thymoquinone
Thuja plicata Donn ex D. Don	Macassar quinone
Dyospiros spp.	Cordiachrom
Cordia goeldiana Huber	Grevillol
Chlofora excelsa	Hlorforin
Machaerium scleroxylon Tul.	Dimethoxy, dalbergion
Populus spp.	Salicylic alcohol
Pinus spp.	Rosin, turpentine
Picea spp.	Rosin, turpentine
Bowdichia nitida Benth	Dimethoxybenzoquinone
Tectona grandis L. f.	Deoxylapachol

MAIN CHARACTERISTICS OF PLANT CONSTITUENTS THAT CAUSE DERMATOSES IN HUMANS

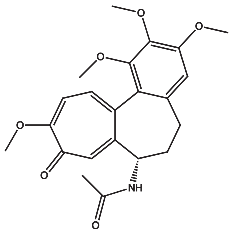
ALKALOIDS

Definition and classification of alkaloids

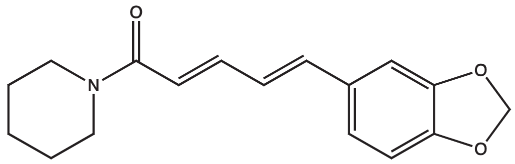
Alkaloids are natural nitrogen compounds of plant origin, as well as bases that have a strong and specific physiological and toxic effect on humans and animals. They are widely distributed in the plant world. Flowers contain the most alkaloids; ferns contain much lower amounts of alkaloids, while algae and moss do not contain any alkaloids at all. Today, there are over 5,000 alkaloids, making them the largest group of natural compounds (Kurek, 2019). The name *alkaloid* is derived from the Arabic word *al-kali* (potash, base) and the Greek word e*idos* (similar). Meissner, a pharmacist from Halle, introduced this term into science as early as 1819. He also discovered the alkaloid *veratrine*. Before that, *Sertűrner*, a German pharmacist, isolated *morphine* as the first pure alkaloid (in 1806), *Robiquet* discovered *narcotic* (in 1817), and *Pelletier* and *Caventou* discovered *strychnine* (in 1818). *Ladenburg* performed the first chemical synthesis of the *canine* alkaloid in 1886. In fact, alkaloids are the biggest group of secondary metabolites, which are very diverse in many of their properties, but their common property is that all alkaloids have one or more nitrogen atoms in the heterocyclic ring. This is evident in the case of caffeine, nicotine, colchicine, morphine. and many other alkaloids.



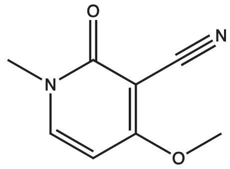
Formula 1-1: Caffeine



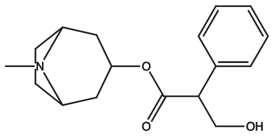
Formula 1-2: Colchicine



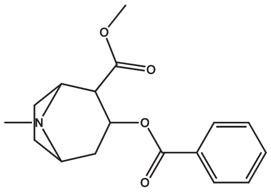
Formula 1-3: Piperine



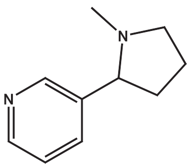
Formula 1-4: Ricinin



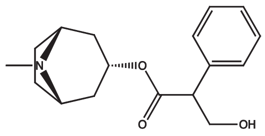
Formula 1-5: Atropine



Formula 1-6: Cocaine



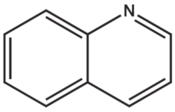
Formula 1-7: Nicotine



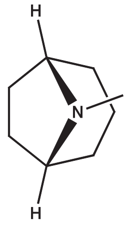
Formula 1-8: Hyoscyamine

Many alkaloids are named after the plant species from which they were first isolated. Thus, for example, nicotine, hyosciamine, atropine, piperine, ricinine, cocaine, and many others are named after the plants from which they are derived.

Alkaloids are classified into different groups, depending on the type of the heterocyclic ring contained in the molecule. The simplest are those containing a pyrrolidine (tetrahydropyrrole) or piperidine (hexahydropyridine) ring. For example, hygrine, which is isolated from the Peruvian coca plant, contains a pyrrolidine ring. Conine isolated from hemlock, which is a poisonous plant, contains a piperidine ring. This poison was already known in Ancient Greece, as Socrates was poisoned by it. One of the most famous simple alkaloids is nicotine, which consists of a five-membered and six-membered heterocyclic ring. Nicotine is one of the major alkaloids contained in tobacco leaves (1.5% of total weight). It is a very toxic compound, which in small doses stimulates breathing, and in higher doses causes paralysis and death.



Formula 1-9: Quinolin



Formula 1-10: Tropane

Most alkaloids contain a polycyclic skeleton in their molecule. Simple alkaloids include cocaine and atropine. Tropane, which consists of a six-membered piperidine and a five-membered pyrrolidine, forms the basis of an alkaloid's bicyclic skeleton. Cocaine has a strong effect on the central nervous system, and it was used as a local anaesthetic. It was later replaced by procaine, as it causes strong addiction. Atropine is a strong poison. In small amounts, it affects the dilation of the pupils; therefore, it is used in ophthalmology. The most famous alkaloid with a quinoline ring is quinine (antimalaric). The synthetically-produced antimalarial products, chloroquine and primaquine, were discovered later. The most studied alkaloids are those derived from opium. Opium is the dried residue of juice obtained from unripe poppy-heads (*Papaver somniferum*). Raw opium contains a mixture of about 20 alkaloids with a high morphine content (10%), which exerts major physiological effects. Morphine and related compounds are among the most effective analgesics. It was first isolated in 1805, its structure was determined 125 years later, and it was chemically synthesised in 1952. Morphine consists of five condensed rings: one of which is aromatic, and another contains nitrogen. Codeine is methylated morphine. In addition to its analgesic effect, codeine is very effective at suppressing the cough reflex. Heroin is the most famous derivative of morphine (diacetyl morphine). In addition, heroin is one of the most dangerous drugs; the ingestion of which leads to death in most cases.

In the last decades of the 20th century, the modern pharmaceutical industry has studied a huge number of plants and isolated thousands of alkaloids in their search for medicines to treat various diseases. Alkaloids represent a very important class as modern medicine has developed many highly effective drugs from this substance. According to some data, there are about 5,000 alkaloids isolated from higher plants in the world, and the structure of nearly 3,500 has been determined (Raffauf, 1970).

Table 1-15: Distribution of alkaloids with determined structures

Class	**Abbreviation**	**Number of alkaloids with determined structure**	**Number of structural variants**
Purine	PUR	11	3
Quinazoline	HZL	24	3
Pyrrolidine	PRL	27	7
Colchicine	KLH	30	2
Imidazoline	IMI	33	9
Indolizine	ILZ	39	9
Aliphatic	ALF	40	7
Various	RAZ	41	-
Ergoline	ERG	42	7
Peptide	PEP	45	18
Tropane	TRP	54	4
Belladine	BEL	103	4
Phenylethylamine	FEM	103	10
Terpene	TER	120	12
Pyrrolizidine	PRZ	175	6
Quinoline	HIN	185	8
Quinolizidine	HLZ	204	16
Pyridine	PIR	215	16
Steroidal	STE	337	9
Isoquinoline	IZH	669	19
Indoline	IND	902	26

Indoline (IND), isoquinoline (IZH), steroidal (STE), piperidine and pyridine (PIR), quinolizidine (HLZ), quinoline (HIN) pyrrolizidine (PRZ), terpene (TER), phenylethylamine (FEM), belladine (BEL), tropane (TRP), peptide (PEP), ergoline (ERG), various (RAZ), aliphatic (ALF), indolizine (ILZ), imidazoline (IMI), colchicine (KLH), pyrrolidine (PRL), quinazoline (HLZ), and purine (PUR).

Alkaloids are distributed in different groups of plants. They are especially present in *Magnoliophyta* plants, where almost 20% of the families contain some alkaloids (Kurek, 2019). There are almost a dozen families among the dicotyledonous plants, and only two families among the monocotyledonous plants that are rich in alkaloids.

Table 1-16: Distribution of alkaloids in some plant families

Family	**Species**	**Main alkaloid**
Liliopsida		
Liliaceae	*Colchicum autumnale*	Colchicine
Amarylidaceae	*Narcissus pseudonarcissus*	Galantamine
Magnoliopsida		
Ranunculaceae	*Aconitium napellus*	Aconitine
Fabaceae	*Cytisus laburnum*	Cytisine
Rutaceae	*Skimmia japonica*	Skimianine
Solanaceae	*Nicotiana tabacum*	Nicotine
Papaveaceae	*Papaver somniferum*	Morphine
Menispermaceae	*Archangelisia flava*	Berberine
Asteraceae	*Senecio jacobaea*	Senecionine
Loganiaceae	*Strychnos nux-vomica*	Strychnine
Rubiaceae	*Cinchona officinalis*	Quinine
Apocynaceae	*Catharantchus roseus*	Ajmalicine

Usually, phylogenetically related plants contain structurally similar alkaloids, although there are many cases where this rule does not apply. For example, peppers, tobacco, and potatoes belong to the same family of *Solanaceae*, but they contain structurally completely different alkaloids. The tobacco alkaloid nicotine (*Nicotiana*) belongs to pyridine and proline compounds, while the potato alkaloid (*Solanum*) belongs to stereoids. It was once thought that alkaloids were specific to certain plants, but today it is known that the same alkaloid can be a constituent of a completely different plant species. Thus, for example, caffeine and ephedrine are found in six different families of plants.

According to current data, plants containing alkaloids make up about 10% of the world's total flora. Depending on the degree of distribution of alkaloid plant species, their families are divided into three groups:

- Families with high alkaloid content that have over 20% of genera with alkaloid species
- Families with medium alkaloid content that have 10–20% of genera with alkaloid species
- Families with low alkaloid content that have 1–10% of genera with alkaloid species

Table 1-17: Distribution of genera in alkaloid plants families

Family	**% of alkaloid genera**	**Number of alkaloids**
Liliaceae	–	232
Amaryllidaceae	45.0	187
Apocynaceae	27.5	886
Berberidaceae	58.3	75
Boraginaceae	15.0	66
Chenopodiaceae	23.0	50
Euphorbiaceae	8.3	130
Fabaceae	17.6	347
Lamiaceae	5.5	17
Ranunculaceae	42.2	306
Solanaceae	31.8	162

They belong to different groups of chemical compounds. Most of them belong to heterocyclic compounds, and a smaller number to aliphatic compounds. These compounds are bases due to the presence of nitrogen. In addition to nitrogen, they often contain oxygen. Alkaloids produce salts of different stability with acids. Alkaloids are the product of the synthesis of amino acids. When plants absorb larger amounts of nitrogen from the soil, then the excess nitrogen is used for the synthesis of alkaloids. It is also believed that when there is not enough nitrogen in the body of plants, their alkaloids can be transformed into amino acids. It should be noted that the biosynthesis of alkaloids, the metabolism of alkaloids, and their importance for the life of plants are not yet fully understood.

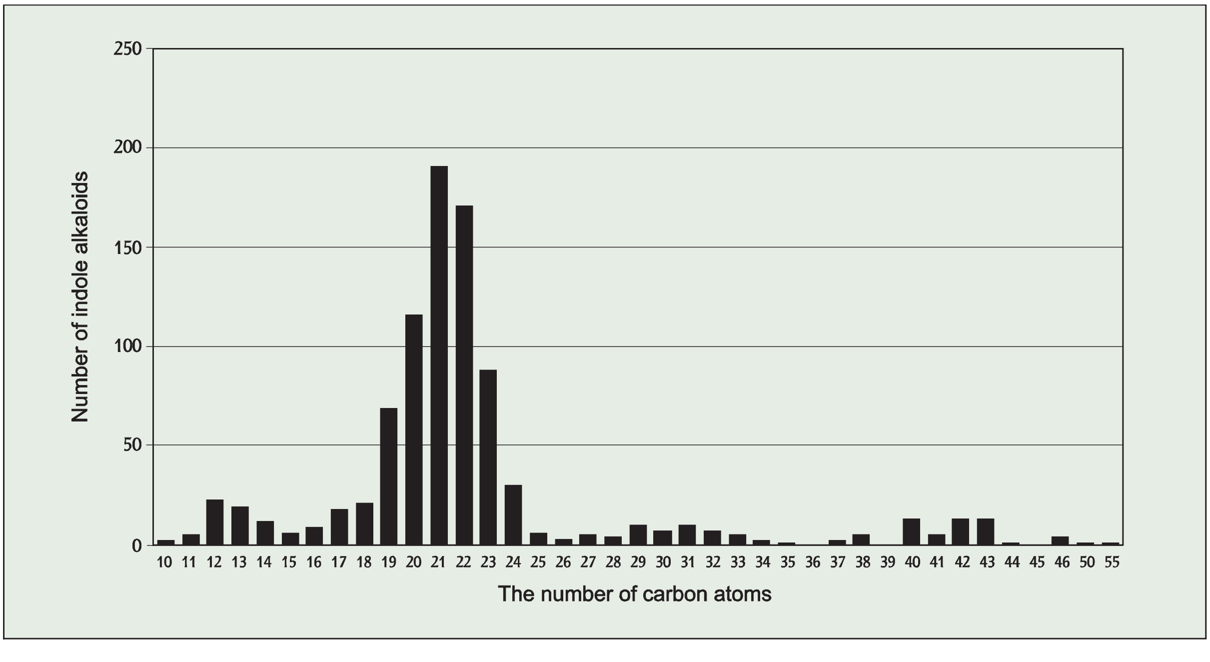


Figure 1-16: Distribution of indole alkaloids by the number of carbon atoms

Most alkaloids' molecules consist of carbon, hydrogen, oxygen, and nitrogen. Very few alkaloids do not contain oxygen in their molecules. Alkaloids that contain oxygen in their molecules are solid, crystalline substances. Oxygen-free alkaloids are liquid at room temperature and evaporate easily; therefore, they are characterised by a strong, specific, and usually unpleasant smell (e.g. *nicotine, canine*). At room temperature, other alkaloids are solid, odourless crystalline substances. They are usually colourless and have a bitter taste. Only *berberine* salts are yellow, while *sanguinarine* salts are red, and *chelidonine* salts are yellowish orange. Some alkaloids are very bitter, such as *strychnine*, whose taste is detectable even at a dilution of 1:5,000,000.

Alkaloids are rarely free in plants but found in the form of salts, esters, and amides. As common salts, they are linked to organic acids, such as acetic, oxalic, lactic, malic, tartaric, and citric, or to other organic acids that are specific to certain types of plants, such as fumaric (in *Fumaria officinalis*), meconic (in *Papaver somniferum*), and aconitic (in *Aconitum variegatum*).

Alkaloids are less commonly found in plants as esters (cocaine), amides (piperine), or bound in the form of insoluble complexes of tannins (*tannates*). *Solanum* alkaloids contain one or more sugars in a molecule, which is why they are called glycoalkaloids.

Alkaloids are insoluble in water, but are very soluble in organic solvents. Alkaloid salts usually dissolve in water, but they dissolve poorly in organic solvents except for alcohol, in which many alkaloid salts dissolve. Alkaloids are insoluble or very difficult to dissolve in water (e.g. codeine 1:150, caffeine, 1:80, ephedrine 1:36), but they dissolve well in alcohol, ether, chloroform, dichloroethane, fatty oils, and other organic solvents. Alkaloid salts are insoluble in organic solvents (other than alcohol) but they easily decompose under the influence of bases and ammonia. Other reactions characteristic for alkaloids depend on their chemical structure, position, and the types of alkaloid functional groups. This is important for their extraction from plants. They can be extracted with water or alcohol. If the plant material is treated with an alkali, the extraction is carried out with organic solvents. In this case, steam distillation is often used. In the extraction process, the crude alkaloid extract also contains other co-extracted substance; therefore, further purification is completed by washing it with a dilute acid solution, whereby the alkaloids enter the acidic aqueous phase, and then are extracted with an organic solvent. Finally, multiple crystallisation takes place. Ion exchangers are often used to separate alkaloids in industry.

The largest number of alkaloid plants belong to the following families: *Solanaceae*, *Papaveraceae*, *Ranunculaceae*, *Berberdiaceae*, *Piperaceae*, *Fumariaceae*, *Fabaceae*, *Ribiceae*, *Euphorbiaceae*, *Liliaceae*, and others. Some plants from the *Papaveraceae* and *Solanaceae* families are particularly rich in alkaloids.

Compounds related to alkaloids, such as adrenaline and histamine, are also produced in animals. In addition, compounds, such as alkaloids, can be formed by the breakdown of protein.

In their natural form, alkaloids are used as a means of enjoyment (drugs) in some countries. One type of alkaloids is among the strongest pharmacological substances (aconitine, atropine, morphine, nicotine, strychnine). There are also non-toxic alkaloids (trigonelline). In addition to naturally occurring alkaloids, semi-synthetic (ethylmorphine, diacetylmorphine, and dichlocodeinone), and non-naturally occurring synthetic alkaloids (homatropine) are used in therapy.

The huge number of alkaloids, the diversity of their structure, and the lack of knowledge about many of them make it difficult for researchers to develop and introduce a simple classification for them. However, the following classification of alkaloids is commonly applied today:

- Alkaloids without heterocyclic ring
- Pyrrolidine (abbreviated PRL) and pyrrolizidine (PRZ) alkaloids
- Piperidine and pyridine (PIR) alkaloids

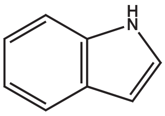
- Quinolizidine (HLZ) alkaloids
- Quinoline (HIN) alkaloids
- Isoquinoline (IZH) alkaloids
- Indole (IND) alkaloids
- Diterpene alkaloids
- Steroidal (STE) alkaloids.

From this classification, it can be seen that alkaloids are very complex and diverse compounds: a small number of which belongs to the group of carbocyclic compounds, while most of them belong to the group of heterocyclic compounds. In addition to the above classification, a chemical classification is also used, wherein alkaloids are regarded as derivatives of a nitrogen-containing chemical compound; they are divided into nine groups:

1. Tropane derivatives
2. Quinoline derivatives
3. Isoquinoline derivatives
4. Pyridine and piperedine derivatives
5. Indole derivatives
6. Imidazole derivatives
7. Purine derivatives
8. Acyclic alkaloids
9. Steroidal alkaloids

Indole alkaloids

Indole alkaloids are a class of alkaloids that have an indole ring in their structure. Many alkaloids include isoprene groups, and these are called terpene indole alkaloids. This is one of the largest classes of alkaloids, which consists of approximately 4,100 compounds (Seigler, 2001). Many of them have significant physiological effects, which means that some of them are also used in medicine (Knunyants, 1988).



Formula 1-11: Indole

The activity of some alkaloids has been known since ancient times. The ancient peoples used mushroom psilocybin and psilocin as medical treatments. For example, in India, reserpine, which is found in the plant *Rauvolfia serpentine*, was used as a common drug as early as 1,000 BC. Africans used the roots of the perennial forest plant IBOGA as a stimulating treatment because it contained ibogaine (Kenneth, 2001).

Rye and other cereals contaminated by the fungus *Claviceps purpurea* lead to the poisoning of humans and animals caused by the alkaloid, which is known as Ergot or ergotism. Such poisoning is caused by the alkaloid ergotamine, which was isolated in 1918 (Aniszewski, 2007).

The first indole alkaloid, strychnine, was isolated by Pierre Joseph Pelletier and Joseph Bienaime Caventou in 1918 from *Strichnos* genus plants. The exact structure of strychnine was determined in 1947, although Adolf von Bayer found the indole nucleus during indigo decomposition as early as 1866 (Manfred, 2002).

Figure 1-17: Pierre-Joseph Pelletier (1788–1842), the founder of alkaloid chemistry

Depending on the alkaloid biosynthesis pathways, there are two types of alkaloids:

- Isoprene alkaloids
- Non-isoprene alkaloids

Non-isoprene alkaloids also include terpenoids synthesised in living organisms from dimethylallyl pyrophosphate (DMAPP) or isopentenyl pyrophosphate (IPP). Non-isoprene alkaloids can be divided into the following:

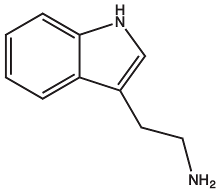
- Indole derivatives
- Beta-carboline derivatives
- Pyrroloindole alkaloids

Isoprenoid alkaloids can be divided into the following:

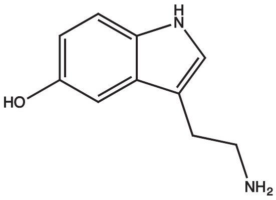
- Hemiterpenoids
- Monoterpenoids

There are far more isoprene alkaloids in nature than non-isopiroid alkaloids. One of the simplest alkaloids that is widespread in flora and fauna is tryptamine and 5-hydroxytryptamine (serotonin). Tryptamine is part of most indole alkaloids (Cseke, 2006). Also, dimethyltryptamine (DMT), psilocin, and its phosphorylated form are the simplest tryptamine derivatives.

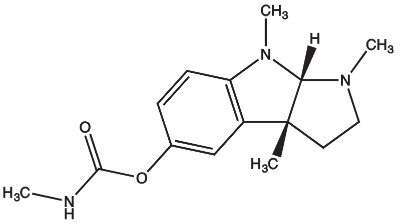
The following shows the structural formula of non-isoprenoid indole alkaloids:



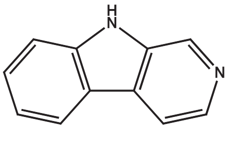
Formula 1-12: Tryptamine



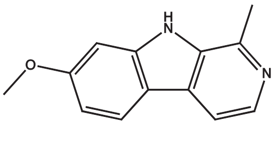
Formula 1-13: Serotinin



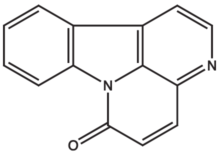
Formula 1-14: Physostigmine



Formula 1-15: β-Carboline



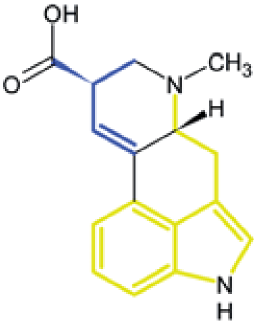
Formula 1-16: Harmine



Formula 1-17: Canthinon

Pyrrolo-indole alkaloids form a small group of tryptamine derivatives. They are produced by the methylation of the indole ring at position 2 and subsequently by a nucleophilic addition to the carbon atom at position 2 in the ethyl-amino group. A typical representative of this group is physostigmine, which was isolated by Jobst and Hesse in 1864.

Isoprenoid indole alkaloids consist of tryptophan or tryptamine residues and isoprenoid moieties derived from dimethylallyl pyrophosphate and isopentyl pyrophosphate.



Formula 1-18: Isoprenoid indole alkaloid (tryptophan fragment colored yelow and isoprenoid moiety DMAPP blue)

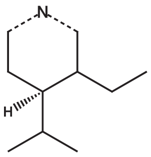
Ergot alkaloids are a class of hemiterpenoid indole alkaloids. Ergometrine and its isomer, ergometrinine, are soluble in water, while their polypeptide derivatives are insoluble in water. Polypeptide derivatives include the following groups:

- Ergotamines (ergotamine, ergosine, and their isomers)
- Ergoxines (ergostine, ergoptine, ergonine, and their isomers)
- Ergotoxines (ergocrystine, ergocryptine, p- ergocryptine, ergocornine, and their isomers).

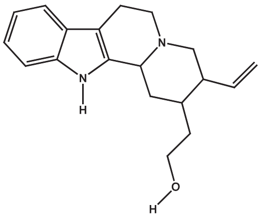
Ergotinine was discovered in 1875 and ergotoxine in 1906, while a great number of alkaloids were discovered later. The first ergot alkaloid ergotamine and its isomer were isolated in pure form by Arthur Stoll in 1918.

Monoterpenoid alkaloids

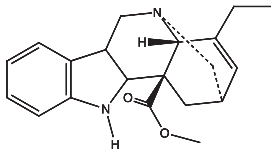
Most monoterpenoid alkaloids, including C_9 and C_{10} fragments, originate from secologanin. Depending on their structure, these alkaloids belong to the Corinthian, IBOGA, and *Aspidosperma* classes, named after the genus or species of plants that contain these alkaloids (Takayama, 2004).



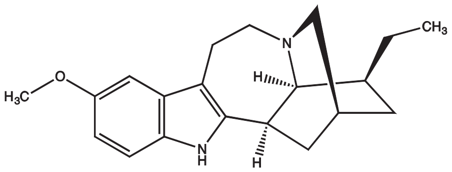
Formula 1-19: Corynanthe



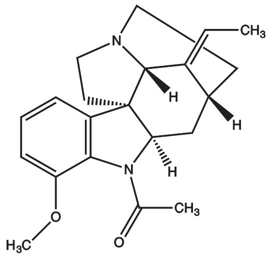
Formula 1-20: Corynantheol



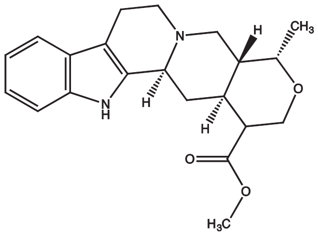
Formula 1-21: Catharanthine



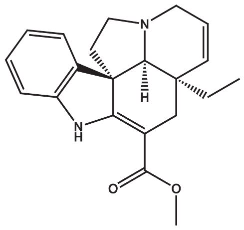
Formula 1-22: Ibogaine



Formula 1-23: Aspidospermatine



Formula 1-24: Ajmacin



Formula 1-25: Tubersonine

Table 1-18: Number of carbon atoms in some monoterpenoid alkaloids

Species	**Number of carbon atoms in some monoterpenoid alkaloids**	
	C_9	C_{10}
Corynanthe	Ajmaline, aquamycin, strychnine, brucine	Ajmalicine, yohimbine, reserpine, sarpagine, mitragynine
Tabernanthe iboga	Ibogaine, ibogamine	Voacangine
Aspidosperma	Eburnamine	Tabersonine, vindoline, vincamine

Ibogaine is an indole alkaloid of the tryptamine group; it is also a strong hallucinogen, which has been recently used to treat alcohol and drug addiction. It is found in the African plant *Tabernanthe iboga*. It was first isolated from *Tabernanthe iboga* in 1901. Dybowsky and Landrin isolated it independently from each other, as well as Haller and Heckel in the same year. Samples of the plant were obtained from Gabon, where it was used in the Bwiti tribe's rituals. George Buchi developed the first synthesis of ibogaine in 1966. Lotsof was the first to propose the use of ibogaine in the treatment of addiction, and began work on it in the USA. He soon moved to the Netherlands (due to legal regulations). In studies on rats, Broderick (1992) concluded that ibogaine reduces the effect of cocaine by suppressing dopamine or, more specifically, that ibogaine stimulates the secretion of serotonin, which inhibits dopamine-producing cells in the presence of cocaine. It is also assumed that ibogaine destroys Purkinje cells, thereby affecting the learning and memory processes.

Table 1-19: Physical and chemical properties of ibogaine

Chemical name	12-methoxybogain
Molecular formula	$C_{20}H_{26}N_2O$
Molecular weight	310.433 g/mol
CAS number	83-74-9
Melting point	152–153 ºC

https://pubchem.ncbi.nlm.nih.gov/

The mechanism of ibogaine effects is very complex, as it affects several different neurotransmitters at the same time and it is not yet known exactly which receptors it has an impact on. The usual dose used in, for example, psychotherapy is 5–11 milligrams, while a higher dose of about 20 milligrams is used in the treatment of addiction.

Proponents of the treatment of addiction with ibogaine have established clinics or self-help associations in Canada, Mexico, the Caribbean, Costa Rica, Czech Republic, France, Slovenia, the Netherlands, Brazil, South Africa, the United Kingdom, and New Zealand, where ibogaine is treated as an experimental drug.

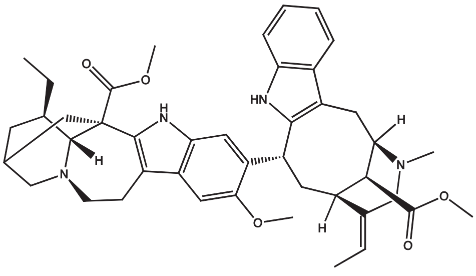
In 1957, Jurg Schneider, and Sigg (1957) found that ibogaine increased the effect of morphine. Further research was discontinued and no additional information was given by CIBA researchers on the subject of the interaction of ibogaine and opiates. Nearly 50 years later, Patrick Kroupa and Hattie Wells (2005) released the first treatment protocol to monitor the interaction of ibogaine and opiates in humans, where it was indicated that ibogaine reduced tolerance to narcotic drugs. Ibogaine is metabolised in the human body by the cytochrome P450 2D6, and the major metabolite is noribogaine (12-hydroxybogamine). Noribogaine is a strong inhibitor of serotonin deposition and it behaves similarly to methadone as an opium substitute. Ibogaine and noribogaine have a half-life of about 30 minutes (Henstra *et al*. 2017). Ibogaine is thought to be deposited in fats and metabolised as noribogaine. Noribogain stays in the organism for a little longer than ibogaine. Noribogain has a hydroxy group instead of a methoxy group at position 12.

A synthetic derivative of ibogaine, 18-methoxycoronaridine (18-MC) is a selective α3β4 antagonist developed by the neurologist Glick and the chemist Kuehne Voakangin; it is naturally closely analogous to ibogaine, and it was found in the bark of the tree *Voacanga africana*. It is a common ingredient in the semi-synthesis of ibogaine. Based on the structural similarity of ibogaine and 18-MC, as well as the binding properties, it can be concluded that other alkaloids (voacangine, ibogamine, and coronaridine) from *T. Iboga* and *V. africana* can also contribute to the treatment of addiction.

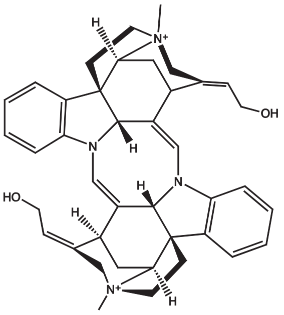
Tabernanthe iboga, or simply IBOGA, is a rainforest shrub native to Central Africa (Gabon, Cameroon, and Congo). The plant belongs to the *Asterids* class, the *Getianales* order, the *Apocynaceae* family, and the *Tabernanthe* genus. It grows to a height of 2 m and can reach up to 10 m in certain conditions. It has small green leaves. Its flowers are white and pink, while the fruits are elongated or round and spherical in shape, and orange in colour. The root of this plant contains 5–6% indole alkaloids, with the highest content of ibogaine. The root material is bitter in taste, which causes an anaesthetic sensation in the mouth and systemic skin numbness.

Diindole alkaloids

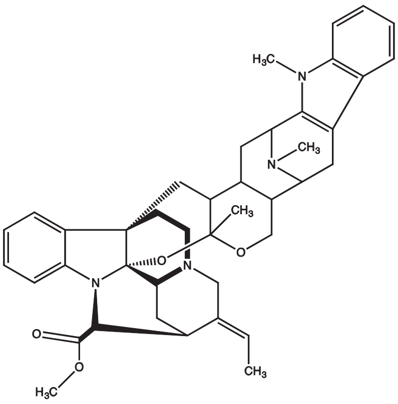
Today, more than 200 dimeric indole alkaloids have been identified. They are formed in living organisms by the dimerization of monomeric indole bases. They are divided according to the functionality of one of their monomers.



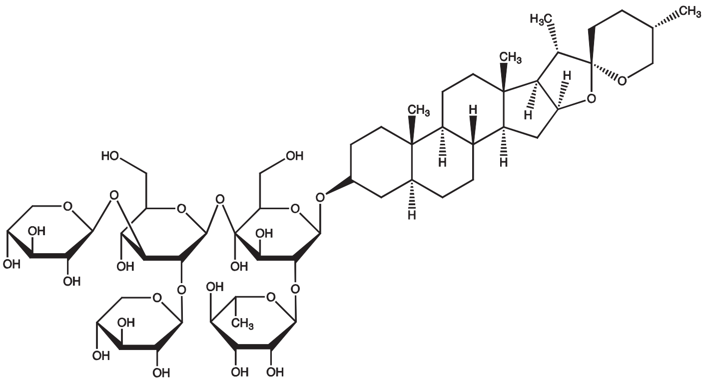
Formula 1-26: Voakamine



Formula 1-27: Toxiferine

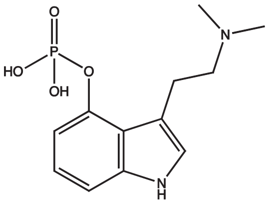


Formula 1-28: Vilalstonin

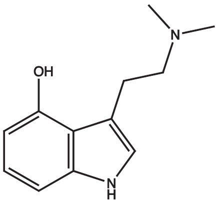


Formula 1-29: Tubulosine

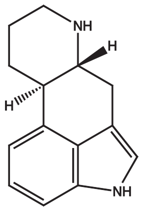
In addition to dimeric indole alkaloids, the dimerization of the indole monomer with another type of alkaloid also occurs. An example of this is tubulosine, which consists of indole and isoxinoline.



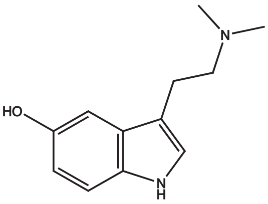
Formula 1-30: Psilocybin



Formula 1-31: Psilocin



Formula 1-32: Ergoline

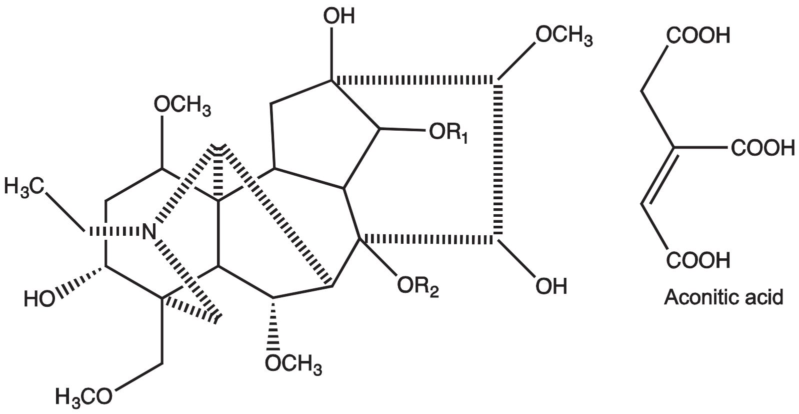


Formula 1-33: Bufotenine

Diterpene and steroidal alkaloids (Pseudoalkaloids)

These secondary metabolites belong to the pseudoalkaloids group because they are not formed by the transformation of amino acids. Instead, they are formed by isoprene biosynthesis, like all terpenoids. A nitrogen molecule is subsequently introduced into their skeleton structure. These alkaloids are formed by metabolism of mevalonic acid. For example, diterpene alkaloids of *Aconitum* occur in the following forms:

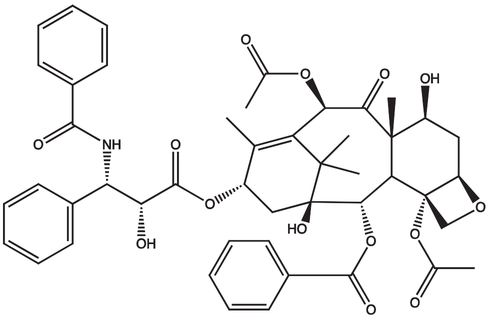
- In free form as amino alcohols
- Acetic and benzoic acid esters (aconine, aconitine, and benzylaconine)



Aconitic acid

Aconitine ($R_1=R_2=H$)
Benzoilaconitine ($R_1=COC_6H_5$, $R_2=H$)
Aconitine ($R_1=COC_6H_5$, $R_2=COCH_3$)

Scheme 1-3



Formula 1-34: Taxol

Taxane type diterpene esters contain nitrogen in the ring-taxanes (taxane A, taxane B, and taxol). The best known and pharmacologically most active compound is taxol (paclitaxel), which was isolated in 1971. This is a diterpene ester with anticarcinogenic properties, and its generic name is Paclitaxel. This alkaloid was isolated from the bark of the Pacific yew (*Taxus brevifolia, fam. Taxaceae*), which is widespread in the forests of Canada and North America. Yew tree bark contains between 0.01 to 0.02% taxol. It is estimated that the annual need for taxol is between 100 to 200 kg. 9,000 kg of tree bark is needed to produce 1 kg of taxol: i.e. more than 2.000 to 3.000 yew trees (Liu *et al.* 2016). Today, there are over 100 different types of these compounds, which are found in different species of plants from the *Taxus* genus. Taxol is also obtained from the European *Taxus baccata*, as baccatin II and 10-deacetylbaccatin III (more than 0.1%), which is converted into taxol through a simple chemical transformation. It is also produced from the fungus, *Taxomyces adreanae*, which is isolated from the bark of *Taxus brevifolia.* Taxol binds to the microtubules of tumour cells, leading to their reorganization, thereby inhibiting cell division. It is poorly soluble in water; therefore, it is dissolved in castor oil and alcohol, and administered as an infusion. Steroidal alkaloids occur in the following forms:

- Free amino alcohols (alcamines)
- Alcohol and sugar heterosides
- Amino alcohol esters

Free amino alcohols have the following derivatives:

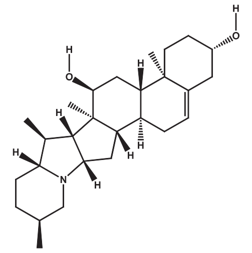
- Cyclopentanoperhydrophenanthrene (rubijervine and isorubijervine)
- Perhydrobenzfluorene (veratramine, jervine, and isojervine)
- Cevane (germine and protoverine).

Amino alcohol and sugar heterosides include the following:

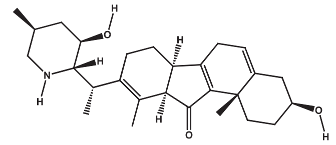
- Veratroside (veratramine and glucose)
- Pseudojervine (jervine and glucose)
- isorubijervosine (isorubijervine and glucose)

Amino alcohol esters include the following:

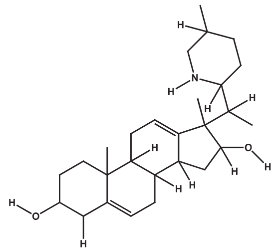
- Germine (germine and organic acids)
- Protoveratrine A (protoverine and acetic acid and methylbutyric acid)
- Protoveratrine B (protoverine and acetic and dihydroxymethylbutyric acid)



Formula 1-35: Rubijervine

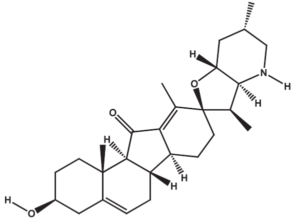


Formula 1-36: Isojervine

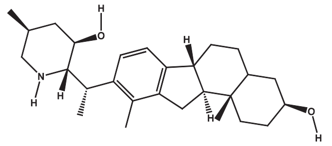


Formula 1-37: Veralakamine

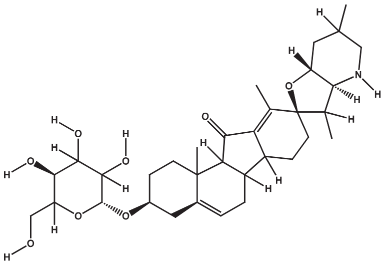
Free alkylamines



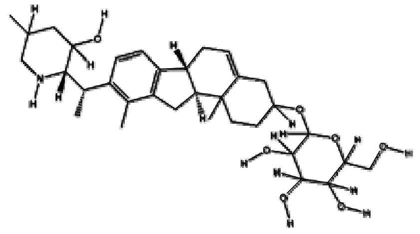
Formula 1-38: Jervine



Formula 1-39: Veratramine

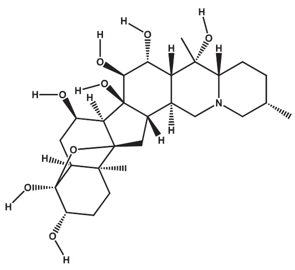


Formula 1-40: Pseudojervine

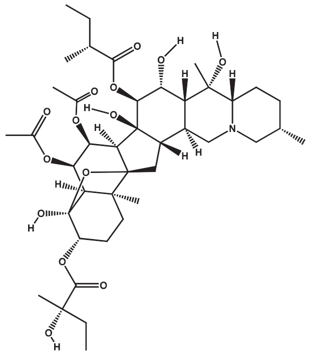


Formula 1-41: Veratrozin

Alkylamines associated with sugars

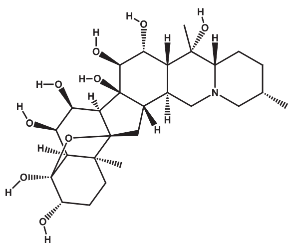


Formula 1-42: Germin

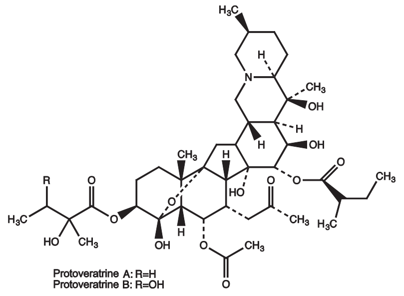


Formula 1-43: Protoveratrine A

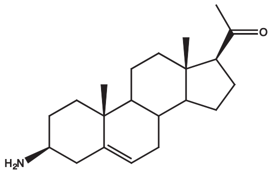
Alkylamines make esters with butiric acid derivatives



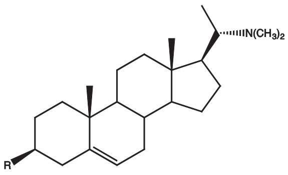
Formula 1-44: Protoverin



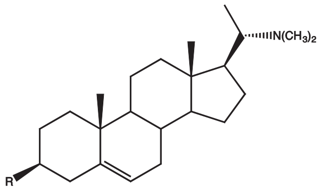
Formula 1-45: Protoveratrine A and B



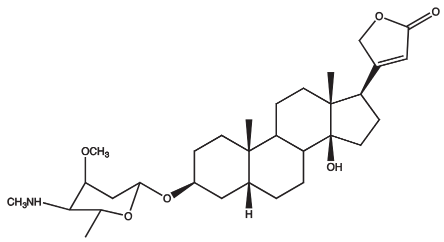
Formula 1-46: Holamine



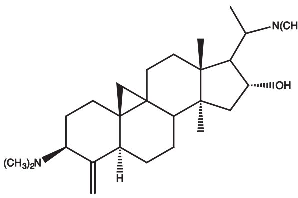
Formula 1-47: Irehine R=OH, Kurchessine R=NCH$_{32}$



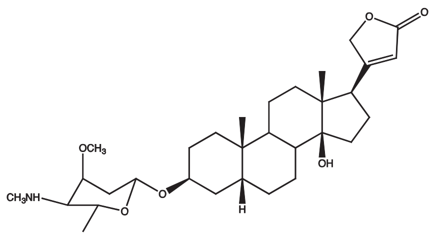
Formula 1-48: Buxamine



Formula 1-49: Mitiphylline



Formula 1-50: Cyclobuxine



Formula 1-51: Konessin

Steroidal alkaloids

C_{21} alkaloids are pregnane derivatives found in plants of the *Apocynaceae* (*Holarrhena*, *Funtmia*, *Kibatalia*, and *Malouetilia*) and *Buxaceae* families. C_{24} alkaloids are cycloartenol derivatives found in plants from the *Buxaceae* family. C_{24} alkaloids are also present in plants from the *Liliaceae* and *Solanaceae* families. In the *Liliaceae* family, there are various types of alkaloids:

- Solanidine type (cyclopentanoperhydrophenanthrene skeleton).
- Perhydrobenzfluorenes, C-nor-D-homo-type steroids (the C-ring loses one atom, the D-ring is expanded, and there is condensation in the indolizidine ring).
- Cevane type (formed by introducing piperidine nitrogen to position C_{18} to create a hexacyclic skeleton).

Solanine alkaloids are present in species from the *Solanum* genus. They are produced by the metabolism of cholesterol, and the nitrogen that is part of their composition most likely originates from arginine (Morillo *et al.* 2020). Steroid solanum alkaloids have two types of skeletons. There are two types of alkaloids within the *Solanaceae* family:

- Spirosolane (solasonine and tomatine, nitrogen is part of the oxoazopyrodecane structure).
- Solanidine (solanine contains indolizidine residue).

If certain classes of alkaloids whose structures are well-known and proven are compared, then it becomes apparent that the most numerous is the class of indoles with 902 different alkaloids, followed by the class of isoquinolines with 669 alkaloids, then the class of steroidal alkaloids with 337 alkaloids, and finally the class of purine alkaloids with 11 different alkaloids.

Table 1-20: Types of alkaloids in plants from the *Solanaceae* family

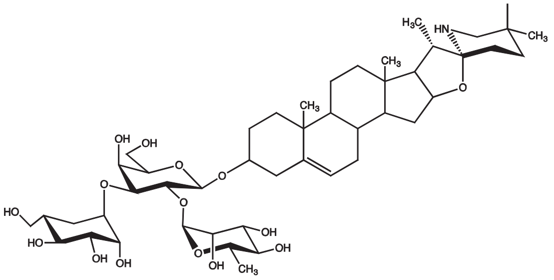
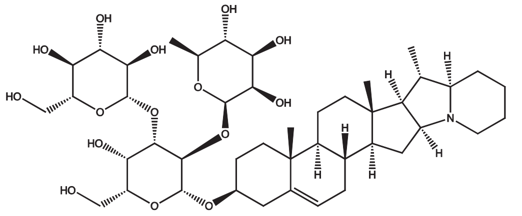
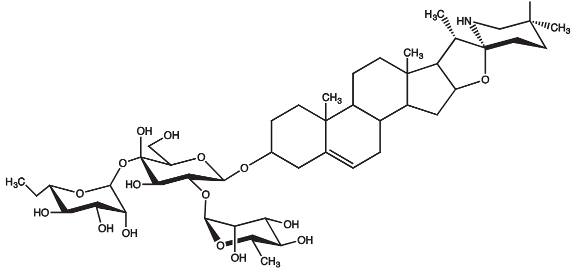
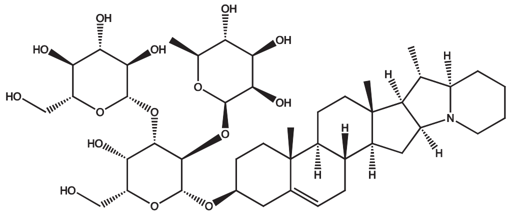
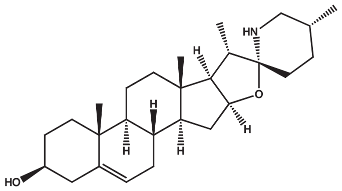
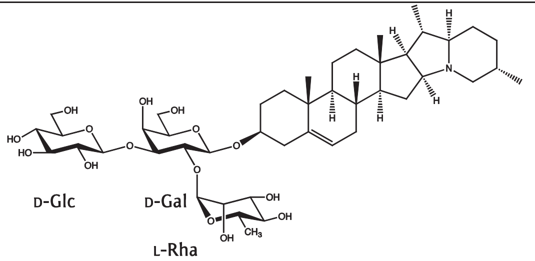
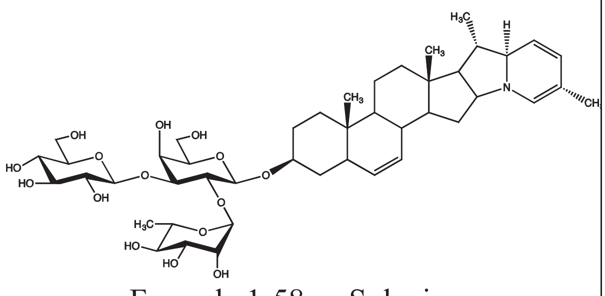
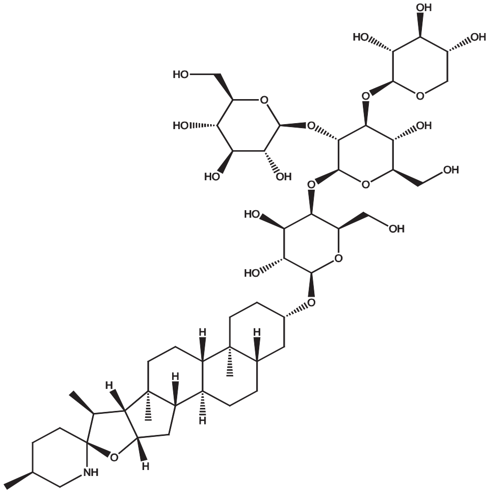
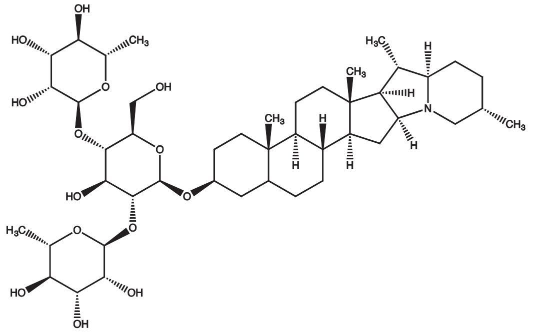
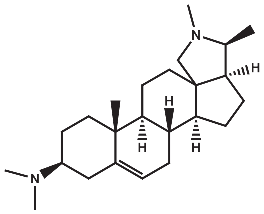
Spirosolane alkaloids	**Solanidine alkaloids**
 Formula 1-52: Solasonine	 Formula 1-53: α- Solanine
 Formula 1-54: Solamargine	 Formula 1-55: Solanine
 Formula 1-56: Solasodine	 Formula 1-57: Solanine

Table 1-21: Structures of some steroidal alkaloids

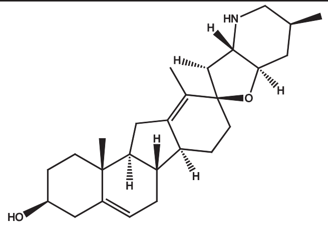
 Formula 1-58: α-Solanine	 Formula 1-59: α-Tomatine



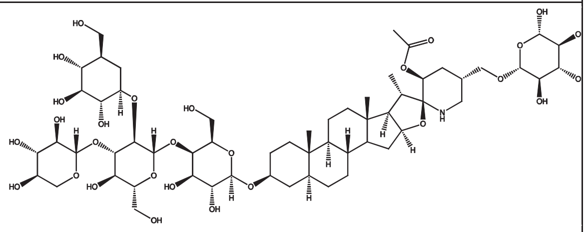
Formula 1-60: Chaconine



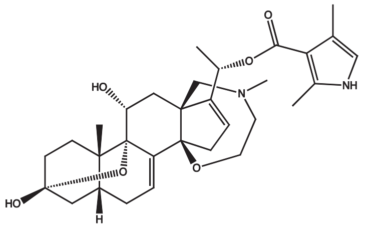
Formula 1-61: Konessin



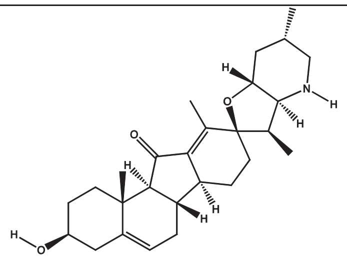
Formula 1-62: Ciclopramine



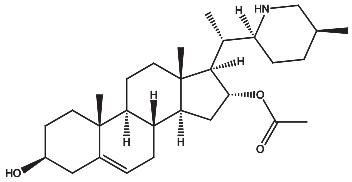
Formula 1-63: Esculeoside A



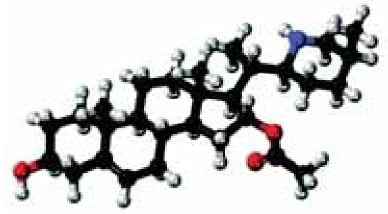
Formula 1-64: Batrachotoxine



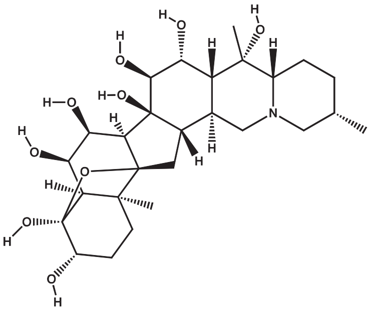
Formula 1-65: Jervine



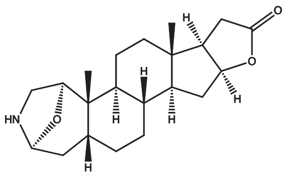
Formula 1-66: Muldamine



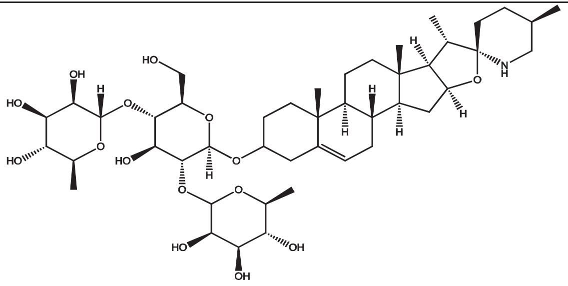
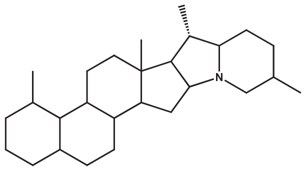
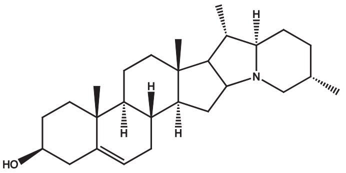
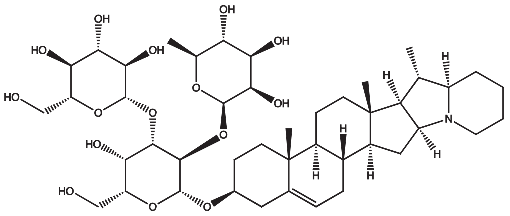
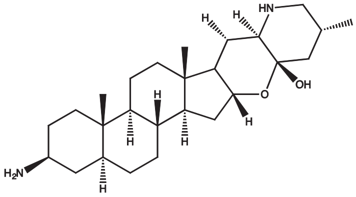
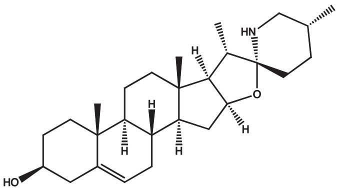
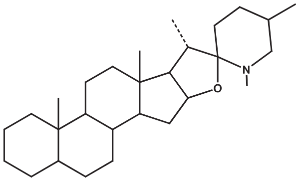
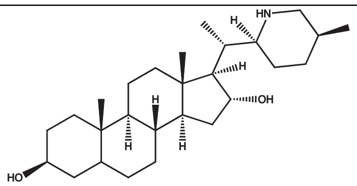
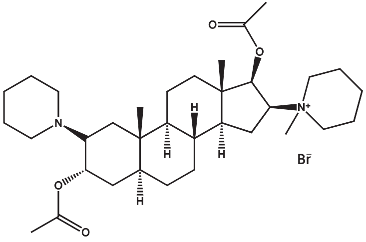
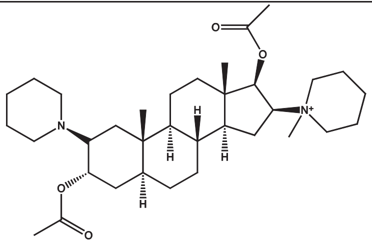
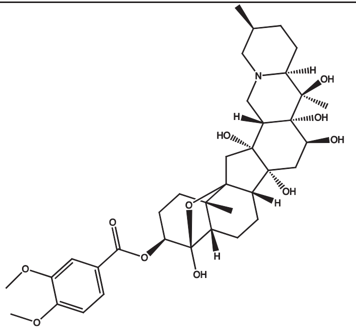
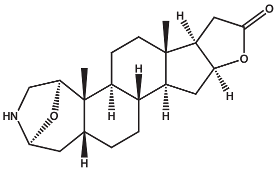
Formula 1-67: Muldamine from *Veratrum californicum*



Formula 1-68: Protoveratrine



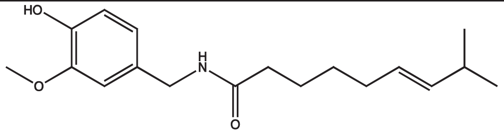
Formula 1-69: Samandaridine

 Formula 1-70: Solamargine	 Formula 1-71: Solanidane
 Formula 1-7: Solanidine	 Formula 1-73: Solanine
 Formula 1-74: Solanocapsin	 Formula 1-75: Salasodin
 Formula 1-76: Spirosalin	 Formula 1-77: Teinemine
 Formula 1-78: Vecuronium bromide	 Formula 1-79: Vecuronium
 Formula 1-80: Veratridine	 Formula 1-81: Samandarine

Capsaicin

Capsaicin is the primary constituent of pepper. It has a distinctive spicy taste and it causes irritation in the mouth that is similar to a burning sensation. It is found in the form of a secondary metabolite in plants from the *Capsicum* genus. Capsaicin is soluble in alcohol and fats.

Table 1-22: Physical and chemical properties of capsaicin

CAS number	404-86-4	
Molecular formula	$C_{18}H_{27}HO_3$	
Molecular weight	305.41 g/mol	
Melting point	62-65 ^{0}C	Formula 1-82: Capsaicin

https://pubchem.ncbi.nlm.nih.gov/

Pure capsaicin is a lipophilic substance, which is colourless and odourless. Different species and varieties of peppers contain different amounts of capsaicin. Small habanero peppers growing on the Yucatan peninsula in Mexico contain several hundred times the amount of capsaicin than standard ones.

Habanero peppers (*Capsicum chinense*) are one of the hottest peppers in the world. Unripe habanero peppers are green, but their colour changes when they become ripe. They are mostly are orange and red, but there are also white, brown, and pink habanero peppers. A ripe habanero pepper is 2–6 cm long. According to the Scoville scale, habanero peppers range from 200,000 to 300,000 Scoville units, while the common red pepper ranges from 30,000 to 50,000 (Canto-Flick *et al*. 2008). SHU pepper spray has about 5.3 million Scoville units. This pepper probably comes from Cuba. It is mostly grown in Mexico, Yucatan, where about 1,500 tons are grown annually. Other places where large quantities of habanero peppers are grown include Belize, Costa Rica, and some USA states (Texas, Idaho, and California).

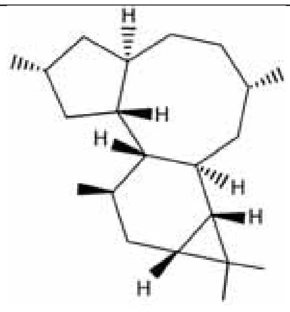
Figure 1-18: "Habanero" pepper (https://pixabay.com/photos/habanero-chilli-peppers-habanero-2804/)

Capsaicin was first isolated from hot peppers in 1816, and 30 years later was obtained in crystalline form by Tresh, who named it. In 1878, the Hungarian researcher, Endre Hogies, isolated capsaicin and proved that it was responsible for the burning sensation when it comes into contact with a mucous membrane and that it increased the secretion of gastric juices. Synthetic capsaicin was obtained in 1930 by Spath and Draga. This substance was later isolated from other plants, and it is collectively referred to as capsaicinoids. The molecular mechanisms of the effects of capsaicin and other similar substances arise as a result of binding to vanilloid receptors. These are specific receptors for the perception of painful stimuli. These receptors are very sensitive; they are able to identify capsaicin and similar substances at very low concentrations.

DITERPENE ESTERS

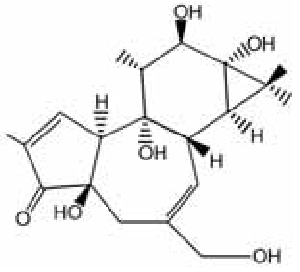
A very good revision paper on this group of compounds was written by Evans (Evans, 1986). There are several types and three main classes of compounds in this group: ingenol, phorbol (tigliane), and daphnan (Evans, 1986). The first phorbol was isolated from *Croton tiglium* (Hecker *et al*. 1967; Van Duuren and Orris, 1965).

Table 1-23: Physical and chemical properties of tigliane

Molecular formula	$C_{20}H_{34}$	 Formula 1-83: Capsaicin
CAS number	67707-87-3	
Molecular weight	274.492 g/mol	

https://pubchem.ncbi.nlm.nih.gov/

Table 1-24: Physical and chemical properties of phorbol

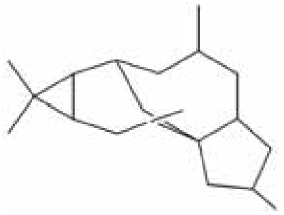
Molecular formula	$C_{20}H_{28}O_6$	 Formula 1-84: Phorbol
CAS number	17673-25-5	
Molecular weight	364.44 g/mol	
Melting point	250-251 ^{0}C	

https://pubchem.ncbi.nlm.nih.gov/

Over 14 different phorbol diesters have been isolated from *Croton tiglium* alone, and one of the major ones is 12-O-tetradecanoylphorbol-13- acetate. Hecker and his associates (Hecker *et al.* 1965) divided esters into two groups. Group A has a long O-acylate chain at position 12 and a short acyl chain at position 13, while the opposite applies to group B (Hacker and Schmidt, 1974). Several species of the *Euphorbia* genus are known for having these irritant and cocarcinogenic components. The most common names for tigliane group derivatives are 12- deoxyphorbols. Also, 16-hydroxyphorbols have been isolated (Kinghorn, 1979).

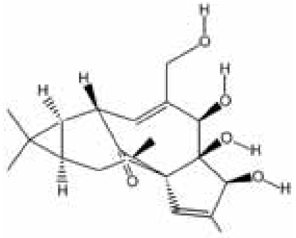
Ingenol esters are another category whose base is hydrocarbon ingenane. Ingenol is a tetracyclic diterpenoid that is very similar to phorbol when considering its third dimension. They also have irritant and carcinogenic potential.

Table 1-25: Physical and chemical properties of ingenane

Molecular formula	$C_{20}H_{34}$	 Formula 1-85: Ingenane
Molecular weight	274.492 g/mol	

https://pubchem.ncbi.nlm.nih.gov/

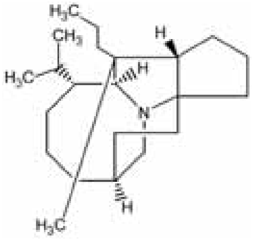
Table 1-26: Physical and chemical properties of ingenol

CAS number	30220-46-3	 Formula 1-86: Ingenol
Molecular formula	$C_{20}H_{28}O5$	
Molecular weight	348.439 g/mol	

https://pubchem.ncbi.nlm.nih.gov/

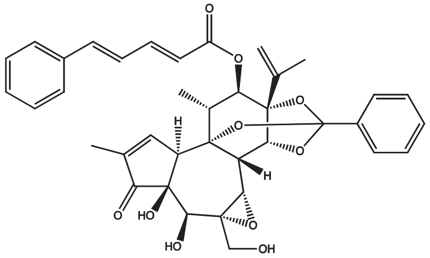
The third major group are daphnan esters, which are tricyclic diterpene daphnans. The first one to be isolated was huratoxin; montanin, resiniferatoxin, and tiniatoxin are also members of this group (Kinghorn, 1979).

Table 1-27: Physical and chemical properties of daphnane

Molecular formula	$C_{22}H_{37}N$	 Formula 1-87: Daphnane
Molecular weight	315.545 g/mol	

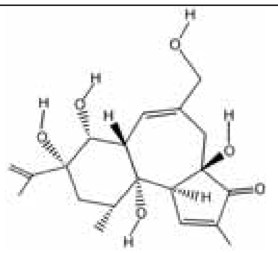
https://pubchem.ncbi.nlm.nih.gov/

Table 1-28: Physical and chemical properties of mezerein

CAS number	34807-41-5	 Formula 1-88: Mezerin
Molecular formula	$C_{38}H_{38}O_{10}$	
Molecular weight	654.712 g/mol	

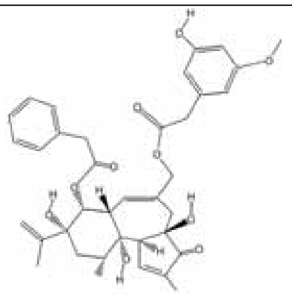
https://pubchem.ncbi.nlm.nih.gov/

Table 1-29: Physical and chemical properties of resinferonal

Molecular formula	$C_{20}H_{28}O_6$	 Formula 1-89: Resinferonal
CAS number	57444-60-7	
Molecular weigth	654.712 g/mol	

https://pubchem.ncbi.nlm.nih.gov/

Table 1-30: Physical and chemical properties of proresiniferatoxin

CAS number	57444-61-8	 Formula 1-90: Proresinferatoxin
Molecular formula	$C_{37}H_{42}O_{10}$	
Molecular weight	654.712 g/mol	

https://pubchem.ncbi.nlm.nih.gov/

Proresiniferatoxin is a representative of this group. Pure phorbol is an anhydrous crystal that melts at 250–251^{0}C. Depending on the degree of hydration of the crystal, the boiling point is 162–163 or 233–234^{0}C. Phorbol is well soluble in polar solvents, including water (Windholz, 1983). Different plants of the *Euphorbiaceae* family are used for medical purposes in almost all of the world. The plant, *Eupforbia balsamifera*, is used as a purgative and to treat gonorrhoea, as well as an antiseptic and haemostatic (Evans and Kinghorn, 1977). *Euphorbia poisonii* is used in Africa as an insecticide plant (Kinghorn, 1979). Many other plants from this family are also used for medicinal purposes (Evans i Kinghorn, 1975; Freeman, 1971).

The dermal effects of these plants vary from medium to severe. However, reactions do not occur immediately. Local exposure to juices occurs after several hours in the form of erythematosis, endomitosis, and blisters. The blisters range from small pimples to large bullae; they can last from 1 to 3 days, and the secondary effects from 4 to 7 days.

These compounds have piscidal, puragative, cocarcinogenic, and irritant effects (Kinghorn, 1979). The primary manifestations of exposure to these plants are skin and eye irritation. The relationship between structure and irritation was studied, and irritation was found to be greater in the following circumstances:

- When the ester is at C-13 position
- In tetracyclic structures
- When the C ring is in the cis-transfiguration
- When the AB ring is in the trans-configuration
- When A has four beta functions

Irritation increases when:

- The R_1 is unsaturated
- The chain length is increased at R_1 position
- When the 12-deoxyphorbol-13-monoester (R_1 is acyl and R_2 is H) is present

The effect on the skin and eyes depends on the plant and the amount of contact. One or two drops of milky sap can cause reactions. Diterpene esters have been found in *Euphorbiaceae* plants, which have about 7,000 species (Webster, 1967).

Table 1-31: Overview of plants containing different diterpene esters

Phorbol diesters and triesters	**Phorbol of the tigliane type**	**Ingenol ester**
Croton tiglium L. *Sapium japonicum* (Siebold & Zucc.) Müll. Arg. *Euphorbia tirucalli* L. *Euphorbia frankiana* A. Berger *Euphorbia coerulescens* Haw. *Croton sparsiflorus* Morong	*Euphorbia resinifera* A. Berger *Aleurites fordii* Hemsl. *Euphorbia triangularis* Desf. ex A. Berger *Euphorbia polyacantha* Boiss. *Euphorbia coerulescens* Hort. *Euphorbia poisonii* Pax *Euphorbia cooperi* N.E. Br. ex A. Berger *Euphorbia helioscopia* L. *Baliospermum montanum* (Wild.) Müll. Arg. *Hippomane manicinella* L.	*Euphorbia lathyris* L. *Euphorbia ingens* E. Mey ex Boiss *Euphorbia kansui* S. L. Liou ex S.B. Ho *Euphorbia myrsinites* L. *Euphorbia biglandulosa* Wild. *Euphorbia segueiriana* Neck. *Euphorbia grandiflora* Boiss *Elaeophorbia drupifera* (Thonn.) Stapf.
Daphnan ester	Resiniferol esters	
Hura crepitans L. *Hippomane mancinella* L. *Excoecaria agallocha* L. *Baliospermum montanum* (Wild.) Muell-Arg *Euphorbia unisipina* N.E. Br. *Euphorbia resinífera* A. Berger	*Euphorbia resinífera* A. Berger *Euphorbia poisonii* Pax *Euphorbia unisipina* N.E. Br.	

Plant alkaloids from the *Amaryllidaceae* family

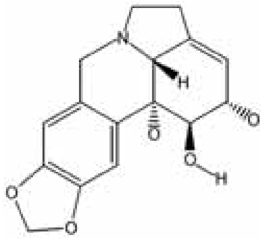
The alkaloids belong to phenanthridine derivatives (Frohne and Pfander 1983; Morton, 1971). About 15 alkaloids have been isolated plants from the *Narcissus* genus (Rumack and Spoerke, 1989; Bastida *et al*. 2007):

Table 1-32: Examples of alkaloids isolated from *Narcissus*

Name	**Name**
Crinamine	Powelline
Crinidine	Precriwelline
Dexoytazettine	Pretazettine
Galanthamine	Pseudolycorine
Haemanthamine	Tazettadiol
Hippacine	Tazettine
Homolycorine	Ungerenine
Lycoramine	Vittatine
Licorine (Narcissine)	6-hyddroxycrinamide
Narciclasine	

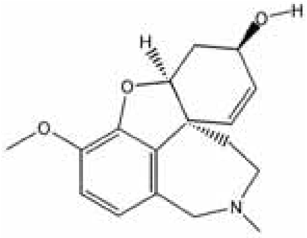
Many plants containing these alkaloids belong to the onion group as well as *Narcissus* and *Amaryllis.* High concentrations of alkaloids are found in bulbs, but have also been found in flowers and stems (Frohne and Pfander, 1983; Vigneau *et al*. 1982). Some plants that contain these alkaloids cause skin irritation, but they also contain substances, such as chelidonic acid and oxalates; therefore, it is not clear what is actually triggering the irritation (Altschul, 1983; Gude *et al*. 1988).

Table 1-33: Physical and chemical properties of lycorine

CAS number	476-28-8	 Formula 1-91: Licorine
Molecular formula	$C_{16}H_{17}O_4$	
Molecular weight	287.315 g/mol	

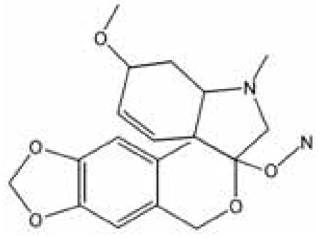
https://pubchem.ncbi.nlm.nih.gov/

Table 1-34: Physical and chemical properties of galanthamine

CAS number	357-70-8	 Formula 1-92: Galanthamine
Molecular formula	$C_{17}H_{21}O_3$	
Molecular weight	287.315 g/mol	

https://pubchem.ncbi.nlm.nih.gov/

Table 1-35: Physical and chemical properties of tazettine

CAS number	507-79-9	 Formula 1-93: Tazettine
Molecular formula	$C_{18}H_{21}NO_5$	
Molecular weight	331.368 g/mol	

https://pubchem.ncbi.nlm.nih.gov/

Localization of alkaloids in plants

Knowledge of the localization of alkaloids in certain plant parts and organs is of enormous practical importance, since it depends which part or organ will be used for the isolation of alkaloids. Rarely are certain alkaloids evenly distributed in a plant; instead, they are usually localised in one or more parts and organs. There is very extensive literature on the localization of alkaloids in certain plant parts and organs. However, little is known about the biosynthesis and pathways of alkaloid transfer in plants.

Today, the prevalent hypothesis is that alkaloids are formed in the leaves and underground organs, and then transported to other organs and parts, such as seeds, fruits, and stems. However, alkaloids can also form in plant seeds. Some authors (e.g. Shmuck) believe that the root system plays a significant role in the formation of alkaloids. According to this author, substances are formed in the roots and without which the process the synthesis of nicotine and atropine, as well as possibly other alkaloids, cannot occur in the leaves.

Alkaloid plants usually contain more alkaloids in their body. In some plants up to 20 alkaloids can be found, but in these cases usually 1–3 alkaloids are present in larger quantities and represent the major mass, while others are present in insignificant quantities. Also, alkaloids with same structures but belonging to different cycles through their chemical structure can be found in the same plant. This may be the case when certain parts and organs are concerned. It is understood that some alkaloids are found in plants in different amounts. In some plants or their organs, the content of some alkaloids can be extremely low (e.g. 0.05%), but there are plants or their organs that can contain up to 15% of some alkaloids.

Alkaloids are most often found as salts of organic or mineral acids in soluble form, as well as in the cell juice of the underlying parenchyma, phloem, and other tissues. Sulphuric and phosphoric acid are most often present in the mineral acids that form salts with alkaloids in alkaloid plants.

Dynamics of alkaloid formation in the process of ontogenetic development

The formation of alkaloids is not evenly distributed during the process of a plant's ontogenetic development. Their amount and composition are subject to changes during ontogenetic development. It is important to note that there are specificities for some plant species and that the dynamics of alkaloid formation, depending on its ontogenetic development, does not have the same flow and intensity in different plants. Knowledge of regularities in the dynamics of alkaloid formation is of great practical importance. If it is known at what stage the alkaloid content is the highest, then it is easy to determine the time to collect the raw material in order to obtain the maximum yield of alkaloids, as well as its toxicological effects if they are not used for pharmacological purposes. The amount and content of alkaloids in plants depends mainly on the following:

- Ontogenetic development stage
- Geographical location
- Environmental factors (humidity, temperature, degree of illumination, and altitude, etc.)

The amount and content of alkaloids change in the course of a plant's ontogenetic development. The alkaloid content increases in tropical and hot areas with a humid climate. This means that, for each plant species, there are certain environmental conditions when it will not reach its highest alkaloid content.

The dynamics of alkaloid formation varies within a wide range; it depends on the phase of plant development, and it is uneven for different organs. In perennial plants, the dynamics of alkaloid formation also depend on the age of a plant. Today, there is a great deal of data on the quantitative changes in the alkaloid content during the process of ontogenetic development (Mu *et al*. 2010). Thus, for example, in the aboveground organs of *Salsola richteri*, the alkaloid content increases from the moment of leaf formation (0.22–0.28%) to fruiting (0.91–1.31). Commonly, the alkaloid content in the leaves will be highest in the flowering stage and then it will decrease. Special and much more complex patterns in the formation of alkaloids depend on ontogenetic development when they accumulate in underground organs. For example, the alkaloid content in *Senecio rhombifolius*'s root is the lowest when it is in the flowering stage (total alkaloid content is 1.36–1.74%; saracin 1.28–1.54%). After this phase, the alkaloid content in the root increases (2.08–3.06%; saracin 1.86–2.74%).

It is necessary to point out that, in some plants, the alkaloid content changes during the same stage of development. Thus, for example, in some plants, the alkaloid content is lower at the beginning of flowering than in the full flowering stage. There are some results that indicate that the movement and content of alkaloids change during day and night. Some plants are known to have up to 40% more alkaloids at night than during the day. Unripe poppy gives a higher yield of opium in the evening than during the day, etc.

In addition to the quantitative composition of alkaloids during ontogenetic development, a plant's qualitative composition will often change. For example, in the process of poppy (*Papaver orientale*) development in spring and summer, the *thebaine* alkaloid transforms into *isothebaine*, which is a substance with a different structure. There are many other examples that indicate that different transformations occur during the ontogenetic development of certain alkaloid plants, which leads to structural changes in individual alkaloids and the transformation of one alkaloid into another. It is necessary to be aware of these changes, especially if certain alkaloid plants are used for the isolation of pharmacological components.

Distribution of alkaloids in plants

According to current estimates, alkaloid plants account for about 10% of the total flora in the world. All of their families are divided into three classes according to the alkaloid plant species' degree of distribution. The first class includes families with over 20% of genera that have alkaloid plant species. Such families are called highly alkaloid. The second class includes families with 10–20% genera with alkaloid plant species. Such families are called middle alkaloid. The third class includes families with 1–10% genera with alkaloid plant species. Such families are called slightly alkaloid.

Highly alkaloid families are localised in the following orders: *Equisetales*, *Lycopodiales*, *Gnetales*, *Liliiflorae*, *Centrospermae*, *Ranales*, *Rhoedales*, *Geraniales*, *Parietales*, *Opuntiales*, *Myrtiflorae*, *Ebenales*, and *Tubiflorae*. The *Ranals* order is particularly rich in alkaloids, as 10 out of its 19 families are highly alkaloid. Middle alkaloid families are present in the following orders: *Piperales*, *Rosales*, *Contortae*, and *Rubiales* (Li and Willaman, 1968*)*. There are many orders whose families do not have alkaloid genera, or which only have slightly alkaloid families (e.g. *Sapondanales*, *Malvales*, and *Coniferales*, etc.).

Table 1-36: Distribution of alkaloids by plant taxons

Taxon	Number	Dicots	Monocots	Total flowering plants
Order	Total	75	19	94
	Alkaloid	57	13	70
	% Alkaloid	76.0	68.4	74.4
Family	Total	363	70	433
	Alkaloid	155	21	176
	% Alkaloid	42.7	30.0	40.6
Genus	Total	9.650	2.748	12.398
	Alkaloid	864	123	987
	% Alkaloid	9.0	4.5	7.9
Species	Total	176.700	66.100	242.800
	Alkaloid	3.429	407	3.836
	% Alkaloid	1.9	0.6	1.6

Table 1-37: Maximum alkaloid content of plant orders

Order	Family			Genus		
	Total in the order	Number of alkaloids	%	Total in the order	Number of alkaloids	%
Papaverales	3	2	67	47	29	62
Nepetales	2	2	100	4	2	50
Ranunculales	10	3	33	142	55	39
Laurales	11	4	36	100	33	33
Cornales	7	4	57	23	6	29
Rutales	11	6	54	367	60	17
Dipsacales	4	3	75	43	7	16
Magnoniales	8	6	75	165	23	14
Polemoniales	3	3	100	69	9	13
Fabales	3	1	33	698	86	12
Gentianales	13	6	46	1.155	125	11
Rhamnales	3	2	67	72	7	10

The following families have the most alkaloid genera and species: *Equisetaceae*, *Lycopodiaceae*, *Ephedraceae*, *Liliaceae*, *Amaryllidaceae*, *Dioscoreaceae*, *Chenopodiaceae*, *Nymphaeceae*, *Ranunculaceae*, *Berberidaceae*, *Menispermaceae*, *Papaveraceae*, *Fabaceae*, *Rutaceae*, *Cactaceae*, *Punicaceae*, *Loganiaceae*, *Apocynaceae*, *Borraginaceae*, *Solanaceae*, and *Rubiaceae* (Муравјева, 1978).

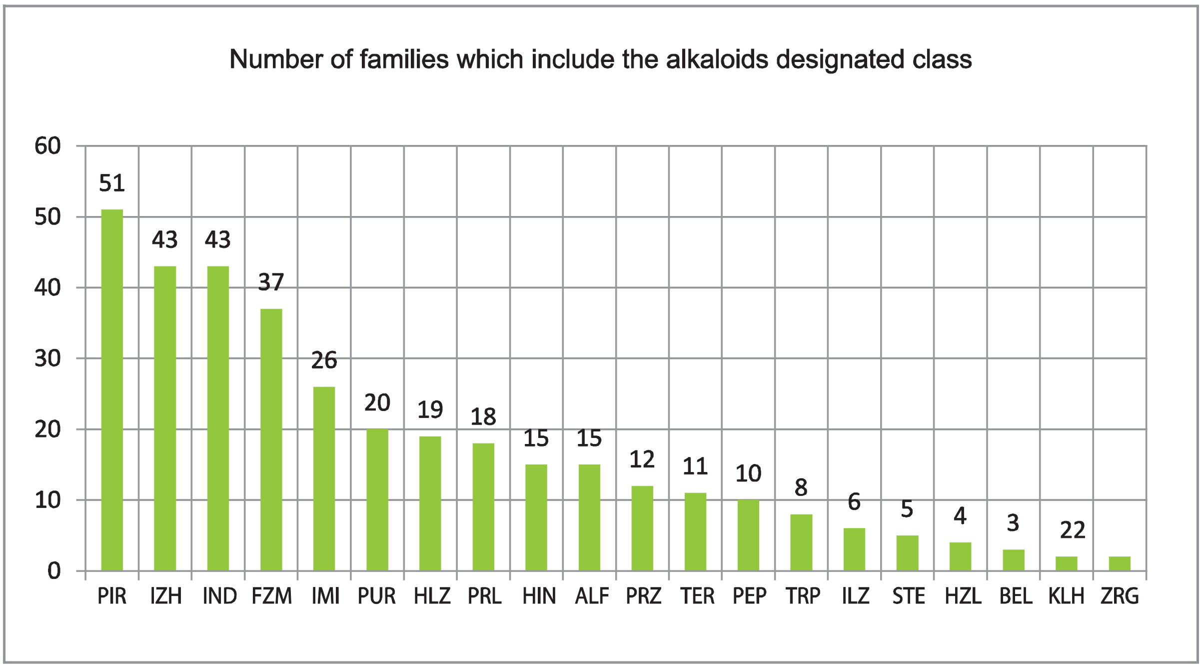
Table 1-38: Number of alkaloid genera and species in some families

Family	**Number of genera**	**Number of alkaloid genera**	**% of alkaloid genera**	**Number of species**	**Number of alkaloid species**	**% of alkaloid species**	**Number of alkaloids in the family's plants**
Apiaceae	300	9	3.0	3,000	28	0.9	15
Apocynaceae	200	55	27.5	2,000	217	10.9	886
Amaryllidaceae	80	36	45.0	860	131	15.2	187
Amaranthaceae	65	4	6.2	900	2	0.2	1
Asteraceae	1,000	31	3.1	20,000	238	1.2	135
Asclepiadaceae	290	12	4.1	2,000	37	1.9	20
Aristolochiaceae	10	4	40.0	600	18	3.0	21
Arecaceae	240	1	0.4	3,400	6	0.2	-
Begoniaceae	5	1	20.0	820	2	0.2	-
Berberiaceae	12	7	58.3	650	62	9.5	75
Buxaceae	5	4	80.0	60	13	21.7	153
Boraginaceae	100	15	15.0	2,000	49	2.5	66
Cactaceae	200	23	11.5	2,000	36	1.8	53
Caryophyllaceae	80	6	7.5	2,100	7	0.3	-
Convolvulaceae	50	7	14.0	1,500	7	1.6	22
Cruciferae	350	11	3.1	3,000	11	1.1	23
Cucurbitaceae	120	4	3.3	1,000	4	0.9	3
Cuscutaceae	1	1	100.0	170	1	0.6	-
Chenopodiaceae	100	23	23.0	1,500	23	5.7	50
Euphorbiaceae	290	24	8.3	7,500	24	1.0	130
Fabaceae	490	86	17.6	12,000	86	4.4	347
Fumariaceae	16	1	6.3	400	1	1.3	-
Gentianaceae	70	7	10.0	1,100	7	3.5	32
Lamiaceae	200	11	5.5	3,500	11	1.4	17
Liliaceae	215	32	14.9	2,500	32	5.0	232
Malvaceae	90	2	2.2	1,570	2	1.0	4
Magnoliaceae	12	5	41.7	210	5	8.1	65
Menispermaceae	70	29	41.7	450	29	11.6	209
Nymphaceae	4	4	100.0	60	4	16.7	37
Orobanchaceae	13	1	7.7	160	1	1.3	1
Papaveraceae	30	28	93.3	450	28	34.9	378
Poaceae	700	16	2.3	10,000	16	0.6	51
Polygonaceae	40	2	5.0	900	2	0.7	9
Portulacaceae	20	2	10.0	500	2	0.4	-
Primulaceae	30	1	3.3	800	1	0.3	1
Phytolocaceae	17	3	17.6	120	3	3.3	3
Ranunculaceae	45	19	42.2	2,000	19	6.2	306
Rosaceae	115	4	3.5	3,000	4	0.7	4
Rubiaceae	450	43	9.6	7,000	43	2.5	174
Rutaceae	180	49	27.2	1,600	49	11.3	308
Scrophulariaceae	200	7	3.5	3,000	7	1.0	17

Solanaceae	85	27	31.8	2,300	27	11.2	162
Typhaceae	1	1	100.0	15	1	20.0	-
Urticaceae	45	8	17.8	700	8	1.1	11
Valerianaceae	13	1	7.7	420	1	1.0	8
Violaceae	16	2	12.5	850	2	0.5	2
Vitaceae	11	1	9.1	700	1	0.3	-

The importance of certain families as a source of alkaloid plants cannot be judged solely by the percentage of their content of the family's genera. For example, *Asteraceae* has more than 1,000 genera, with only 10 (1%) alkaloid genera, and among these 10 genera is the highly alkaloid *Senecio* genus.

Usually, phylogenetically related plants contain alkaloids that are similar in structure. However, there are also cases where, in two very similar species, one species is rich in alkaloids, and the other does not contain them or contains alkaloids with completely different structures. For example, the *Capsicum* genus contains capsaicin, which is very distant from tropane (phenylalkylamine group). Alkaloid tobacco (*Nicotiana*) contains nicotine, which belongs to the pyridine and pyrrolidine compounds, while *Solanum* alkaloids have a steroidal structure.



Piperidine and pyridine (PIR), isoquinoline (IZH), indole (IND), phenylethylamine (FZM), imidazoline (IMI), purine (PUR), pyrrolidine (PRL), quinoline (HIN), aliphatic (ALF), pyrrolizidine (PRZ), terpene (TER), peptide (PEP), tropane (TRP), indolizine (ILZ), steroidal (STE), quinolizidine (HLZ), belladine (BEL), and colchicine (KLH).

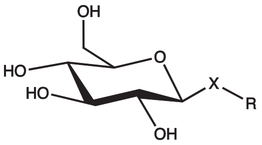
Figure 1-19: Number of plant families containing alkaloids of a particular class

It was long thought that some alkaloids are only specific to certain systematic groups of plants (genera, species). However, it is now known that the same alkaloid can be found in plants that are botanically unrelated to each other. Thus, *caffeine* can be found in *Theaceae*, *Rubiaceae*, *Sterculiaceae*, *Aquifoliaceae*, *Sapindaceae*, and *Geraniaceae*, while *ephedrine* can be found in the following phylogenetically distant families: *Ephedraceae*, *Ranunculaceae*, *Papaveraceae*, *Malvaceae*, *Taxaceae*, and *Celastraceae* (Desgagne-Penix, 2017).

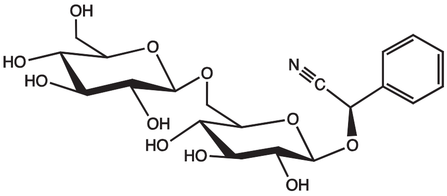
GLYCOSIDES (HETEROSIDES)

Basic terms and classification of glycosides

According to the degree of distribution in the plant world, glycosides come right behind alkaloids. They are widespread in nature in different plants. They are widely used for medical purposes, especially cardiotonic glycosides, which have a specific effect on the heart. They have toxic effects, especially on cold-blooded organisms. The glycoside molecule consists of two components: one component is sugar, which is often glucose (rarely fructose, arabinose, etc.), and the other is aliphatic and aromatic, such as alcohol, phenol aldehyde, ketone, or some other compound (Kytidou *et al.* 2020). The non-sugar component of glycosides is called aglycone, which causes its toxic effects. The two parts are linked by an ester-glycosidic bond. Heterosides are specific plant metabolites with complex structures. They are found in different parts of the plant, dissolved in the alveolar cell sap. In the glycoside molecule, these components are linked by oxygen, carbon, nitrogen, and sulphur; depending on the nature of these bonds, there are: O-glycosides, C-glycosides, N-glycosides, and S-glycosides. The properties of glycosides depend on both the nature of the sugar and that of the aglycone. In the glycoside molecule, monosaccharides are most common sugar components, but oligosaccharides (disaccharides, trisaccharides, etc.) can also be found.



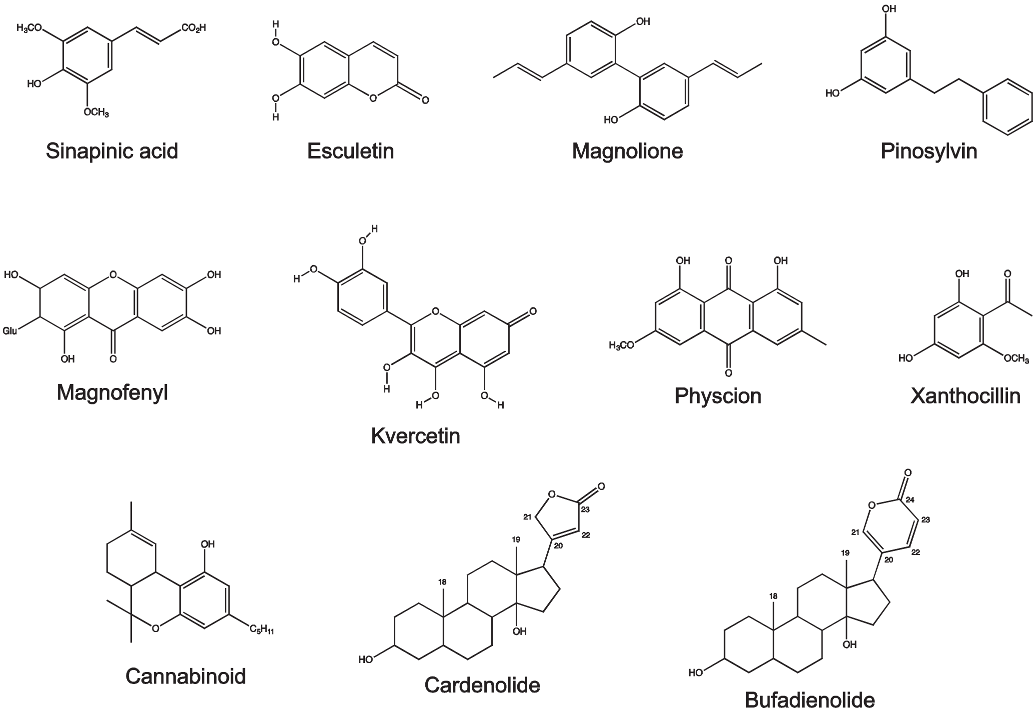
Formula 1-94: Glucozide



Formula 1-95: Amygdalin

The influence of enzymes, acids, bases, or heating leads to their degradation. Then sugars (one or more monosaccharide molecules) and an organic, non-sugary compound (aglycone component: secondary metabolite) are released. The stability of heterosides varies; the most difficult to hydrolyze are C heterosides. The formation process takes place in the presence of more or less specific enzymes. The degradation of heterosides results from the activity of certain enzymes, such as glucosidases and hydrolases. The enzymes involved in the degradation of heterosides are spatially separated from the heterosides; the plant probably protects itself in this way from the harmful effects of the released agluconic components.

Some glycosides are pigments and are responsible for the colour of leaves, flowers, and fruits. They are essential for the enzyme systems' ability to function in the plant cell; they have a protective role, as they absorb the violet part of the sunlight, and their toxicity is reduced by binding aglycones to sugars.



Sinapinic acid

Esculetin

Magnolione

Pinosylvin

Magnofenyl

Kvercetin

Physcion

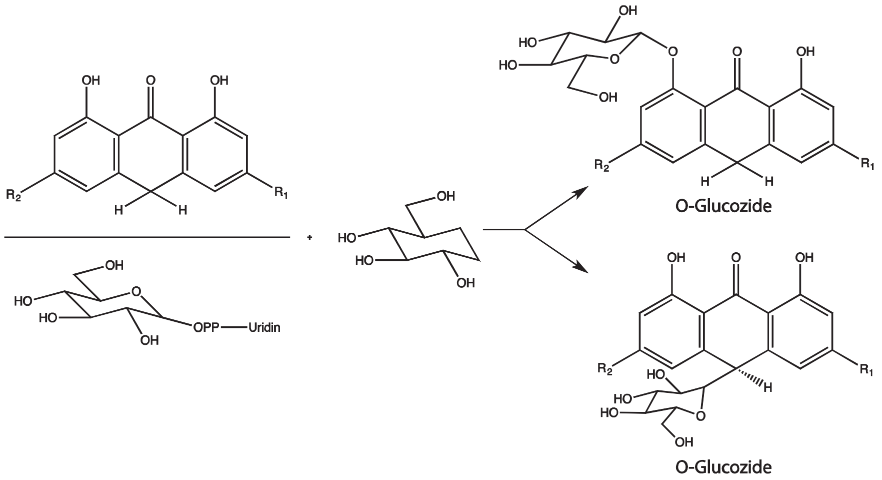
Xanthocillin

Cannabinoid

Cardenolide

Bufadienolide

Scheme 1-4: The most common aglycones of natural heterozoids



Scheme 1-5: Connecting sugar with aglukons component

Glycosides are found in different parts of plants. They are dissolved in the cell sap and can only be proven by means of specific microchemical reactions. Isolated from plants in the pure state, glycosides are crystalline, non-volatile, and mostly bitter organic substances with a neutral reaction. They are soluble in water, not so much in alcohol, and almost insoluble in non-polar organic solvents. They are optically active. In the body of plants, there are enzymes involved in the processes of synthesis and hydrolysis of glycosides, whose effects are specific and depend on both the structure of the aglycone and the tautomeric form of the monosaccharides. In the body of animals and humans, they decompose under the influence of specific glycoside enzymes to glycol and aglycone.

O-glycosides are the most prevalent in nature. Depending on the chemical nature of the aglycone, O-glycosides are categorised into the following groups:

1) Cyanogenic glycosides (glycosides containing hydrocyanic acid in their aglycone part of the molecule).
2) Cardiac glycosides (glycosides containing 1,2 cyclopentanoperhydrophenanthrene in their aglycone part of the molecule).
3) Saponin glycosides or saponins (glycosides containing triterpene and steroid compounds in their aglycone part of the molecule).
4) Antraglycosides (glycosides containing anthracene compounds in their aglycone part of the molecule).
5) Bitter glycosides (glycosides whose aglycone has an intense bitter taste).

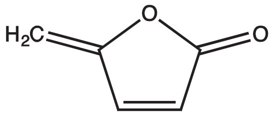
There are also groups of glycosides categorised according to the nature of the aglycone:

- Cyanogenic glycosides, which contain the cyanide group.
- Anthraquinone glycosides, which contain anthraquinone.
- Quinone glycosides, which contains quinone.
- Qoumarin glycosides, which contain coumarin derivatives.
- Chromonic glycosides, which contain benzo-gamma-pyroneon.
- Phenolic glycosides, which contain phenols.
- Flavoid glycosides, which contain flavonoids.
- Monoterpene glycosides, which contain monoterpenes.
- Saponins.
- Steviol glycosides.
- Sulphur or thioglycosides, which contain sulphur compounds.
- Steroidal or cardiotonic glycosides, which contain steroids.

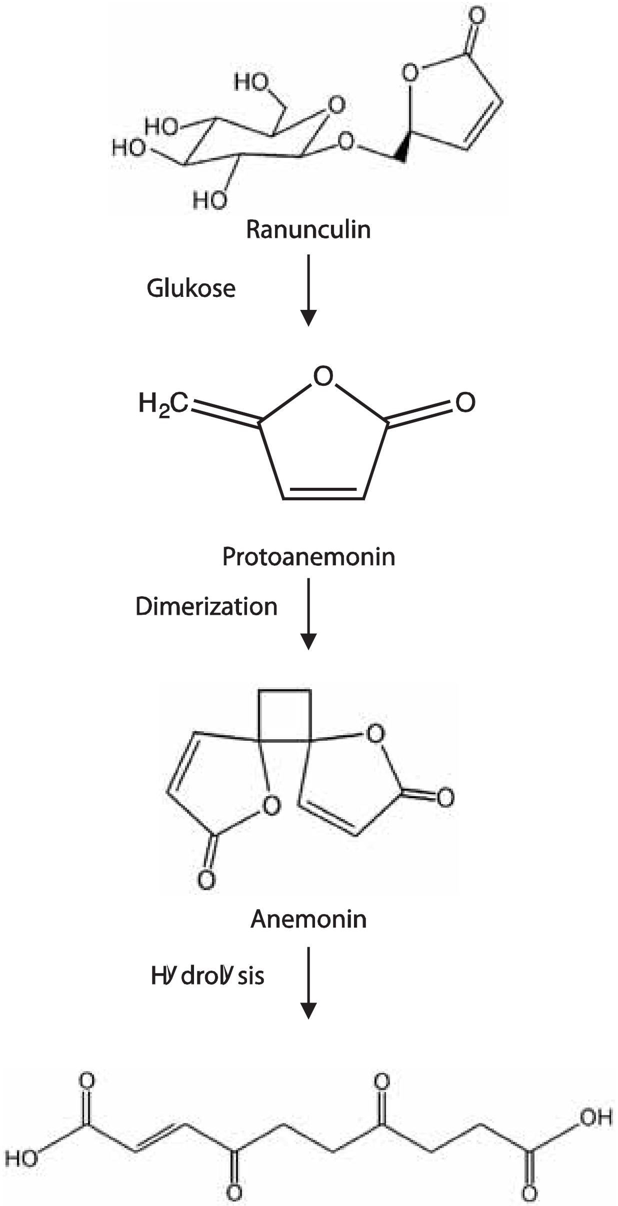
Protoanemonin

Protoanemonin (sometimes called only anemonol or ranunculol) has been found in plants from the *Ranunculaceae* family. In plants, protoanemonin is found as a glycoside (ranunculin). When the plant is damaged, ranunculin, an unstable glucoside found in the plant, is enzymatically degraded into glucose and toxic protoanemonin (Berger and Wachter, 1998). It is actually 4-hydroxy-2,4-pentadienoic acid lactone. Skin or mucous membrane contact with a damaged plant causes itching, a rash, or blisters. Ingestion causes nausea, vomiting, dizziness, cramps, acute hepatitis, or paralysis. In the process of drying the plant, protoanemonin is dimerized to anemonin on contact with the air, and then further hydrolysed to non-toxic carboxylic acids.

Table 1-39: Physical and chemical properties of protoanemonin

CAS number	108-28-1	 Formula 1-96: Protoanemonin
Molecular formula	$C_5H_4O_2$	
Molekular weight	96.08 g/mol	
Boiling point	45 ^{0}C	
Melting point	<25 ^{0}C	

https://pubchem.ncbi.nlm.nih.gov/



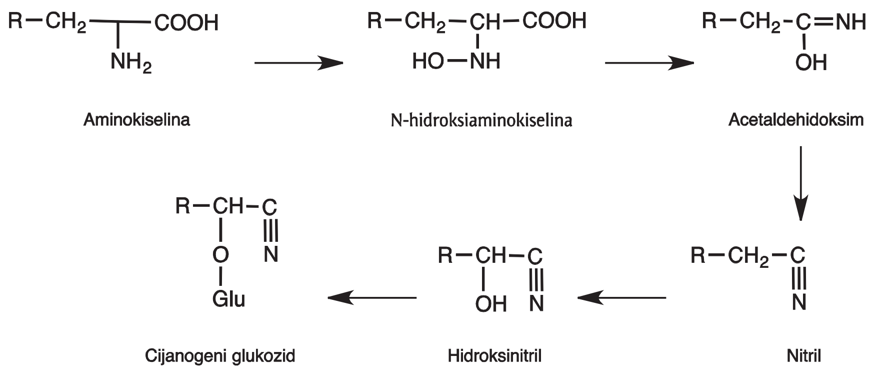
Scheme 1-6

CYANOGENIC GLYCOSIDES

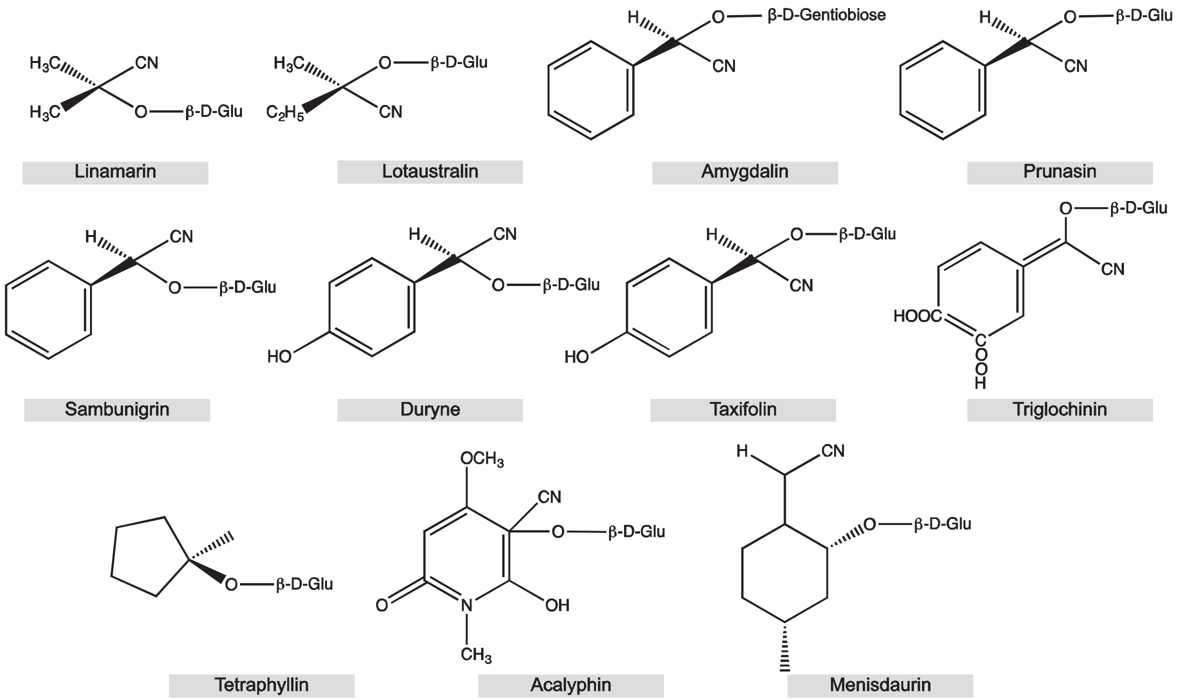
The aglycone component is found in the cyanide group, which makes it toxic. These are compounds with a characteristic odour, similar to bitter almond, which are distributed in about 500 genera of about 100 plant families (Bolarinwa *et al.* 2016). Their hydrolysis releases hydrocyanic acid. Bitter almond (*Prunus amygdalis*) contains glycoside amygdalin.

The aglycone component of these heteroids is found in unstable compounds, such as α-hydroxynitriles (cyanhydrins). The formation of these heterosides protects the plant from the harmful effects of cyanide ions. Heterosides are localised in seed cells or young, herbaceous parts. They are spatially separated from the enzymes that can cause their hydrolysis. This enzyme is emulsin, which is a mixture of β-glucosidase and hydroxynitrilase.

They are formed by the metabolism of the phenylalanine, tyrosine, leucine, isoleucine, and valine amino acids. As a sugar component, glucose or gencibiosis are almost universally bound.



Scheme 1-7: Biosynthesis of cyanogenic glycosides



Scheme 1-8: Structural formulae of some glycoside cyanogenics

Cyagene heterosides are found in species of plants of the following families: *Rosaceae*, *Amygdalaceae*, *Fabaceae*, *Poaceae*, and *Araceae i Euphorbiaceae*.

Hydrolysis occurs if β-glucosidase and heterosides come into contact. In a neutral environment, the sugar separates, and aglycone, an unstable cyanhydrin compound, is released. The effects of hydroxynitrile lyase lead to the aglycone decomposition, and volatile hydrocyanic acid is released from that complex with an aldehyde or ketone. Increased acidity and high temperature can lead to the spontaneous hydrolysis of cyanogenic heteroids. The process of isolation and chemical characterization of cyanogenic heterosides is very difficult because of their instability. The isolation of cyanogenic heterosides must be preceded by enzyme inactivation. The amount of heterosides is indirectly determined based on the amount of hydrocyanic acid. The therapeutic effects of heterosides are small, and many attempts to use them to treat tumours or in cosmetics have largely been abandoned.

The basis of heteroside toxicity is the release of cyanide ion. This ion binds to the cytochrome C-oxidase and prevents cytochrome reoxidation. In this way, the cells are prevented from using molecular oxygen. The symptoms of poisoning are rapid and shallow breathing, headache, dizziness, and coma, while death occurs by cessation of breathing. Toxic doses range from 0.5 to 3.6 mg/kg. Despite such toxicity, consuming plants with cyanogenic heterosides rarely leads to poisoning. Such plants and their parts have an unpleasant and warning taste. Even if a significant amount of plant material is ingested, the hydrolysis of heterosides occurs in the digestive tract, while the cyanide ion is relatively quickly converted to thiocyanates by the enzyme thiosulphate/sulphur transferase, and eliminated through urine.

Cyanogenic glycosides, such as amygdalin, prunasin, prulaurasin, and sambunigrin, contain benzaldehyde in the aglycone moiety. In some glycosides, hydrocyanic acid forms a compound with acetone (linamarin) or methylethylketone (lotaustralin). These alkaloids are usually localised in seeds. Of cyanogenic glycosides, amygdalin, which was discovered as early as 1830, has been used in medical practice.

Cyanogenic glycosides are composed of alcohol and carbohydrates (sugar) and the CN nitrile group. Enzymatic decomposition produces hydrocyanic acid, *HCN*. The following most important representatives of this group of compounds:

- Amygdalin, found in plum, apricot, and almond seeds
- Dhurrin, found in sorghum and millet
- Linamarin, found in plants such as cassava (*Manihot esculenta*), lima beans (*Phaseolus lunatus*), and flax
- Lotaustralin, found in lima beans, white clover, and other plants
- Sambunigrin, found in *Sambucus nigra* plants and apple seeds
- Simmondsin, found in jojoba (*Simmondsia chinenis*)
- Vicianin, found in the tropical plant *Phlebodium aureum*
- Linustatin and neolinustatin, found in flaxseeds

Cyanogenic glycosides are not toxic by themselves, but cleavage of the molecules results in the formation of hydrocyanic acid (HCN), which is actually a toxic substance. Degradation occurs either spontaneously or by enzymatic catalysis by hydroxynitrile lyase. When hydrogen cyanide is released, cyanogenic glycosides are highly toxic to almost all animal species (Bolarinwa *et al.* 2016). HCN binds to the cytochrome C oxidase, which represent the basic redox system in the respiratory chain. These glycosides are found in the following:

- Plum (*Prunus domestica*)
- Blackthorn (*Prunus spinosa*)
- Apricot (*Prunus armeniaca*)
- Almond (*Prunus dulcis*)
- Peach (*Prunus persica*)
- Cherry (*Prunus cerasus*)
- Sorghum (*Sorghum halepense*)
- Cassava (*Manihot esculenta*)

Cyanogenic glycoside polymorphism occurs in Europe in various clover populations. In this plant, one gene controls the synthesis of cyanogenic glycosides, and the other controls the enzyme that catalyses the cleavage of glycosides. There are four different types of clover, which are categorised according to their toxicity mediated by cyanogenic glycosides. Cyanogenic glycosides only have toxic effects if both genes are dominant.

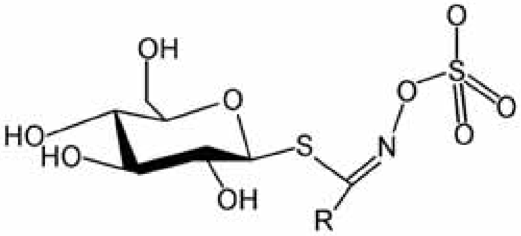
Glucosinolates and sulphur heterosides

Glucosinolates are a unique and important group of secondary metabolites in some plant species. They belong to a specific group of chemical compounds that is present in 16 botanical families of the order *Capparales*. The most important for human diet is the *Brassicaceae* family, which includes cabbage, broccoli, cauliflower, Brussel sprouts, radish, turnip, and mustard. Glucosinolates are chemically stable until they come into contact with the myrosinase enzyme (β-thioglucoside glucohydrolase). They are hydrolysed into a number of biologically active substances (isothiocyanates, indole-3-carbinol).

Table 1-40: Glucosinolate content (mg/100 g) in vegetables of the *Brassicaceae* family (cited and adapted from McNaughton and Marks, 2003; Possenti *et al.* 2016)

Vegetables of the *Brassicaceae* family	**Glucosinolate content (mg/100 g)**
Brassica oleracea var. italica	19.3–127.5
Brassica oleracea var. gemmifera	80.1–445.5
Brassica oleracea var. capitata	42.7–108.9
Brassica chiniensis	17.3–54.8
Brassica oleracea var. sabauda	59.5–209.0
Brassica oleracea var. botrytis	11.7–78.6
Armoriaca lapathifolia	106.1
Brassica juncea	11.1–544.5
Brassica rapa	20.4–140.5

The myrosinase enzyme catalyses the hydrolysis of glucosinolates. It is found in plant cells separated from glucosinolates. When the cells are damaged, for example by cutting or chewing, myrosinase comes into contact with glucosinolates and then the hydrolysis occurs. When vegetables are cooked, the myrosinase is inactivated, but the thermal degradation and reduction of glucosinolate content by 30–60 % occurs (De Vos and Blijleven, 1988). Myrosinase cleaves glucose, and sulphur is then eliminated from the unstable aglucon. The products of glucosinolate hydrolysis significantly contribute to the typical aroma of vegetables from the *Brassicaceae* family. To date, about 120 glucosinolates have been characterised, but few have been researched (Possenti *et al*. 2016). Research on the distribution of glucosinolates in different plants shows that the glucosinolate content varies over a wide range and depends on the species of plant, cultivar, and growing conditions (Kushad *et al*. 1999). Glucosinolates known as sinigrin (2-propenyl or glucosinolate) and sinalbin (4-hydroxybenzyl glucosinolate) were isolated as early as 1830: the first from black mustard seeds (*Brassica nigra*), and the second from white mustard seeds (*Sinapis alba*).



Formula 1-97: Glycosinolate structure

Table 1-41: Overview of the major glucosinolates and their presence in vegetables from the *Brassicaceae* family (cited and adapted from Hansen *et al.* 1995; Vig *et al.* 2009; Possenti *et al.* 2016.)

Name of glucosinolate	Trivial name	Cabbage	Kale	Cauliflower	Broccoli
Allyl	Sinigrin	+	+	+	+
But-3-enyl	Gluconapin	+	+	+	+
Pent-4-enyl	Glucobrasicanapin	-	-	+	+
(2R)- hydoxibut-3-enyl	Progoitrin	+	+	+	+
3-methylthiopropyl	Glucoibervirin	+	-	+	+
4-methylthiopropyl	Glucoerucin	+	+	+	+
3-methylsulphinylbutyl	Glucoraphanin	+	+	+	+
4-methylsulphinylbutyl	Glucoraphanin	+	+	+	+
5-methylsulphinylpentyl	Glucoalysin	-	-	-	-
4-methylsulphonylbutyl	Glucoerisolin	+	-	-	-
Benzyl	Glucotropaeolin	+	-	-	-
Phenethyl	Gluconasturtin	+	+	-	+
Indole-3-yl-methyl	Glucobrassicin	+		+	+
N-methoxyindole-3-yl-methyl	Neoglucobrassicin	+	+	+	+
4-hydroxyindole-3-yl-methyl	4-hydroxyglucobrassicin	+	+	+	+
4-methoxyindole-3-yl-methyl	4-methoxyglucobrassicin	+	+	+	+

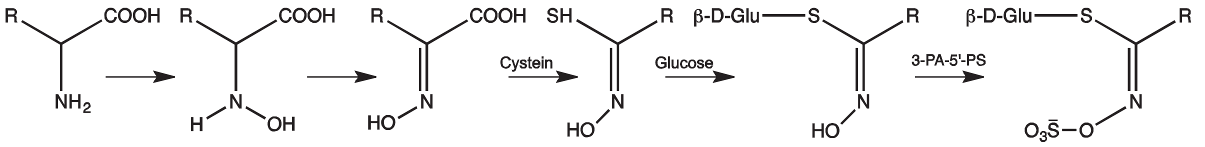
According to their chemical structure, glucosinolates are β-thioglucoside-N-hydroxysulphates in which glucose and the sulphate group are bound to aglucon synthesised from amino acids and their analogues. The side chain structure of glucosinolates, by which glucosinolates differ from one another, is determined by the amino acid. The general structure of glucosinolates is shown in Scheme 1-9. According to the side chain structure, glucosinolates can be classified into the following groups:

- Aliphatic
- Aromatic
- Indole

Glucosinolates are heterosides containing sulphur within the aglycone component. They are mainly responsible for the characteristic aroma of plants and their fruits. They give the aroma to plants of the *Brassicaceae* family, especially to those used as vegetables (radish, horseradish, cabbage, etc.). They are less often found in plants from families such as *Tropeolaceae* and *Resedaceae.* They are localised in the vacuoles of the parenchymal cells from different plant parts and tissues (leaves, seeds, bulbs).

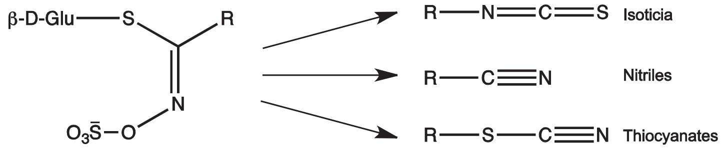
The aglycones of these heterosides are formed from amino acids. Depending on the amino acid, different structures of sulphur heteroside aglycones occur in nature:

- p-hydroxybenzylglucosinolate is formed from tyrosine, sinalboside in white mustard seeds, *Brassica alba*.
- Benzylglucosinolate is formed from phenylalanine, glucotropeoylin in garden nasturtium, *Tropaeolum majus*.
- 3-indolylmethyl-glucosinolate is formed from tryptophan, glucobrassicin in cabbage.
- Sinigroside aglycosinolate is formed from homomethionine in black mustard seeds, *Brassica nigra*.



Scheme 1-9: The biosynthesis of sulphur heterozidoids aglycone

The hydrolysis of glucosinolates occurs under the influence of a specific thioglucosidase enzyme, trivially named myrosinase. This enzyme is found in almost all plants which synthesise sulphur heterosides, but is spatially separated from them. Damage to a plant's tissues leads to their activation and the hydrolysis of heterosides. The released aglycone component is unstable and is rapidly transformed further. In a neutral environment, aglycone is transformed into reactive and often volatile isothiocyanates.

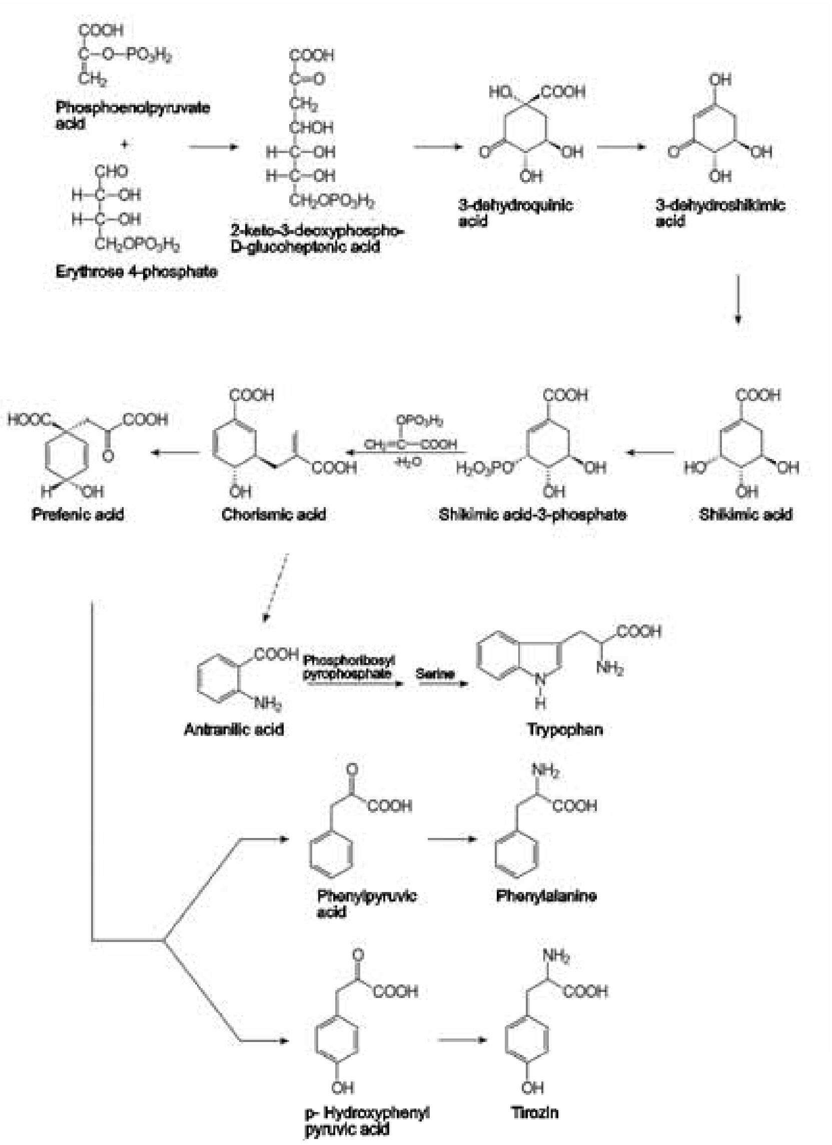


Scheme 1-10: The transformation of aglycone under neutral conditions

Whether or not isothiocyanates or nitriles will form during the degradation of glucosinolates depends on the specificity of the glucosinolate, the part of the plant, and the pH. Isothiocyanates are usually formed at a pH of 5–7, while nitriles are generally formed when the hydrolysis occurs under acidic conditions. Most hydrolysis products are stable except for glucosinolates containing a β-hydroxylated side chain. Indole glucosinolates, such as glucobrassicin, produce unstable isothiocyanates and are subject to further hydrolysis.

All glucosinolates are biologically inactive compounds, but their degradation products are active. Isothiocyanates are responsible for bitterness (Van Doorn *et al*. 1998; Mithen *et al*. 2000), and nitrites have an impact on health (Tanii *et al*. 2004). Thiocyanates, thiourea, and oxazolidinedione may affect the availability of iodine to the thyroid and thus may also affect the function of the thyroid gland (Wallig *et al*. 2002).

Sulphur glucosinolates have antimicrobial activity but are rarely administered as antiseptics. Sulphur glucosinolates irritate mucous membranes and have irritant effects. They affect the capillaries in the outer layers of the skin and lead to their expansion, better blood circulation, an increased sensation of warmth, and a reduced sensation of pain.



Scheme 1-11: The biosynthesis of aromatic derivate via shikimic acid

CARDIOTONIC (CARDIAC) GLYCOSIDES (STEROIDAL HETEROSIDES)

Cardiotonic glycosides are a broad and very important group of natural glycosides used in medicine. Plants containing cardiotonic glycosides have been known for a long time. People from various countries have used them for centuries to treat diseases of the heart and other organs. The ancient Egyptians and Romans used squill (*Scilla maritima*) as a cure for certain diseases. Many plants containing cardiotonic glycosides have been used by some African and Asian tribes to make poison for arrows and spears. *Digitalis* was known in England as a folk remedy as early as the XI century.

Over 400 cardiotonic glycosides have been isolated from plants. These glycosides are found in plants from the following families: *Apocynaceae*, *Liliaceae*, *Ranunculaceae*, *Celastraceae*, and *Scrophylariaceae*. They are dissolved in the cell sap, but only in very low concentrations. The following table shows data on glycosides, families, genera, and aglycones (David and Susan, 1990; Chen *et al.* 1950; Dybing *et al.* 1952).

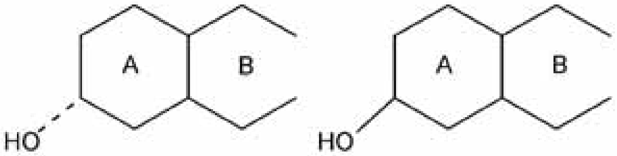
Table 1-42. Data on glycosides, families and genera of plants containing glycosides and their aglycones

Family	Genus/species	Glycoside	Aglycone	Type
Liliaceae	*Convallaria*	Convallatoxin	Convallatoxygenin (Strofantidine)	C
		Convallamarin	Convallamarogenin	B
	Urginea/Scilla	Proscillaridin A (Scillarenin A)	Scillaridin A	B
	Ornithogalum *Bowiea volubilis*	Convallatoxin	Convallamarogenin	C
		Bovocides A, B, C, D	Bovogenin E	B
		Hellebrin	Hellebrigenin	B
Ranunculaceae	*Helleborus*	Hellebrin	Hellebrigenin	B
Celastraceae	*Euonymus*	Evonoside	Evonogenin	C
Scrophulariaceae	*Digitalis purpurea*	Digitoxin	Digitoxigenin	C
		Gitoxin	Gitoxygenin	C
		Gitalin	Gitaligenine	C

C-Cardenolide, B-Bufadienolide

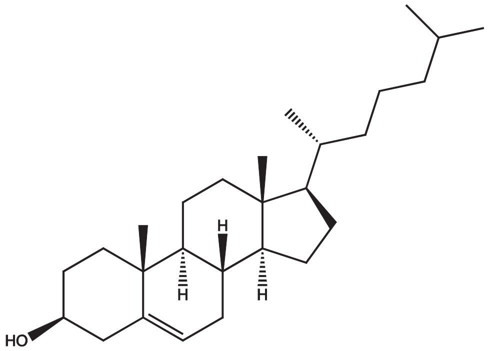
The glycosides found in some plants (e.g. *Digitalis*) have an effect on the heart muscle even in small doses; they are known as cardiac glycosides. In higher doses, they are strong poisons. During the hydrolysis of cardiac glycosides, their molecules are broken down into several monosaccharide molecules (e.g. digitoxosis and glycosis) and a specific aglycone of theroid nature, which is often referred to as genin, while their acetic acid is separated in some glycosides. Genins contain a cyclopentanoperhydrophenanthrene ring linked to an unsaturated five or six membered lactone ring.

Steroids contain the carbon skeleton of cyclopentanoperhydrophenanthrene. R' and R" are found in most methyl group steroids: R is a hydrocarbon chain, while X is a hydroxyl or keto group. A/B and C/D rings can be condensed at cis- or trans-positions. B/C rings of natural products always have the trans-configuration and C/D rings always have trans-, while A/B rings can have a trans or cis position (Moss 1989; IUPAC, 1989). Naturally, six-membered rings are the most stable. The spatial arrangement of the substituents in the molecule is indicated by the letters α and β. In the α configuration, the substituent is behind the plane of the ring (its link is indicated by dots), and in the β configuration, it is in front of the plane of the ring (its link is indicated by a solid line).



Formula 1-98

Natural steroids are optically active and have several asymmetric carbon atoms. Plants containing cardiotonic glycosides are widespread in nature. They can be found in the flora of all continents. About 45 botanical genera have been known to contain cardiotonic glycosides. In its stereoidal structure, cardiotonic glycosides are very similar to significant natural compounds found in the animal body, such as bile acid, cholesterine, sex hormones, adrenal hormones, and vitamin D. The human body contains over 100 grams of cholesterine.



Formula 1-99: Cholesterol (cholesterine)

Table 1-43: Names of cardiotonic glycosides found in plants

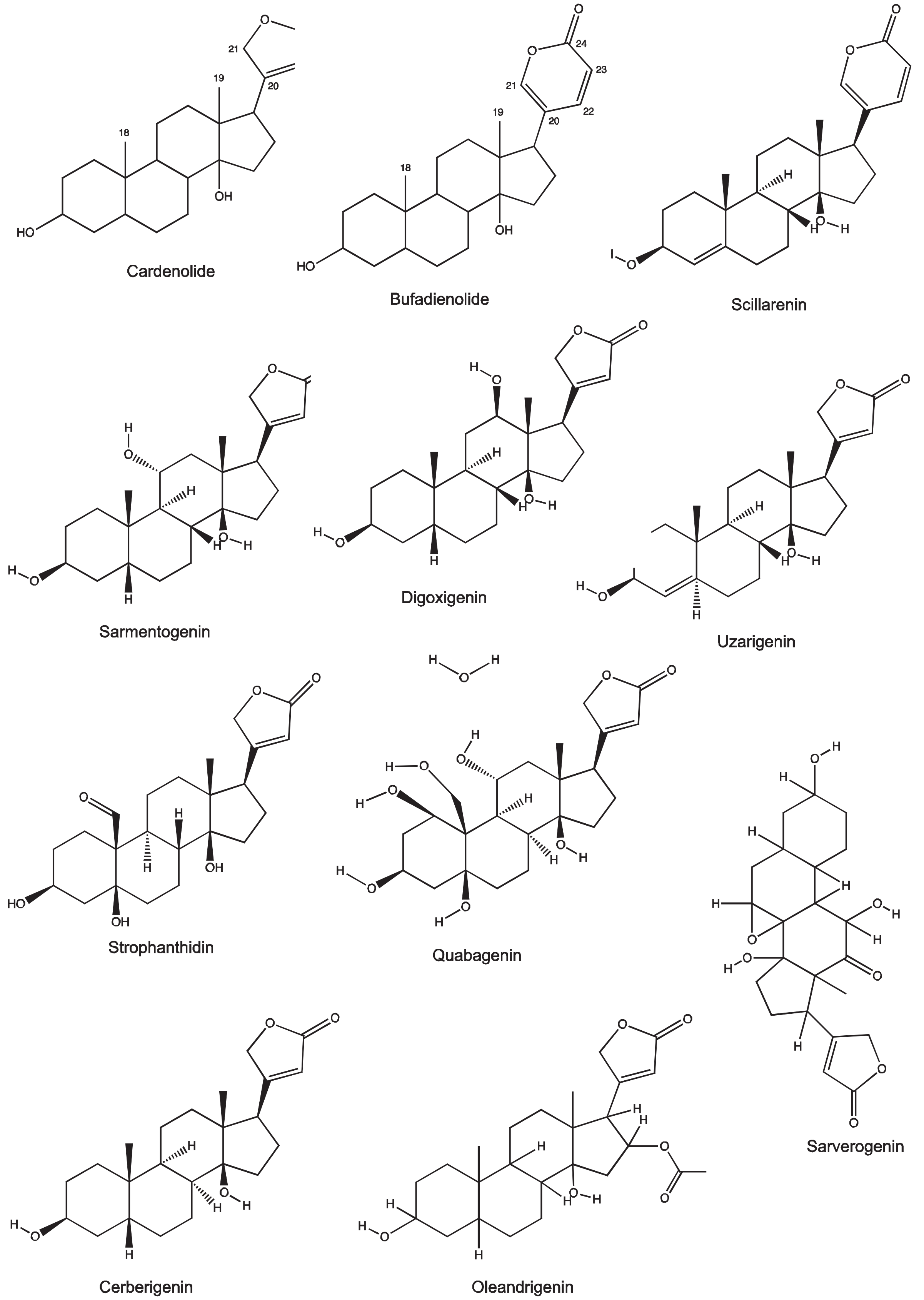
Trivial name	Chemical name
Convallarin	Cannogenol-3-O-6-deoxy-β-D-allosido-β-D-glucoside
Convallamarin	Cannogenol-3-O-6-deoxy-β-D-allosido-α-L-rhamnoside
Convallatoxin	Strophanthidin-3-O-6-deoxy-β-D-allosido-α-L-rhamnoside
Convallotoxoloside	Strophanthidin-3-O-6-deoxy-β-D-allosido-α-L-arabinoside
Convallosid	Strophanthidin-3-O-α-L-rhamnosido-2-β-D-glucoside
Neoconvalloside	Sarmentogenin-3-O-6-deoxy-β-D-allosido-α-L-rhamnoside
Glucoconvalloside	Sarmentogenin-3-O-6-deoxy-β-D-guloside
Majaloside	19-Hydroxy-sarmentogenin-3-O-α-L-rhamnoside)
Convallatoxon	19-Hydroxy-sarmentogenin
Corglycon	Arabinosido-6-deoxyallose

Cardiotonic glycosides are herbal or semi-synthetic drugs for the treatment of congestive heart failure because they enhance the force of heart muscle contraction. Plants containing cardiotonic glycosides include purple foxglove or lady's glove (*Digitalis purpurea*), woolly foxglove (*Digitalis lanata*), squill (*Urginea maritima* or *Scilla maritima*), pheasant's eye (*Adonis vernalis*), lily-of-the-valley (*Convallaria majalis*), and oleander (*Nerium oleander*) (Hollman, 1985). In addition, they are also found in the frog skin (bufotalin). Due to their complicated structure, no synthetic analogues of these natural compounds have been synthesised to date; therefore, all cardiotonic glycosides are still obtained from plants or semi-synthetically by chemical modification of the natural glycosides isolated from plants. Cardiotonic glycosides are also called cardiotonic heterosides.

In cardiotonic heterosides, aglycones are compounds of a steroidal nature with 23 or 24 carbon atoms. The basis of the aglycone is a tetracyclic skeleton in which an unsaturated lactone ring is attached to position 17 on the basic skeleton. There are two types of aglycones, depending on the type of lactone:

- The cardenolide type of aglycone (cardenolide heteroside, α,β- unsaturated ϒ-actone, butenolide, and C_{23}).
- The bufadienolide type of aglycone (bufadienolide heteroside, ϒ-lactone with two unsaturated bonds, pentadienolide, and C_{24}).

Cardenolide make up a large group of cardiac glycosides. Digitoxigenin is the genin of digitoxin. The hydroxyl group at position 3 is compounded with carbohydrate in the glycoside formation. Heterosides are found in the parenchymal cell sap in different organs of the plant. Their concentration in plants is very low and does not exceed 1 %.



Scheme 1-12

Strophanthidin is the genin of strophanthin and it differs from digitoxigenin in that it contains an aldehyde group instead of a methyl group at position 10, and it has an OH group at position 5. Of the sugars that form cardiac glycosides, D-digitoxosis, which belongs to methylpentoses, is significant (the hydrogen atom is replaced by a methyl group at C-5).

Cardiac glycoside activity originates from aglycone steroids in nature, while sugar residues enable the dissolution of glycosides.

The most common substitutions on the aglycone are as follows:

- Hydroxyl groups at 1β, 11β, 12β, 16β, and 5β
- Esterification of hydroxyl groups with formic or acetic acid
- Keto group at position 12
- Epoxy function between 11, C_{12} or C_7, and C_8
- Double bond at C_4 (scillarenin)
- Methyl group at C_{10} may be oxidized to a secondary alcohol or aldehyde group

For a cardiotonic heteroside to have pharmacological value, its aglycone must have the following properties:

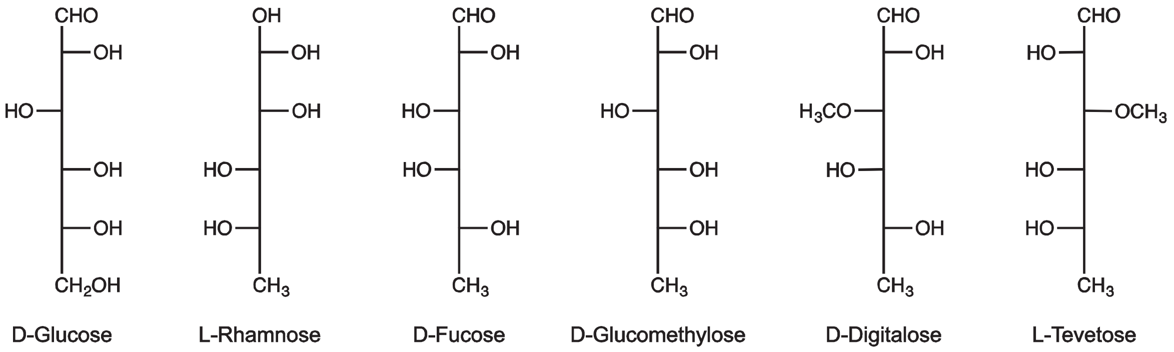
- β-configuration of an unsaturated lactone ring at C_{17}
- basic skeleton configuration

When the basic skeleton is in the cis-trans-cis configuration, then a glycoside has maximum activity, and if it is trans-trans-cis, then it has a very reduced action and increased toxicity. In order for a glycoside to have action, the C and D rings need to be in the cis configuration. Also, their action depends on the following various substitutions:

- Active in case of C-3β of C-14β
- A very reduced action if C-3 is deoxy
- Inactive derivatives if C-3 is deoxy or C-14 is α
- Very weakly active if C-14 is deoxy or C-14 is β

The following regular sugars can be found:

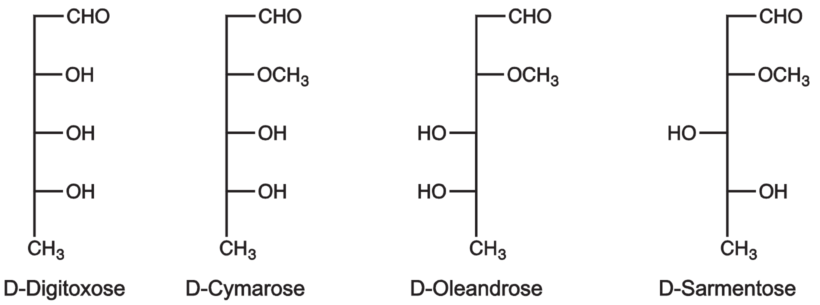
- L-isomers of sugar
- 6-deoxyhexoses (L-rhamnose, D-fucose).



Scheme 1-13

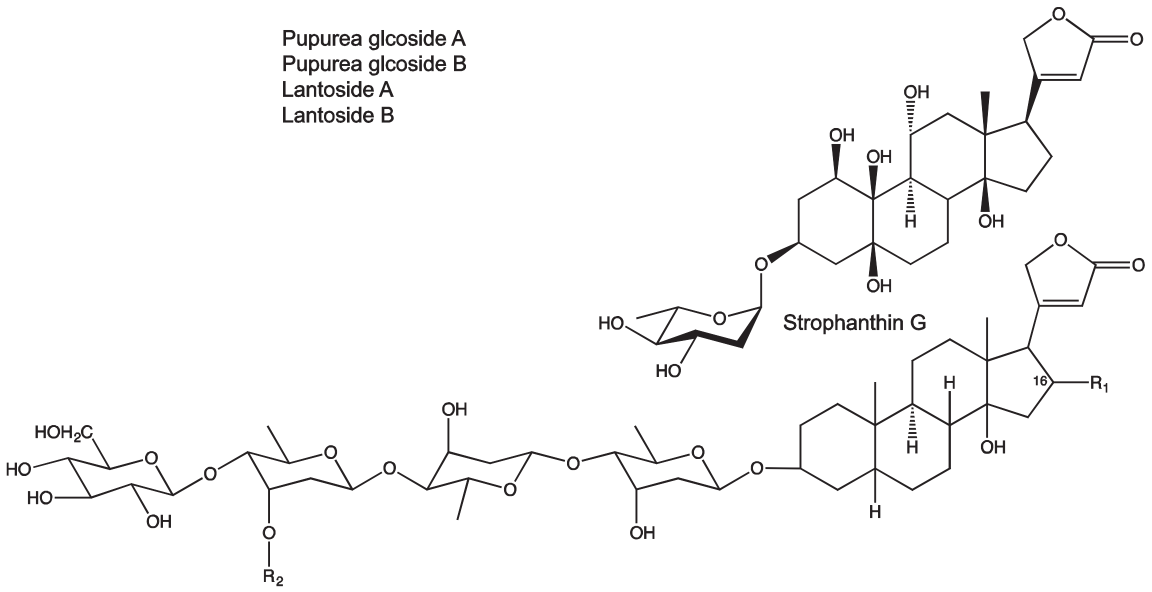
The following sugars may also participate in the composition of cardiotonic heterosides:

- 6-deoxy-3-methylhexose (L-tevetose, D-digitalose)
- 2,6-dideoxyhexose (D-digitoxose)
- 2,6- dideoxy-3-methylhexose (L-oleandrose, D-cymarose, D-sarmentose)



Scheme 1-14

Sugars bind via the hydroxyl group at position C3 in the cardiotonic heterosides structure. Thus, monosaccharides and, more often, oligosaccharides may participate in the composition of heterosides; in addition, when it comes to glucose, it almost always occupies the terminal position. It is weakly bound; therefore, in the course of glycolysis, the glucose is separated, and thus the primary heterosides convert to secondary heterosides. This process can also occur when drying plant material or drugs.



Scheme 1-15

Table 1-44: Purple foxglove’s (*Digitalis purpurea*) most important heterosides

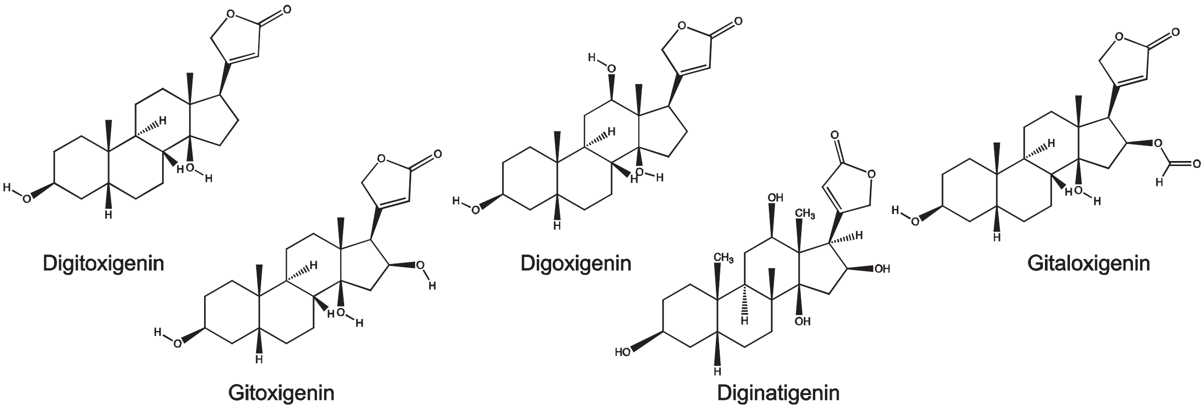
Series	**Aglycone**	**Primary heteroside**[1]	**Secondary heteroside**[2]
A	Digitoxigenin 3β, 14β-dihydroxy	Purpureaglycoside A Lanatoside A	Digitoxin
B	Gitoxigenin 3β, 14β, 16β-trihydroxy	Purpureaglycoside B Lanatoside B	Gitoxin
E	Gitaloxigenin 16-formylgitoxigenin	Purpureaglycoside E Lanatoside E	Gitaloxin

1. Aglycone+3 D-digitoxoses+D-glucose; 2. Aglycone+3 D-digitoxoses

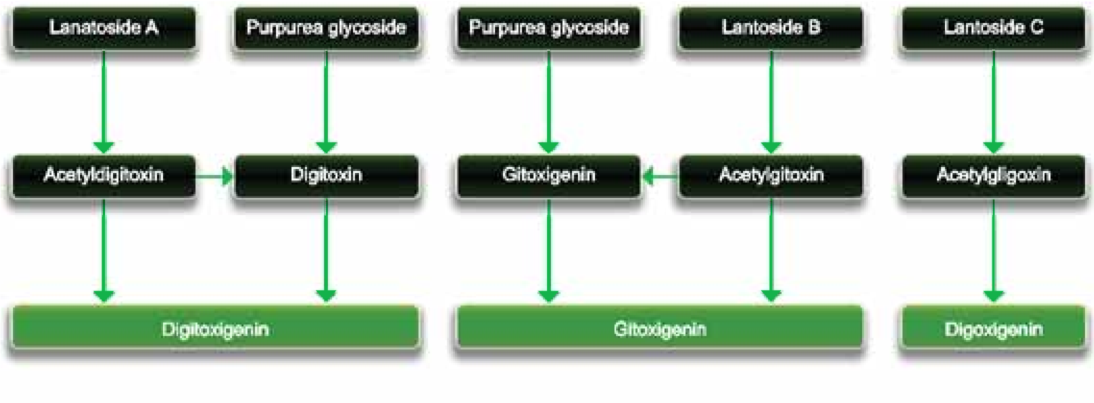
Table 1-45: Woolly foxglove's (*Digitalis lanata*) most important heterosides

Series	Aglycone	Primary heteroside[1]	Secondary heteroside[2]
A	Digitoxigenin 3β, 14β-dihydroxy	Lanatoside A	Acetildigitoxin
B	Gitoxigenin 3β, 14β, 16β-trihydroxy	Lanatoside B	Acetylgitoxin
C	Digitoxigenin 3β,14β, 12β-hydroxy	Lanatoside C	Acetildigoxin
D	Diginatigenin 3β,14β,12β, 16β- tetrahydroxy	Lanatoside D	Acetildiginatin
E	Gitaloxigenin 16-formylgitoxigenin	Lanatoside E	Acetylgitaloxin

1. Aglycone+2D-digitoxoses+3-acetyl-D-digitoxoses+D-glucose; 2. Aglycone+2D-digitoxoses+3-cetyl-D-digitoxoses



Scheme 1-16



Scheme 1-17: Links for purple and woolly digitalis leaf ingredients

Digitoxin is a lipophilic substance. It is completely absorbed in the body; it binds to plasma proteins and is slowly excreted through bile and urine. Its half-life is about 6 days. Digoxin contains one hydroxyl group, is not very lipophilic, is absorbed in the digestive tract to a limited extent, only binds to plasma proteins to a limited, is rapidly diffused into tissues, is gradually metabolized, and is eliminated through urine. Its half-life is about 36 hours. Strophantosides and lanatoside C are highly polar, soluble in water, not absorbed in the digestive tract, not bound to plasma proteins, have a quick action, are rapidly metabolized, and eliminated through urine.

The steroid aglycone component is active in cardiotonic heterosides. The steroid nucleus, lactone ring, and sugar are involved in binding to the receptor. Cardiotonic heterosides affect the heart muscle in the following ways:

- They increase the strength and rate of cardiac contraction due to the increase in intracellular Ca^{2+} concentration (the inhibition of Na^+/K^+-ATP-ase, an increase of Na^+, and the decrease of K^+ leads to an increase in Ca^{2+}).
- They slow down the rhythm of cardiac contraction in patients with heart failure.
- They slow down the impulse conduction and prolong the relaxation period.
- They extend the refractory period.

The result is that heart contracts more strongly in a slow and steady rhythm, which reduces the resistance in the arterial part of the bloodstream. The risk of plant poisoning or the possibility of drug overdose is due to the following:

- Small therapeutic range
- Lipophilicity and the cumulation effect

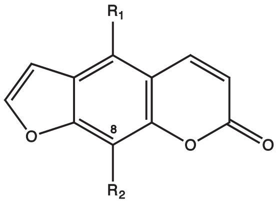
Poisoning with plants that contain digital heterosides is manifested by the following symptoms:

- Digestive
- Visual
- Neurological
- Cardiac

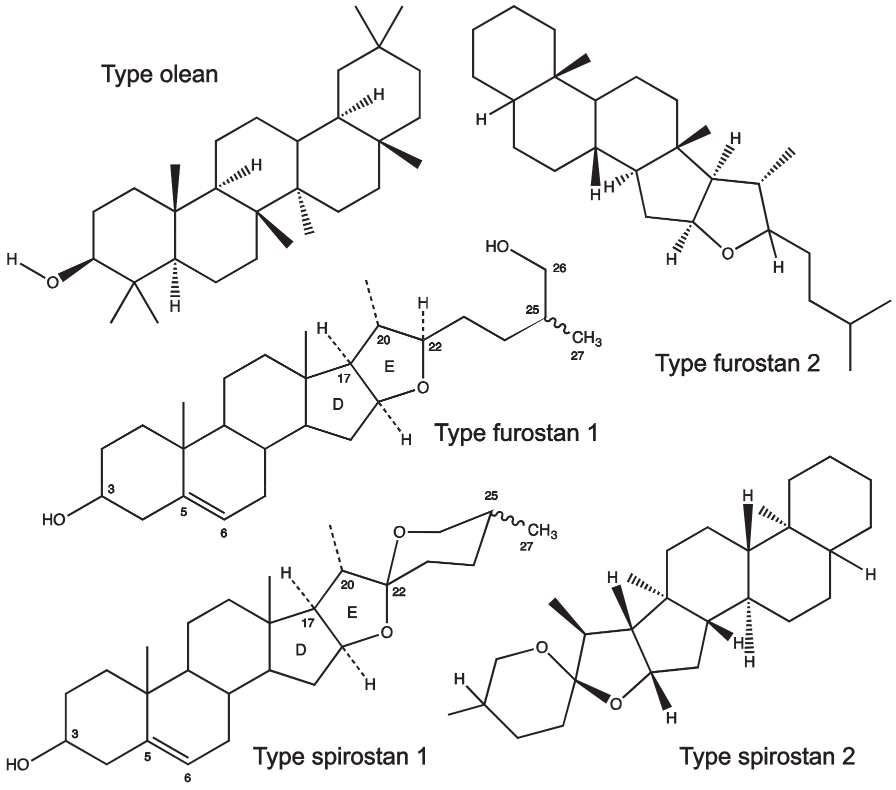
The biggest disadvantage of cardiotonic heterosides is their small therapeutic range, that is, their therapeutic and toxic doses are very close.

SAPONINS

Saponins are organic glycosidic compounds that are widespread in the plant world. They can be found in more than 70 families and the plants that are the richest in saponins are from following families: *Caryophyllaceace*, *Primulaceae*, *Polygalaceae*, *Lillaceae*, and *Buxaceae*. Saponins are surface and hemolytically active toxic compounds (Kregiel *et al*. 2017). They are not found in plants with lots of tannin. Many are used in industry. Foamy fire extinguishing solutions are made from them. They are very absorbent. Saponin preparations are particularly used for washing delicate fabrics (silk and wool). Shampoos, lotions, and similar cosmetic products also contain saponins.



Formula 1-100: Saponins



Scheme 1-18

The aglucon from saponins consists of hexose, pentose, uronic acid, and sapogenin (sapogenol). The following saponins are in triterpene aglycones with C_{30} carbon atoms:

- Tetracyclic (curbitan and damaran type)
- Pentacyclic (oleane type)
- Steroidal saponins with C_{27} (furostane type and spirostane type)

Saponins are colourless substances that are more or less soluble in water. Aqueous solutions form stable foam, which, in the last century, was the reason why they were called saponins. Saponins are soluble in diluted ethyl and methyl alcohol (60–70%), and even more in absolute alcohol (80–90%). They are insoluble in ether, chloroform, acetone, benzene, and other organic solvents. Not all saponins have the same physical and chemical properties. For example, some of them are insoluble in water, while others do not have haemolytic activity.

Saponins are found dissolved in the plant's cell sap. They are most commonly found in underground organs, as well as in fruits and seeds. In some plants, they are found in the whole plant.

Saponins are hydrolysed to sugar and aglycone (so-called sapogenol) through cooking with dilute acids. Some plants' saponins irritate the mucous membranes of the mouth, stomach, and intestines; they can also cause increased gland secretion. This is why the saponin from some plants (senega, primrose, dense-flowered mullein, and sweet potato, etc.) is used for the stimulation of bronchial secretion. In addition, saponins from other plants cause increased diuresis and diaphoresis (smooth rupturewort, birch, horsetail, couch grass, and wild pansy, etc.). Saponins increase the permeability of cells and thereby cause the faster absorption of drugs, toxins, and other substances. There are two groups of saponins:

- Steroidal saponins
- Triterpene saponins

Steroidal saponins are a very broad group of naturally occurring compounds that exhibit a variety of specific biological functions (Escobar-Sanchez *et al.* 2015). All steroidal saponins' carbon skeletons are similar. The carbon skeleton is a cyclic system known as cyclopentanoperhydrophenanthrene. Such a skeleton underlies sterols, cardiac glycosides, and sex hormones.

Previous research has provided data on the degree of steroidal saponins distributions in plants throughout the world. It was found that some species from the *Lilliaceae* family (*Allium*, *Anthericum*, *Aspargus*, *Clintonia*, *Ruscus*, and *Trillium*) and some species from other families contain steroidal saponins. They have also been found in some plants, such as *Coronilla varia*, *Tribulus terrestris*, *Helleborus abschasicus*, and *Helleborus caucasicus*.

Steroidal saponins are non-toxic to humans and higher animals, but they are toxic to lower organisms (e.g. fish). They are significant precursors in the synthesis of steroid hormones.

Triterpene saponins are actually pentacyclic terpenoids. The physical and chemical properties of triterpene saponins vary within a wide range (Mroczek, 2015). Most of them are amorphous substances with no characteristic melting point (they usually degraded at that temperature). There are some representatives in a crystalline form that do not have more than four monosaccharide residues. With the increase in the number of monosaccharides, the solubility of saponins in water and other polar solvents increases. Saponins with 1–4 monosaccharide residues are not very soluble in water. Triterpene saponins can be neutral and acidic compounds. Their acidic character is caused by the carboxyl groups present in the sapogenol molecule, as well as by uronic acid if it is present in the composition of the hydrocarbon moiety.

Acidic saponins form salts, which are soluble with monovalent and insoluble with two or more valent metals. Many saponins form complex molecules with proteins, lipids, sterols, and tannins.

The basic biochemical property of triterpene saponins is its capacity of lysing erythrocytes with the release of haemoglobin (haemolysis), which is associated with the formation of the saponin complex with the erythrocyte membrane cholesterol. The especially high toxicity of triterpene saponins in certain cold-blooded animals (e.g. fish) is explained by the disruption of the function of the gills, which are not only a respiratory organ, but also affect the circulation of fluids and osmotic pressure in the body.

Unlike saponins, their sapogenins are, as a rule, crystalline substances with a clear melting point. Usually, they do not have haemolytic activity.

Pentacyclic triterpene saponins are very widespread in plants. According to the latest data, they are found in 70 families, wherein their content is typical for 150 genera. The largest number of triterpene genera is found in the following families: *Fabaceae*, *Sapotaceae*, *Caryophyllaceae*, *Asteraceae*, *Primulaceae*, *Polygalaceae*, *Chenopodiaceae*, *Apiaceae*, and *Lamiaceae*, etc. (Moses *et al.* 2014).

Considering the fact that triterpene glycosides are found in almost all plant organs, it can be assumed that they have a significant role in their vital activities. Some low concentrations of these saponins have been found to accelerate seed germination, as well as the growth and development of plants, while concentrated solutions retain germination, that is, their effect is similar to that of a growth hormone. Although they are, as already mentioned, found in all plant organs, it is essential to note that the largest amounts are found in underground organs. Their content will be up to 20% in dry matter. They are soluble in cell sap. When the triterpene saponins content is higher, they can be seen under a microscope. It is important to note that the starch content decreases with the accumulation of saponin. There is a broad range of pharmacological effects from triterpene saponins, which can be used to treat various diseases, but their emulsifying properties are also widely used for the stabilization of various dispersion systems (emulsions, suspensions).

Antraglycosides are a distinct group of compounds in which the aglycone is an aromatic compound from the quinone group. Depending on the number of rings, these include the following:

- Benzoquinones
- Naphthoquinones
- Anthraquinones
- Phenanthrenhinones

Only one simple benzoquinone-2,6-dimethoxybenzoquinone is found in higher plants, which is also present in some representatives of the *Ranunculaceae*, *Simarubaceae*, and *Meliaceae* families. Benzoquinones, which are complex structures with various substituents, are found in some fungi and lichens. Naphthoquinones are found in plants from the following families: *Juglandaceae*, *Plumbaginaceae*, and *Droseraceae*.

Natural anthraquinones are products of anthracene. Anthraquinones are a very broad group of natural compounds due to their variety and number of substituents.

Phenanthrenhinone derivatives are also found in a number of representatives of higher and lower plants. Quinones are prone to condensation, which causes the formation of very complex natural compounds. Anthraquinone derivatives and their breakdown products, anthron and anthranol, are widespread in plants. They are most commonly found in plants of the following families: *Rubiaceae*, *Rhamnaceae*, *Polygonaceae*, *Fabaceae*, and *Lilliaceae*.

There are different opinions on the role of anthracene products in plants. Some researchers think that oxymethylanthraquinones protect plants from parasites. Others think that they encourage the accumulation of polysaccharides. It is likely that anthraquinones play an important role in the oxidation reduction processes. Antraglycosides are very soluble in water, ethanol, and methanol, and almost all are insoluble in other solvents. In this regard, they are isolated from the plant material by extraction with water in an aqueous alkaloid solution, or methanol. Enzymatic or acid hydrolysis is used to obtain the aglycone, after which the anthraquinones are isolated by ether or chloroform.

Bitter substances in plants belong to glycosides due to their nature. Compared to other glycosides, they are the least studied. Many glycosides in this group have empirical names (taraxacin, meniantin, etc.) that are more indicative of their origin than their chemical nature. The bitter substances belonging to glycosides do not have clearly defined general properties, and many have a bitter taste (e.g. quinine, strychnine), specific activity, and high toxicity.

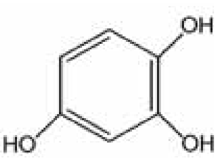
C-glycosides are found in nature and belong exclusively to the class of flavones. They are most commonly found in these four families: *Rosaceae*, *Saxifragaceae*, *Crassulaceae*, and *Fabaceae*.

N-glycosides are products of glycosoamines. Since the amino group (NH_2) has two hydrogen atoms, there are two types of N-glycosides: 1-substituted glycosylamine and 2-substituted glycosylamine. N-glycosides with a complex structure have antibiotic properties.

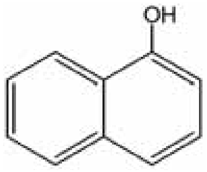
S-glycosides typically have a complex aglycone structure, which degrades into its components upon hydrolysis. For example, the mustard aglycone thioglycoside consists of p-oxybenzylisothiocyanate, bisulphate choline, and sinapic acid.

PHENOLIC COMPOUNDS AND THEIR GLYCOSIDES

The term phenol is used to refer to compounds containing a six-membered aromatic ring on which a hydroxyl group (OH) is directly bound to the aromatic nucleus; therefore, its empirical formula is C_6H_5OH. The molecule consists of a phenyl group ($-C_6H_5$) bound to a hydroxyl group (-OH). According to the IUPAC classification, phenols are compounds in which the OH group is directly bound to the aromatic nucleus. It is produced in large amounts (about 7 billion kg/year), because it is used as a precursor for the production of many chemical compounds (Kütt *et al*. 2008). According to the IUPAC nomenclature, the hydroxy derivatives of benzene and other aromatic carbocyclic systems are named by adding the suffixes -ol, -diol, and -triol, etc. to the name of the hydrocarbon.

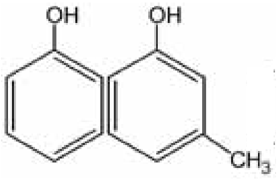


Formula 1-101: 1,2,4-benzenetriol

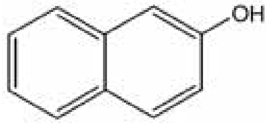


Formula 1-102: 1-naphthalenol

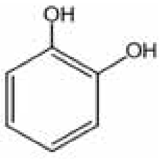
Some trivial names have been kept:



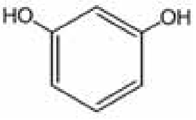
Formula 1-103: Phenol m-kresol



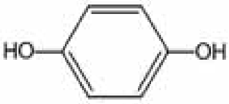
Formula 1-104: 2-naphthol



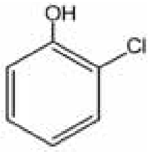
Formula 1-105: Pyrokatechol



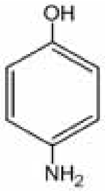
Formula 1-106: Resorcinol



Formula 1-107: Hydrochinon



Formula 1-108: o-chlorophenol

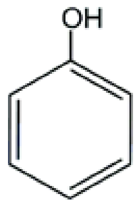


Formula 1-109: p-aminophenol

Phenols are divided into a number of hydroxyl groups:

- Monohydroxy phenols
- Dihydroxy phenols
- Polyhydroxy phenols

Table 1-46: The physical and chemical properties of phenol

IUPAC name	**Phenol**	 Formula 1-110: Phenol
CAS number	108-95-2	
Molecular formula	C_6H_6O	
Molecular weight	94.11 g/mol	
Density	1.07 g/cm^3	
Melting point	40.5 ^{0}C	
Boiling point	181.7 ^{0}C	
Solubility in water	8.3 g/100 ml (20 ^{0}C)	

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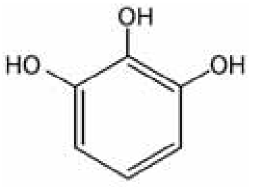
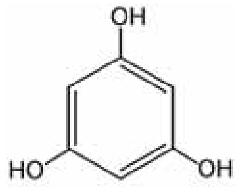
Pure phenols are clear liquids or solids with a low melting point but a fairly high boiling point. Phenol is soluble in water (9 g in 100 g of water at 25^{0}C) mainly due to the hydrogen bonds it builds with the water. Phenols are colourless unless certain colour groups are present. However, they are easily oxidized; therefore, unless they are well purified, most phenols are reddish in colour, which comes from their oxidized products. Oxidation of phenol by air or another oxidizing agent produces a mixture of oxidation products. Quinone is one of the products of phenol oxidation with air. The most significant representatives of trihydroxy phenols are as follows:

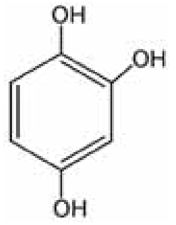
- Pyrogallol (1,2,3-trihydroxybenzene, vicinal trihydroxybenzene)
- P{hloroglucin (1,3,5-trihydroxybenzene, sim-trihydroxybenzene)
- Oxy-hydroquinone (1,3,4-trihydroxybenzene, unisim trihydroxybenzene)



Formula 1-111: Pyrogallol



Formula 1-112: Phloroglucin



Formula 1-113: Oxyhydrochinon

Phenol is slightly acidic. The molecule has a slight tendency to release H$^+$ from a hydroxyl group, thereby forming a phenolic anion $C_6H_5O^-$(phenoxide), which is very soluble in water (Michael and Jerry, 2007). Phenol is about a million times more acidic than aliphatic alcohols, but it is less acidic than carboxylic acids, such as carbonic acid.

Phenolic compounds and their derivatives comprise many substances which contain a hydroxyl group in the aromatic ring. Phenolic compounds which have more than one hydroxyl group in the aromatic ring are called polyphenols.

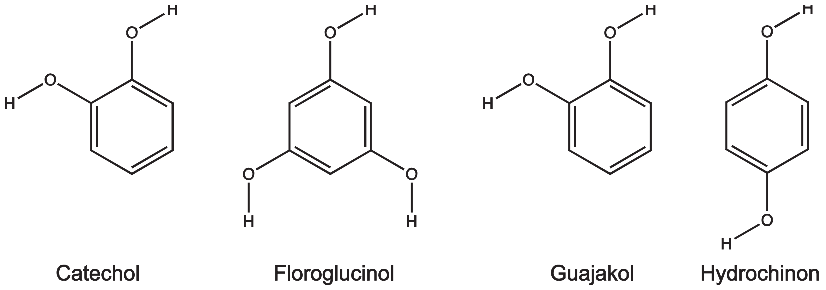
For a while, polyphenols were regarded as end products of plant metabolism. Today, polyphenols are considered to be active metabolites of cell transport and they play multiple roles in various physiological processes-photosynthesis, respiration, growth, and resistance to infections. The biological importance of polyphenols is inferred from their distribution in the plant organism (Teplova *et al*. 2018). First of all, the largest number of polyphenols is found in the functional organs—leaves, flowers, fruit, and covering tissues—which all have a protective function. Different organs and tissues contain not only different amounts of polyphenols, but also polyphenols with a different composition.

The following may occur as aglycones:

- Simple phenols
- Phenolcarboxylic acids

Phenols are most commonly found in nature as catechol, phloroglucinol, and hydroquinone derivatives. Phenolcarboxylic acids (phenolic acids) are compounds that contain at least one carboxylic and one phenolic hydroxyl group. They are biosynthesised from acetate via shikimic acid. In practice, the term, phenolcarboxylic acids, includes two types of metabolites:

- Benzoic acid derivatives (C_6-C_1)
- Cinnamic acid derivatives (C_6-C_3)



Scheme 1-19: Simple phenols

Simple phenols inhibit certain enzymatic reactions (lipid peroxidase) and can, therefore, be used as preservatives and antioxidants. They are used in liver function disorders. According to their chemical structure, all phenolic compounds can be classified into three main groups:

- With one aromatic ring
- With two aromatic rings
- Polymeric compounds

Phenolic compounds with one aromatic ring include:

- Dioxy- and trioxybenzenes and their products (simple phenols)
- Phenolacids, phenolalcohols, acetophenols, and phenolsacetic acid
- Lignans
- Coumarins and hormones

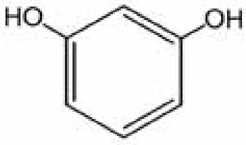
Simple phenols are rarely found in plants. Phenol has been found in pine needles and cones (*Pinus silvestris*), as well as essential oils from *Nicotiana tabacum* and *Ribes nigrum*. Pyrocatechin, which belongs to this group of phenols (1,2-dioxybenzene), is found in onion leaves and grapefruit. Hydroquinone (1,4-dioxybenzene) is also widespread. Glycoside arbutin is found in the following families: *Ericaceae*, *Vacciniaceae*, *Rosaceae*, *Saxifragaceae*, and *Asteraceae*. Arbutin is found in larger amounts in some plants. Hydroquinone's methyl and ethyl esters are found in plants from the following families: *Pyrolaceae*, *Liliaceae*, and *Magnoliaceae*, etc.

Phenolic acids are widespread in plants (Maqsood *et al.* 2014). Salicylic acid and its methyl ester are part of the essential oils from *Gaultheria procumbens*, *Viola tricolor*, and *Betula lenta*, etc. Some plants contain phenolic acids with an unusual arrangement of hydroxyl groups. For example, *Primula officinalis* contains 2-oxy-6-methoxy and 3,5-dioxybenzoic acid, and *Calchicum autumnale* contains 2-oxy-6-methoxybenzoic acid. Phenol-alcohols, acetophenols, and phenyl-acetic acid are also found in some plants. Acetophenol is characteristic of *Paeonia* (*Ranunculaceae*), and has also been found in plants from the *Lilliaceae* family.

Resorcinol

Resorcinol (E 103, 1,3-dihydroxybenzene, and m-hydroxyphenol) $C_6H_4(OH)_2$ is an organic compound from the phenol group, which has two hydroxyl groups bound to a benzene ring in the meta-position.

Table 1-47: Physical and chemical properties of resorcinol

Molecular formula	$C_6H_4(OH)_2$	 Formula 1-114: Resorcinol
CAS number	108-46-3	
Molecular weight	110.11 g/mol	

https://pubchem.ncbi.nlm.nih.gov/

It is widely used as a substrate in the organic synthesis and production of synthetic resins and formaldehyde.

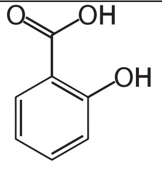
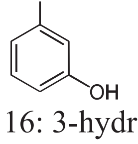
Phenolic acids

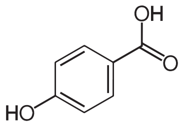
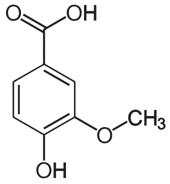
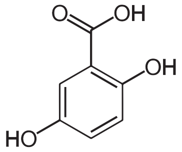
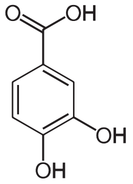
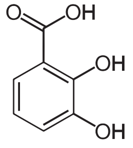
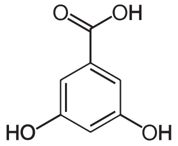
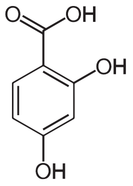
Phenolic acids or phenocarboxylic acids are types of organic compounds containing a phenolic ring and an organic carboxyl group (Golenniowski *et al*. 2013). There are several categories of phenolic acids:

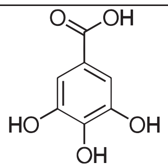
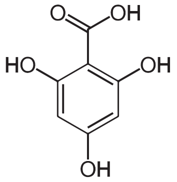
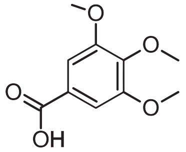
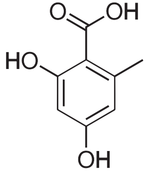
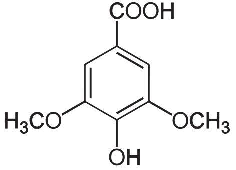
- Monohydroxybenzoic acid [2-hydroxybenzoic acid (salicylic acid), 3-hydroxybenzoic acid, and 4-hydroxybenzoic acid]
- Dihydroxybenzoic acid [4-hydroxy-3-methoxybenzoic acid (vanillic acid), 2,5-dihydroxybenzoic acid (gentisic acid), and *3,4-dihydroxybenzoic acid*]
- Trihydroxybenzoic acid [3,4,5-trihydroxybenzoic acid (gallic acid), 2,4,6-trihydroxybenzoic acid, 4-hydroxy-3,5-dimethoxybenzoic acid (Syringic acid), and 3,4,5-trimethoxybenzoic acid]

Phenolic acids can be found in small amounts in different parts of many plants, especially their fruits.

Table 1-48: Physical and chemical properties of phenolic acids

Structural formula and IUPAC name	**CAS number**	**Molecular formula**	**Molecular weight**
Monohydroxybenzoic acids			
 Formula 1-115: 2-hydroxybenzoic acid (Salicyl acid)	69-72-7	$C_7H_6O_3$	138.12 g/mol
 Formula 1-116: 3-hydroxybenzoic acid	99-06-9	$C_7H_6O_3$	138.12 g/mol

 Formula 1-117: 4-hydroxybenzoic acid (p-hydroxybenzoic acid)	99-96-7	$C_7H_6O_3$	138.12 g/mol
Dihydroxybenzoic acids			
 Formula 1-118: 4-hydroxy-3-methoxybenzoic acid	121-34-6	$C_8H_7O_4$	167.14 g/mol
 Formula 1-119: 2,5-dihydroxybenzoic acid	490-79-9	$C_7H_6O_4$	154.12 g/mol
 Formula 1-120: 3,4-dihydroxybenzoic acid	99-50-3	$C_7H_6O_4$	154.12 g/mol
 Formula 1-121: 2,3-dihydroxybenzoic acid	303-38-8	$C_7H_6O_4$	154.12 g/mol
 Formula 1-122: 3,5-dihydroxybenzoic acid	99-10-5	$C_7H_6O_4$	154.12 g/mol
 Formula 1-123: 2,4-dihydroxybenzoic acid	89-86-1	$C_7H_6O_4$	154.12 g/mol

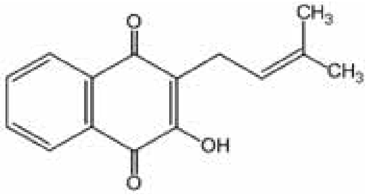
Trihydroxybenzoic acids			
 Formula 1-124: 3,4,5-trihydroxybenzoic acid	149-91-7	$C_7H_6O_5$	170.12 g/mol
 Formula 1-125: 2,4,6-trihydroxybenzoic acid	83-30-7	$C_7H_6O_5$	170.11954 g/mol
 Formula 1-126: 3,4,5-trimethoxybenzoic acid	118-41-2	$C_{10}H_{12}O_5$	212.20 g/mol
 Formula 1-127: 2,4-dihydroxy-6-methylbenzoic acid	480-64-8	$C_8H_8O_4$	168.15 g/mol
 Formula 1-128: 4-hydroxy-3,5-dimethoxybenzoic acid	530-57-4	$C_9H_{10}O_5$	198.17 g/mol

https://pubchem.ncbi.nlm.nih.gov/

Lapachol

Lapachol is naphthoquinone, which was isolated from *Tabebuia avellanedae* (Bibnoniaceae) in 1982. It is also found in plants from other families: *Verbenaceae*, *Proteaceae*, *Papilionaceae*, *Sapotaceae*, *Scrophuriaceae*, and *Mavaceae* (Hussain et al. 2007), as well as in many vegetable plants from the Bignoniaceae family, especially those from the *Tebubuia* genus (Nepomuceno, 2014). It is actually a derivative of vitamin K (Louis, 1964). Bark powder irritates the skin.

Table 1-49: Physical and chemical properties of lapachol

CAS number	84-79-7	 Formula 1-129: Lapachol
EC number	201-563-7	
Molecular formula	$C_{15}H_{14}O_3$	
Molecular weight	242.27	

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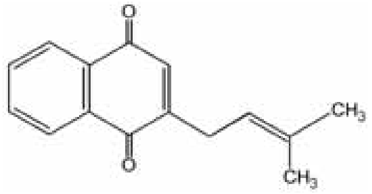
Deoxylapachol

Deoxylapachol was first isolated from *Tectona grandis. Tectona grandis* is a tropical woody plant from the *Verbenaceae* family. This is a deciduous tree that grows in mixed forests. It is especially appreciated for its durability; therefore, it is used for making boats, furniture veneers, and carving. It originates from South and Southeast Asia. It is grown in many countries in Africa and the Caribbean. The state of Myanmar meets almost half of the world's need for teakwood.

Deoxylapachol is found in the timber of *Tectona grandis* in high concentrations between 0.1 to 0.5 % (Anon., 2012). Data exists about skin inflammation of the face, hands, and genital region caused by working with teakwood (Burry *et al.* 1973; Gan *et al.* 1987). Of the 112 individuals exposed to *Tectona grandis*, 35 had contact dermatitis and 16 did not have any symptoms on the skin (Anon., 2012).

Table 1-50: Physical and chemical properties of deoxylapachol

CAS number	3568-90-9	 Formula 1-130: Deoxylapachol
Molecular formula	$C_{15}H_{14}O_2$	
Molecular weight	226.2705	

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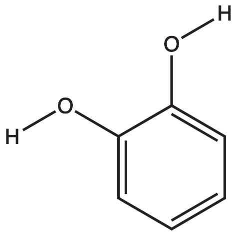
Catechol

Catechol is also known as pyrocatechol or 1,2-dihydroxbenzene. It is the ortho isomer of the three benzenediol isomers. Today, huge amounts (about 20 million kg) are synthesised worldwide for the chemical industry. Edgar Hugo Emil Reinsch first isolated catechol by distillation from the *Acacia catechu* plant. In the industry, it is produced by the hydroxylation of phenol with hydrogen peroxide: $C_6H_5OH+H_2O_2 \rightarrow C_6H_4(OH)_2+H_2O$

Table 1-51: Physical and chemical properties of catechol

CAS number	120-80-9	 Formula 1-131: Catechol
EC number	204-427-5	
Molecular formula	$C_6H_6O_2$	
Molecular weight	110,1 g/mol	
Density	1.344 g/cm^3	
Melting point	105 ^{0}C	
Boiling point	245.5 ^{0}C	
Solubility in water	430 g/L	
Vapour pressure	20 Pa (20 ^{0}C)	

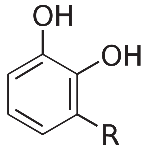
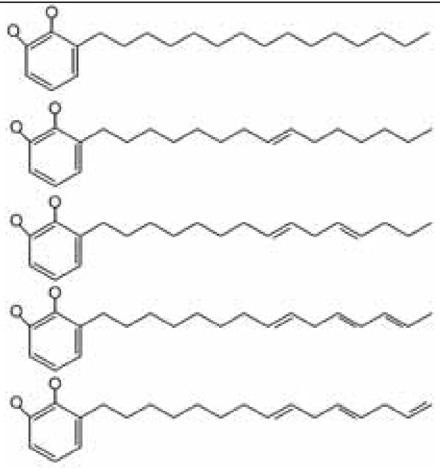
https://pubchem.ncbi.nlm.nih.gov/

Small amounts of catechol are found in fruits and vegetables, along with small amounts of the polyphenol oxidase enzyme (also known as catecholases or catechol oxidases). About 50% of catechol is used in the pesticide industry and the rest in the pharmaceutical and perfumery industries (Fiegel, 2002). Catechol is widespread in nature. It is bound to protein in chitin in arthropods. Catechol is produced in the metabolism of cholesterol in some bacteria, such as *Mycobacterium tuberculosis*. Urushiol is a natural compound that has catechol and diphenol in its structure, with an alkyl group substituted on the aromatic ring.

Urushiol

Urushiol is an organic allergen found in plants from the *Anacardiaceae* family, especially in plants from the *Toxicodendron* spp. genus (Cruse and Robert, 2010). In people sensitive to irritation, urushiol causes skin lesions known as urushiol-induced contact dermatitis. The name urushiol comes from the Japanese word, because they call the Toxicodendron vernicifluum tree “urushi”. The urushiol from the sap becomes strong lacquer through oxidation and polymerization in the presence of humidity; this is a traditional Chinese, Korean, and Japanese product. Urushiol is pale yellow liquid with a specific weight of 0.968 and boiling point of 200^{0}C. The alkyl group can be saturated and unsaturated. Therefore, the exact composition of urushiol depends on the type of plant. Some plants have 17 carbon atoms, while others have 15 in the side chains. The severity of the allergic reaction also depends on the alkyl chain’s degree of unsaturation. Urushiol with longer chains causes more severe allergic reaction (McGovern and Barkley, 1998). Urushiol is absorbed in 10 minutes. Immediately after coming into contact with the skin, urushiol can be removed with water and soap but, after it penetrates the skin, rinsing with water will be ineffective (McGovern and Barkley, 1998).

Table 1-52: Physical and chemical properties of urushiol

 Formula 1-132: Urushiol	R= $(CH_2)_{14}CH_3$ or R= $(CH_2)_7CH=CH(CH_2)_5CH_3$ or R= $(CH_2)_7CH=CHCH_2CH=CH(CH_2)2CH_3$ or R= $(CH_2)_7CH=CHCH_2CH=CHCH=CHCH_3$ or R= $(CH_2)_7CH=CHCH_2CH=CHCH_2CH=CH_2$	 Formula 1-133

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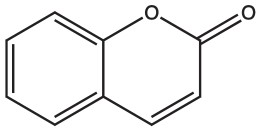
COUMARINS AND COUMARIN HETEROSIDES

Coumarin was first isolated in 1820 from the seeds of *Dipteryx odorata* (syn. *Coumarouna odorata, Tonquino beans*,) *Fabaceae*. Coumarin is a chemical compound with a benzopyran base that gives many plants their aroma. It is found in high concentrations in *Dipteryx odorata*, *Anthoxanthum odoratum*, *Galium odoratum*, *Verbascum* spp., *Hierochloe odorata*, and *Cinnamomum aromaticum* (Matos *et al.* 2015*)*. It has a pleasant smell, which is easily recognisable as being reminiscent of mowed hay, and it has been used in perfumes since 1882. It has also been used to enhance pipe tobacco and some alcoholic beverages. Coumarin acts as a bitter appetite suppressant for animals when it occurs in high concentrations in fodder.

Table 1-53: The physical and chemical properties of coumarin

CAS number	91-64-5	 Formula 1-134: Coumarin
Molecular formula	$C_9H_6O_2$	
Molecular weight	146.14 g/mol	
Density	0,935 g/cm^3	
Melting point	71 ^{0}C	
Boiling point	301 ^{0}C	

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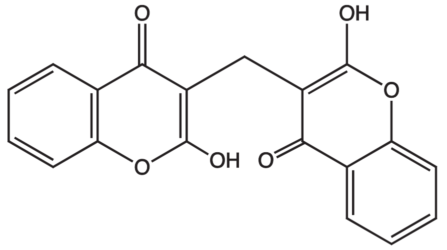
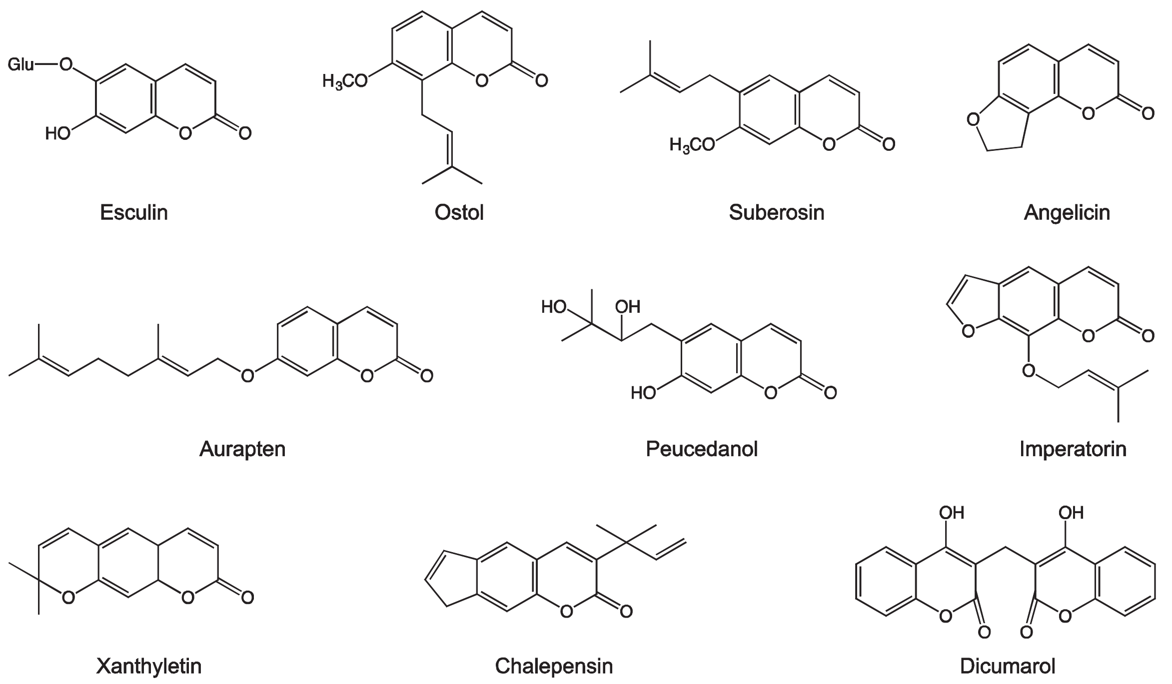
Dicoumarol is a natural chemical substance, which is a coumarin derivative, with a bitter taste. It affects blood coagulation, and it was detected in hay made from moist clover. It has been used in medicine as an anticoagulant drug since 1950. It has been used with heparin to treat venous thrombosis (Duff and Shull, 1949; Wardrop and Keeling, 2008).

Table 1-54: Physical and chemical properties of dicoumarol

CAS number	66-76-2	 Formula 1-135: Dicoumarol
Metabolism	Liver	
Excretion	Faeces, urine	



Scheme 1-20: Examples of various types of coumarin (simple, heterocyclic, and dicoumarine)

Coumarins are divided into the following:

- Simple coumarins
- Complex coumarins

Simple coumarins differ from each other in the C-6, C-7, and C-8 positions, which are most commonly hydroxy and methoxy groups. Complex coumarins are divided into the following:

- Furocoumarins
- Pyranocoumarins

Like most other phenylpropionic compounds, coumarins are also formed from phenylalanine via cinnamic and p-coumaric acid. The following may be present in plant tissue:

- Heterosides of o-hydroxy-Z(E)-cinnamic acid
- Coumarin heterosides
- Free coumarins

Coumarins are formed from the hydroxy-cinnamic acid heterosides during the drying process (the process is accompanied by the smell of mown hay).

Simple coumarins differ in their substituents, which are most often hydroxyl and methoxy groups. For this reason, they are called hydroxy- or methoxycoumarins.

Dicoumarins are formed by binding two coumarin molecules with a methylene bridge. This bond is formed during the fermentation process, but only under the following specific conditions:

- In the presence of microorganisms
- When the plant mass is moist

The most famous compound in this structure is dicoumarol (4-hydroxy coumarin), which was isolated from mouldy hay.

Coumarins are widespread in the plant world. So far, over 1,000 different coumarin structures have been isolated. Simple coumarins are mostly found in plants from the *Asteraceae* and *Fabaceae* families, while heterocyclic coumarins are found in plants from the *Rutaceae* and *Apiaceae* families. Both free coumarins and coumarin heterosides are distributed in all of the plant's aboveground and underground organs. It is believed that coumarins play a dual role in plants:

- Protection from microorganisms (phytoalexins)
- Protection from ultraviolet radiation

Coumarins are easily dissolved in water. They have a specific smell. They absorb UV radiation, reduce the permeability of the capillary walls and lymphatic vessels, reduce the exudation and onset of oedema, intensify glomerular filtration, and act as diuretics. Dicoumarol prevents blood coagulation. Coumarins are used as diuretics, in sunscreen preparations, rodent suppressants, and in the cosmetic, food, tobacco, and liquor industries.

Coumarins are natural compounds that have a coumarin ring as the base (benzo - α - pyrone). Simple coumarin and furocoumarin derivatives are most often found in plants. They are usually found in the form of free compounds, but may sometimes be in the form of glycosides. Their amount in plants varies within a wide range of 0.2 to 10%. Some species may sometimes contain 5–10 coumarins with different structures. These constituents accumulate most often in the root, bark, and fruit, and less often in leaves and stems.

The qualitative and quantitative composition of coumarin varies within different species from the same genus. Coumarin composition also changes during the ontogeny of plants.

Some things in the biosynthesis of coumarin have not yet been clarified. The basis of coumarin formation is the synthesis of shikimic acid, which first forms oxycoumaric acid and then the coumarin nucleus after hydroxylation and lactonization. Coumaric acid in its pure form has not been found in plants.

The role of coumarin in the body of plants is not yet fully understood. It is certain that some of them are growth inhibitors, others are stimulators, while some protect from some diseases and ultraviolet radiation.

Coumarins and furocoumarins are toxic to fish. They have a narcotic effect on worms and rabbits, and sedative and hypnotic effects on mice. Coumarin and amino-alkaline substituents stimulate the central nervous system. Photosensitizing activity and the bacteriostatic and fungistatic effects of coumarin are also known.

Hormones are phenolic compounds that are similar in structure to coumarins and flavonoids. They can condense with a furan ring to form furanchromones. Oxychromones and oxyfuranchromones are usually found in nature.

Flavonoids are a large group of natural compounds within phenolic compounds with two aromatic rings. Depending on the structure, there are 10 groups of flavonoids: catenins, laucoanthocyanides, anthocyanides, flavanones, flavanonols, flavones, chalcones, and dehydrochalcones. Flavonoids are widespread in plants. They accumulate in all plant organs, most often in the form of glycosides.

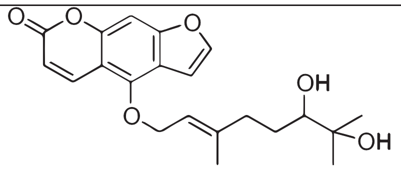
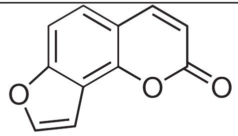
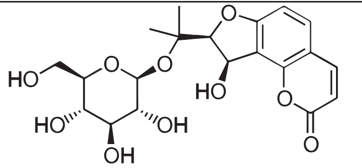
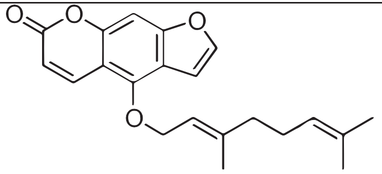
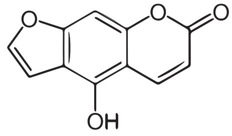
Dipteryx odorata (or tonquin beans, tonka beans, which are commonly known as "cumaru" or "kumaru") is a perennial woody plant of the *Fabaceae* family. This family belongs to the *Rosids* class and the *Fabales* order. The word "tonka" is taken from the Caribbean language, which is spoken by natives of French Guiana. It originates from Central, North, and South America (Jang *et al*. 2003). As with other plants in this family, the fruit is a pod, and there is one seed in each pod. The pods are black and have a wrinkled surface, as well as a strong smell similar to *Galium odoratum*, due to the high content of coumarin. The yield per stem is about 1.0–3.5 kg/year. The plant grows 25–30 m in height and up to 1 m in the diameter of the stem. It is pollinated by insects. Its main pests are bats, as they like to eat its fruit.

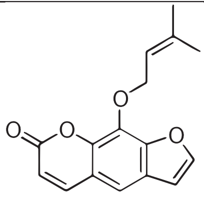
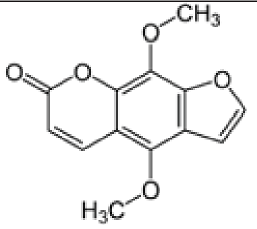
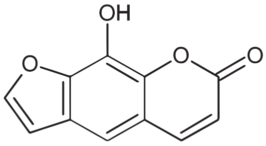
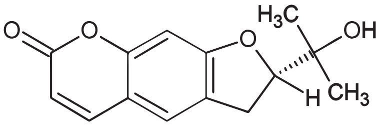
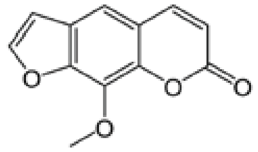
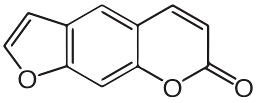
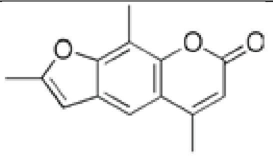
Coumarin was first chemically isolated from the plant after which it was named. The seeds contain 1 to 3% of coumarin (James and du Cellier, 1993). Because of its pleasant scent, it is used in the perfume industry. Today, the main producers of this plant are Venezuela, Nigeria, Brazil, and Colombia, and the main importer is the USA, where it is used in the tobacco industry (Duke and du Cellier, 1993).

Furanocoumarins

Furanocoumarins include 6',7'-dihydroxybergamottin, angelicin, apterin, bergamottin, bergapten, bergaptol, imperatorin, isopimpinellin, xanthotoxol, marmesin, methoxsalen, psoralen, and trioxsalen.

Table 1-55: Physical and chemical properties of some furanocoumarins

 Formula 1-136	6',7'-Dihydroxybergamottin	
	CAS number	145414-76-2
	Molecular formula	$C_{21}H_{24}O_6$
	Molecular weight	372.41 g/mol
 Formula 1-137	Angelicin	
	CAS number	523-50-2
	Molecular formula	$C_{11}H_6O_3$
	Molecular weight	186.16 g/mol
 Formula 1-138	Apterin	
	CAS number	53947-89-0
	Molecular formula	$C_{20}H_{24}O_{10}$
	Molecular weight	424.4 g/mol
 Formula 1-139	Bergamottin	
	CAS number	7380-40-7
	Molecular formula	$C_{21}H_{22}O_4$
	Molecular weight	338.4 g/mol
 Formula 1-140	Bergaptol	
	CAS number	486-60-2
	Molecular formula	$C_{11}H_6O_4$
	Molecular weight	202.16 g/mol

 Formula 1-141	Imperatorin	
	CAS number	482-44-0
	Molecular formula	$C_{16}H_{14}O_{4}$
	Molecular weight	270.28 g/mol
 Formula 1-142	Isopimpinellin	
	CAS number	482-27-9
	Molecular formula	$C_{13}H_{10}O_{5}$
	Molecular weight	246.27 g/mol
 Formula 1-143	Xanthotoxol	
	CAS number	2009-24-7
	Molecular formula	$C_{11}H_{6}O_{4}$
	Molecular weight	202.16 g/mol
 Formula 1-144	Marmesin	
	CAS number	13849-08-6
	Molecular formula	$C_{14}H_{14}O_{4}$
	Molecular weight	246.26 g/mol
 Formula 1-145	Methoxsalen	
	CAS number	298-81-7
	Molecular formula	$C_{12}H_{8}O_{4}$
	Molecular weight	216.190 g/mol
 Formula 1-146.	Psoralen	
	CAS number	66-97-7
	Molecular formula	$C_{11}H_{6}O_{3}$
	Molecular weight	186.16 g/mol
 Formula 1-147	Trioxsalen	
	CAS number	3902-71-4
	Molecular formula	$C_{14}H_{12}O_{3}$
	Molecular weight	228.24 g/mol
	Boiling point	234.5 ^{0}C

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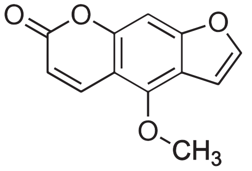
Furocoumarins are natural products found in plants and are thought to act as a defence against fungal attacks. Fresh celery (*Apium graveolens*) contains between 10 and 100 mg/g of psoralen in a healthy plant, and about 320 mg/g in a plant infected by *Sclerotina sclerotium* (Afek, 2000). Resistant species of celery produce large amounts of furocoumarins in leaves and stems. It has been found that infected plants induce greater amounts of furocoumarins. Furocoumarins are tricyclic components formed by linking furan rings in positions 1' to 5' with bicyclic benz-α-pyrone to form two linear products: psoralen and angelicin or isopsoralen (Pathak, 1986; Lovell, 1993; Kavli and Volden, 1984). Thus, there are two forms of furanocoumarins in nature. In a molecule's linear form, 3'2' furan is bound to 6,7 coumarin. The 3'2' bond can also be at 7,8 coumarin, thereby producing angular furocoumarins. Linear furocoumarins (psoralen) are more phytotoxic than angular furocoumarins (angelicin). An exception is the angular furocoumarin known as pimpinellin, which is found in plants from the *Heracleum* genus. The most reactive are 5-methoxypsoralen (5-MOP, bergapten), which is isolated from *Citrus bergamia* (*Rutaceae*), and 8-MOP (xanthotoxin), which is isolated from *Fagara xannthoxyloides* (*Rutaceae*). Psoralen is more phototoxic than 8-MOP and 5-MOP (Pathak, 1986; Lovell, 1993).

The phototoxic effect of furocoumarins is based on their absorption of photons. After the formation of short-lived, high-energy states, energy is released, which causes subsequent damage (Kavli and Volden, 1984). Psoralen has maximum absorbance at 300 nm and a maximum action spectrum at 335 nm (Kavli and Volden, 1984). In oxygen-dependent reactions, ultraviolet light excites psoralen to the triplet state, which then causes the psoralen molecule to bind to the DNA molecule. A monofunctional bond is then formed between 4 '5' furan or 3,4 double bond and 5,6 bond with pyrimidine (cytosine or thymidine). When the 4'5' bond with furan is formed, the resulting product is bifunctional and can form cross-links between the pyrimidine bases. Such changes can induce mutations, inhibit DNA synthesis and cell proliferation, and stimulate melanogenesis.

Bergapten

Bergapten (5-methoxypsoralen) is a naturally occurring substance found in the essential oils of various plants, such as bergamot oil and oil from *Citrus* genus' plants (*Calvaranoi et al. 1995*). It was first synthesised in 1937 by the condensation of 3,4,6-triacetoxy coumarin with ethyl sodium formyl acetate, followed by the methylation of the obtained product. It has been found in anise oil. It is the main ingredient in bergamot oil (*Citrus bergamia*). It is present in celery, especially in the outer leaves and other vegetables. It belongs to the group of psoralens, which are also known as furocoumarins. These are polycyclic aromatic components that contain a furan ring linked to coumarin. Bergapten, like other linear furocoumarins of the psoralen type, damages sensitive skin in the sun and ultraviolet radiation (Francesco *et al.* 2004). It exhibits a high degree of binding to serum proteins and is almost 98–99% protein bound. It causes erythema, dermatitis, and mild hyperpigmentation on the face and neck. It can also cause phototoxic reactions on the skin. Symptoms include extreme destruction of the mucous membranes and upper respiratory tract, eyes, and skin; photosensitization; a burning sensation; coughing; sneezing; laryngitis; and shortness of breath. Other symptoms include headache, nervousness, insomnia, itching, arousal, depression, hyperpigmentation, cataracts, liver damage, and nail pigmentation. In cases of bergapten activity, its effects should be first removed and eliminated, and then the eyes should be rinsed with water or saline solution for 20–30 minutes. It is used to treat psoriasis in combination with UVA. It is also produced synthetically for perfumes. It is practically insoluble in warm water. It is poorly soluble in glacial acetic acid, chloroform, benzene, and warm phenol. In absolute alcohol, it dissolves 1 part of alcohol into 60 parts (Budavari, 1989).

Table 1-56: Physical and chemical properties of bergapten

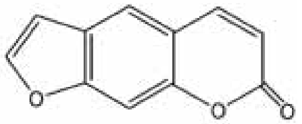
CAS number	484-20-8	 Formula 1-148: Bergapten
EC number	207-604-5	
Molecular formula	$C_{12}H_8O_4$	
Molecular weight	216.19 g/mol	
Melting point	188 ^{0}C (with sublimation)	

https://pubchem.ncbi.nlm.nih.gov/

Psoralen

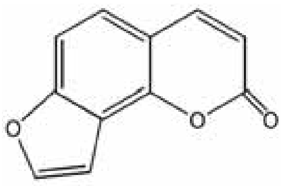
Psoralen is a representative of natural products known as furocoumarins. It is a compound structurally linked to coumarin by the binding of furan rings. It is found in the seeds of *Psoralea corylifolia*, as well as celery, parsley, figs, and citrus fruits. Psoralen is formed from coumarin on the shikimic acid pathway. Despite some of its undesirable properties, it is used in some creams because it increases the skin's sensitivity to sunlight. People with fair skin produce four times more psoralen than those with a darker tone (Zajdela and Bisagni, 1981; *Autieri et al. 1997*). It has been used as a sun protection activator since 1996. It is used in molecular biology research. The photochemical reaction centre in psoralen is localised on each carbon atom with double bonds in the furan ring. Another important property of this class of compounds is their ability to produce single oxygen. This process is in direct competition with an alternative pathway for the extraction of excited energy.

Table 1-57: Physical and chemical properties of psoralen

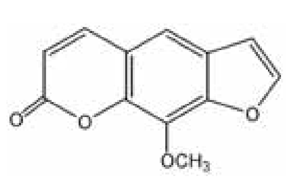
CAS number	66-97-7	 Formula 1-149: Psoralen
Molecular formula	$C_{11}H_6O_3$	
Molecular weight	186.16 g/mol	
Boiling point	158-161 ^{0}C	

https://pubchem.ncbi.nlm.nih.gov/

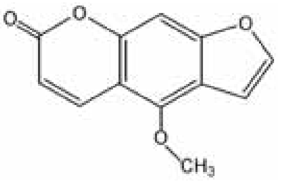
Angelicin is one of the psoralen isomers and so most furocoumarins are considered to be psoralen or angelicin derivatives. The most important psoralen derivatives are imperatorin, xanthotoxin, bergapten, and nodakenetin.

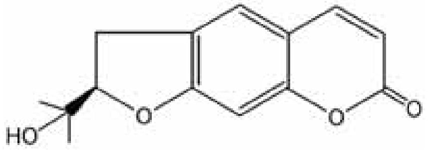


Formula 1-150: Angelicin



Formula 1-151: Xanthotoxin



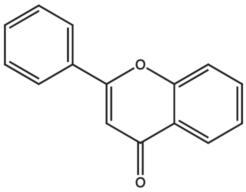


Formula 1-152: Bergapten Formula 1-153: Nodakenetin

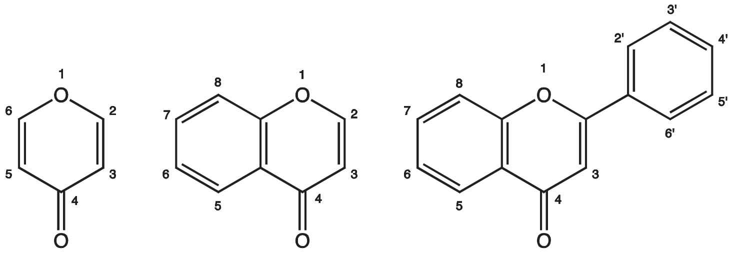
Ficus carica is probably the most widespread source of psoralen. In small amounts it can also be found in *Ammi visnaga*, *Pastinaca sativa*, *Petroselinum crispum*, *Levisticum officinale*, *Foeniculum vulgare*, *Daucus carota*, *Psoralea corylifolia*, and *Apium graveolens*.

FLAVONOIDS AND FLAVONOID HETEROSIDES

A flavonoid molecule is the aglycone component in these compounds. Kostanesku isolated the basic compound in 1895 and named it flavon (*flavus* means yellow in Latin), after a large group of chemically similar compounds. The basis of the aglycone molecule is ϒ-pyrone (pyranone-4), benzo-ϒ-pyrone (chromone), and 2-phenyl-benzo-ϒ-pyrone (flavon).



Formula 1-154: Flavon

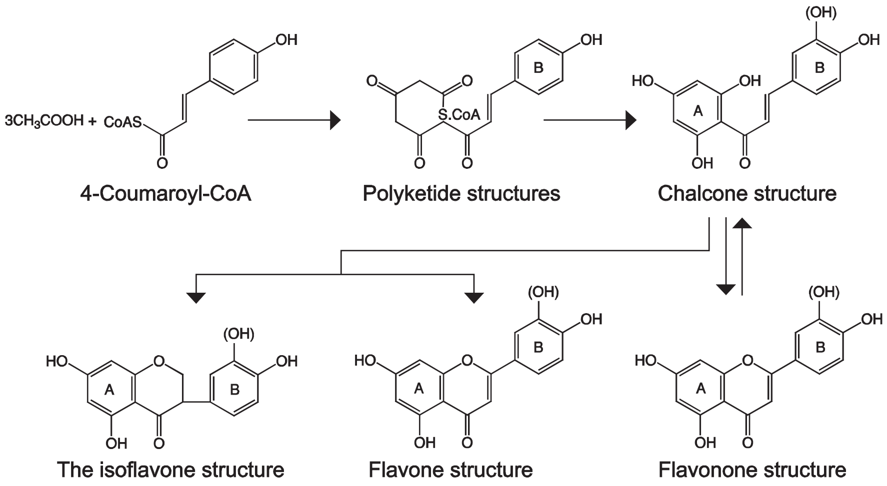


Scheme 1-21: Basis of the structure of the skeleton flavones aglycone

The basic structure of different types of flavonoid compounds is comprised of the following:

- 2-phenylchromones (true flavonoids)
- 2-phenylchromanes (tannin building blocks)
- 2-benzylidene coumarins (aurons)

The sugar residue of these compounds may contain one, two, or three monosaccharides, which are bound linearly or with branches. Most often, the glucoside bond is formed via phenolic groups of aglycones. It is almost a rule that flavones form 7-O-heterosides, and flavonols 3-O-heterosides (Sterner *et al.* 1980). Flavonoids often form C-heteroglycosides. The asymmetric C-atom of sugar is bound to the C_6 or C_8 aglycone.



Scheme 1-22: Biosynthetic origin of the different flavones molecules

There are several types of C-heterosides:

- Mono C-heterosides
- Di-C-heterosides
- Combined C-i O-heterosides
- Acyl-C-heterosides (sugar hydroxyl groups can be esterified by some aliphatic or aromatic acids).

Table 1-58: Plants rich in flavonoids (adapted from Mahajan and Chaudhari, 2012)

Plant organ or part	**Latin name (family)**
Japanese acacia buds	*Sophora japonica* (Fabaceae)
Black currant fruits	*Ribes nigrum* (Grossulariaceae)
Buckwheat leaves	*Fagopyrum esculentum* (Polygonaceae)
Birch leaves and buds	*Betula pendula* (Betulaceae)
Elder flowers	*Sambucus nigra* (Sambucaceae)
Blueberry fruits	*Vaccinium myrtillus* (Vacciniaceae)
Linden flowers	*Tila plathyphyllos* (Tiliaceae)
Grape fruits	*Vitis vinifera* (Vitaceae)
Ginkgo leaves	*Ginkgo biloba* (Ginkgoaceae)
Citrus fruit pericarp	*Citrus sp.* (Rutaceae)
Eucalyptus leaves	*Eucalyptus macrorryncha* (Myrtaceae)

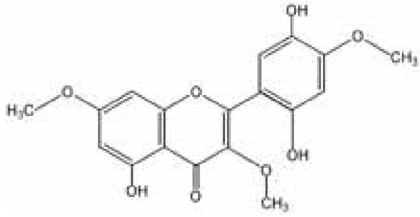
Flavonoid heterosides are soluble in water, alcohols, and polar solvents. Aglycones are lipophilic and soluble in non-polar solvents. Flavonoid heterosides can be extracted from plant tissue with diluted alcohol or acetone, at higher temperatures. Primary pharmacological activity is associated with their effects on the wall of peripheral blood vessels, as it reduces their permeability and increases the elasticity and intrinsic tone of the capillary wall. They are used in the treatment of various diseases caused by blood and lymphatic vessel insufficiency and peripheral circulation disorders.

Isoflavones and isoflavone heterosides. The basis of isoflavone aglycones is 3-phenyl-chromone. Compounds of this structure are widespread in nature, mainly in plants from the *Prunus* and *Iris* genera and some genera of the *Fabaceae* family (*Genista and Ononis*) (Szeja *et al.* 2017). To date, over 700 isoflavones have been identified. Isoflavones are found in plants in the form of O-and C-heterosides. Plants synthesise them when attacked by various fungal infections, which is why they are believed to have a phytoalexin nature. Experiments have shown that isoflavones can have estrogenic effects and cause infertility in animals. These effects were first observed in animals grazing on grasses rich in genistein and other isoflavones (*Genista tinctorum*). In addition, some compounds of the isoflavone structure are used as insecticides (rotenoids in *Derris*, *Lonchocarpus*, *Miletia*, *Mundulea*, *Tephrosia*, and *Fabaceae*).

Oxyayanin A and B

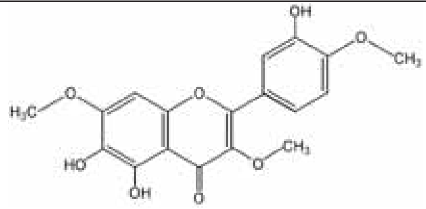
Oxyayanin A and B are formed as metabolites in a plant's metabolic reactions; this includes flowering plants and other gymnosperms. It is a trihydroxyflavone where a hydroxyl group at position 5, 2' and 5' and a methoxy group at the 3, 7 and 4 position are substituted in the flavone ring.

Table 1-59: Physical and chemical properties of oxyayanin A

CAS number	549-17-7	 Formula 1-155: Oxyayanin A
Molecular formula	$C_{18}H_{16}O_5$	
Molecular weight	360.318 g/mol	

https://pubchem.ncbi.nlm.nih.gov/

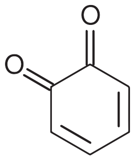
Table 1-60: Physical and chemical properties of oxyayanin B

CAS number	548-74-3	 Formula 1-156: Oxyayanin B
Molecular formula	$C_{18}H_{16}O_8$	
Molecular weight	360.318 g/mol	

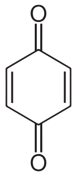
https://pubchem.ncbi.nlm.nih.gov/

QUINONES AND QUINONE HETEROSIDES

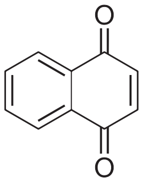
Quinones are organic compounds derived from aromatic compounds (benzene or naphthalene) by the conversion of CH groups to -C (=O), which requires the reorganization of double bonds (March, 1985). The prototype of this class of compounds is 1,4-benzoquinone or cyclohexadienedione, which are simply called quinones. Other significant quinones are benzoquinone (ortho-quinone), 1,4-naphthoquinone, and 9, 10- anthraquinone.



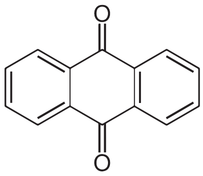
Formula 1-157: 1,4-benzoquinone



Formula 1-158: 1,4-benzoquinone



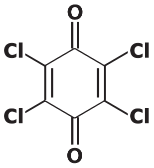
Formula 1-159: 1,4-Naphthoquinone



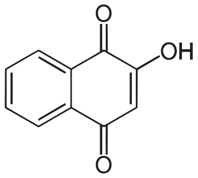
Formula 1-160: 9,10-Anthraquinone

Quinones are oxidised derivatives of aromatic compounds and are often formed from reactive aromatic compounds with substituents and electron donors, such as phenols and catechols, which then increase the nucleophilicity of the ring and thus contribute to the redox potential necessary for the termination of aromaticity. Depending on the quinone and the location, the reduction may re-aromatise or disrupt the conjugation. The addition of a conjugate always ends the conjugation. Quinone derivatives are biologically active compounds. Some are used as electron acceptors in the electron transport chain in the process of photosynthesis (plastoquinone, philoquinone) or in the process of aerobic respiration (ubiquinone). They are used in medicine, in the paint industry, and as oxidising reagents in organic chemistry.

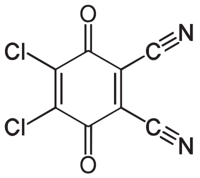
The term quinones is also used for a large class of compounds derived from aromatic quinones by substituting hydrogen atoms with other atoms or radicals.



Formula 1-161: Chloranil

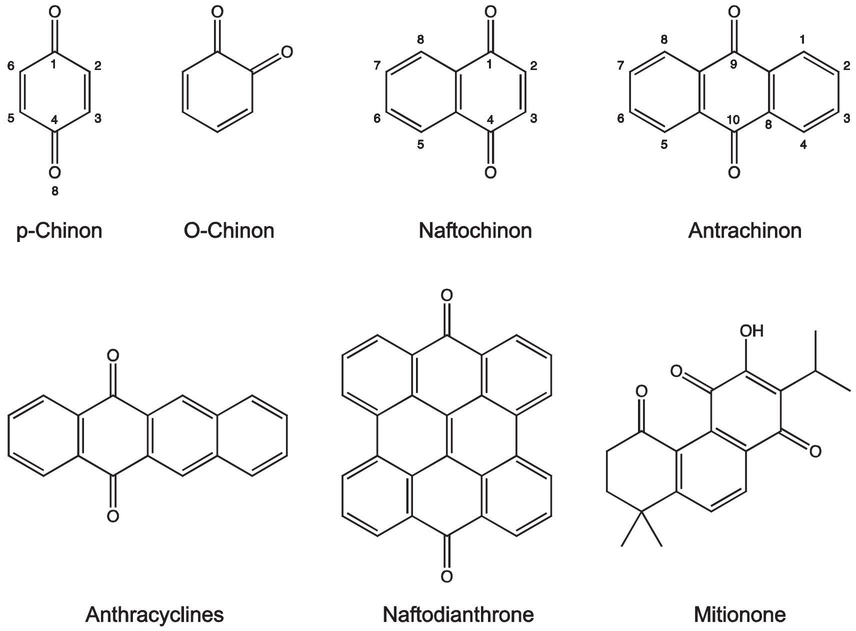


Formula 1-162: Lawsone



Formula 1-163: DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone)

Quinones are plant pigments, which are yellow, orange, and red in colour. Most quinones are isolated from fungi, lichens, gymnosperms, and angiosperms. They are rarely found in ferns and insects. These compounds are rarely found in plants as simple quinones. Quinones are often condensed in different types of compounds with an aromatic nucleus: naphthoquinones and anthracyclines. They occur as free or in the form of heterosides in plants. Quinone aglycones are lipophilic and dissolve in non-polar organic solvents.



p-Chinon O-Chinon Naftochinon Antrachinon

Anthracyclines Naftodianthrone Mitionone

Scheme 1-23: Quinones heterosides

They are products of plant's secondary metabolism and are distributed in some of the world's flora. In addition to the pigment compounds, there are quinone structures involved in the processes of primary metabolism; they are also universally found in the plant cell (Xu *et al.* 2014). They are benzoquinones, naphthoquinones (ubiquinone, plastoquinone), and tocopherolylquinones (menachinone). These compounds are electron carriers, and are involved in cellular respiration and photosynthesis processes.

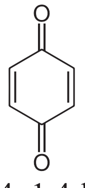
Anthraquinone heterosides (anthranoids). Anthranoids are anthracene derivatives. They can also be considered to be p-quinone derivatives and di benzo p-quinones. They differ from one another by the degree of oxidation of the ninth and tenth C atom (anthrons, anthranols, and anthraquinones), but they are all hydroxylated at C_1 and C_8. Anthron and anthraquinone heteroids are restrictedly distributed in plants from the following families: *Liliaceae*, *Rhamnaceae*, *Poygonaceae*, and *Fabaceae* (Patel *et al.* 2016).

Benzoquinones

Benzoquinone is a quinone with a simple benzene ring, and the most important ones are as follows:

- 1,4-benzoquinone (para-benzoquinone, p-benzoquinone, para-quinone, or just quinone)
- 1,2-benzoquinone (ortho-benzoquinone, o-benzoquinone, or ortho-quinone)

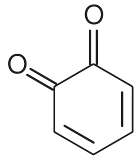
Table1-61: Physical and chemical properties of 1,4-benzoquinone

CAS number	106-51-4	 Formula 1-164: 1,4-benzoquinone
Molecular formula	$C_6H_4O_2$	
Molecular weight	108.10 g/mol	
Density	1.318 g/cm^3	
Boiling pont	115 ^{0}C	
Solubility in water	11 g/L (18 ^{0}C)	

https://pubchem.ncbi.nlm.nih.gov/

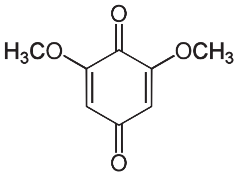
1,4-benzoquinone causes dark brown spots on the skin, as well as skin erythema, which can cause tissue necrosis on the localised part. It especially irritates eyes and the respiratory system.

Table 1-62: Physical and chemical properties of 1,2-benzoquinone

CAS number	548-74-3	 Formula 1-165: 1,2-Benzoquinone
Molecular formula	$C_{18}H_{16}O_8$	
Molecular weight	360.318 g/mol	
Density	1.424 g/cm^3	
Boiling point	213.3 ^{0}C	

https://pubchem.ncbi.nlm.nih.gov/

Table 1-63: Physical and chemical properties of 2,6-dimethoxybenzoquinone

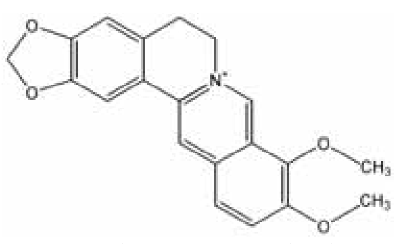
CAS number	530-55-2	 Formula 1-166: 2,6-dimethoxybenzoquinone
Molecular formula	$C_8H_8O_4$	
Molekular weight	168.15 g/mol	

https://pubchem.ncbi.nlm.nih.gov/

Berberine (Umbellatine)

Berberine is a quaternary ammonium salt of protoberberine belonging to the benzylisoquinoline alkaloids group. It has been found in *Hydrastis canadensis* of the *Berberidaceae* family. It is also found in many other plants, such as *Berberis vulgaris*, *Berberis aristata*, *Mahonia aquifolium*, *Xanthorhiza simplicissima*, *Phellodendron amurense*, *Coptis chinensis*, *Tinospora cordifolia*, *Argemone mexicana*, and *Eschscholzia californica* (Birdsall and Kelly, 1997). It is a relatively toxic substance. It is found in the root, rhizomes, stem, and bark., berberine was used for dyeing wool, leather, and wood. In northern India, berberine is still used for wool dyeing. Berberine has a strong yellow fluorescence in ultraviolet light; therefore, it is used in histology to stain livers that have fat cells. The index of this colour is 75 160.

Table 1-64: Physical and chemical properties of berberine (umbellatine)

CAS number	2086-83-1	 Formula 1-167: Berberine (umbellatine)
EC number	218-229-1	
Molecular formula	$C_{20}H_{18}NO_4^+$	
Molecular weight	336.367g/mol	
Boiling point	145^{0}C	

https://pubchem.ncbi.nlm.nih.gov/

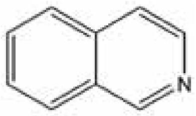
Isoquinoline

Isoquinoline is a heterocyclic aromatic organic compound, and a quinoline structure isomer. Both isoquinoline and quinoline are benzopyridines, which consistof a benzene ring condensed with a pyridine ring (Katritzky and Pozharskii, 2000). In a broad sense, the term isoquinoline is used to refer to isoquinoline derivatives. 1-Benzylisoquinoline is the structural basis of natural alkaloids, such as papaverine and morphine. In these natural compounds, the isoquinoline ring is derived from tyrosine, which is an aromatic acid (Gilchrist, 1997; Katritsky and Pozharskii, 2000; Katritsky *et al.* 1996; Nagatsu, 1997; Susan Budavari, 2001).

Isoquinoline is colourless (pale yellow) hygroscopic liquid at room temperature with an unpleasant smell. The impure samples are brown, which is typical of nitrogen heterocyclic compounds. Its crystallisation produces flakes that have low solubility in water but dissolve well in ethanol, acetone, diethyl ether, carbon disulphide, and other common organic solvents. It is also soluble in dilute acids. Isoquinoline is a weak base, with a pKb of 5.1. It forms salt, such as HCl, upon treatment with strong acids.

Hugeverf and van Dorp first isolated isoquinoline from coal tar in 1885 by fractional crystallisation of acid sulphate. Veisgerber developed a faster method in 1914 through the selective extraction of resin by relying on the fact that isoquinoline is a better base than quinoline.

Table 1-65: Physical and chemical properties of isoquinoline

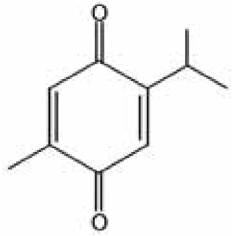
CAS number	119-65-3	 Formula 1-16: Isoquinoline
EC number	204-341-8	
Molecular formula	C_9H_7N	
Density	1.099 g/cm^3	
Molecular weight	129.16 g/mol	
Melting point	26-28 ^{0}C	
Boiling point	242 ^{0}C	

https://pubchem.ncbi.nlm.nih.gov/

Thymoquinone

Thymoquinone is a phytochemical component found in *Nigella sativa*. It is also found in *Monarda fistulosa*, which is grown in the USA for the production of essential oils.

Table 1-66: Physical and chemical properties of thymoquinone

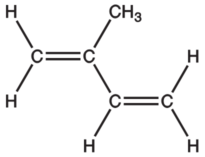
CAS number	490-91-5	 Formula 1-169: Thymoquinone
Molecular formula	$C_{10}H_{12}O_2$	
Molecular weight	164.20 g/mol	

https://pubchem.ncbi.nlm.nih.gov/

TERPENES

Terpenes are a large and diverse group of organic compounds found in many plants. Some insects, such as termites, and some species of butterflies also produce terpenes in their bodies. They are the main constituents of resins and turpentines. In addition to being the final products of decomposition in the body of many organisms, they are significant biosynthetic materials for many compounds in living organisms. Steroids are derivatives of triterpene squalene. Oxidation or alteration in the carbon skeleton of terpenes produces compounds called terpenoids. Therefore, terpenoids are oxygen derivatives of terpenes. Terpenes and terpenoids are the primary constituents of essential oils (Perveen, 2018). Essential oils are widely used as natural additives to improve the taste of food, as fragrances in perfumery, and in traditional medicine. Synthetic variations and derivatives of natural terpenes and terpenoids have significantly expanded their applications in perfumery and food production. The aroma and taste of beer comes from terpenes, which are most commonly found in hops (myrcene, β-pinene, β-caryophyllene, and α-humulene).

Terpenes are biomolecules consisting of a number of isoprenoid units (McNaught and Wilkinson, 1997). Terpenes or terpenoids, as well as isoprenes or polyisoprenoids, have a carbon skeleton composed of isoprene units containing five carbon atoms each.



Formula 1-170: Isopren

Terpenes are classified by the number of C atoms (C_5 units) as follows:

- True terpenes
- Terpenes in the broader sense

True terpenes are divided into the following:

- Monoterpenes, 10 C (2 C_5 units)
- Sesquiterpenes, 15 C (3 C_5 units)
- Diterpenes, 20 C (4 C_5 units)
- Sesterterpenes, 25 C (5 C_5 units)
- Triterpenes, 30 C (6 C_5 units)
- Triterpenes, 35 C (7 C_5 units)
- Tetraterpenes, 40 C (8 C_5 units)
- Polyterpenes, > 40 C (> 8 C_5 units)

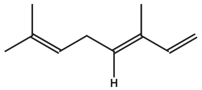
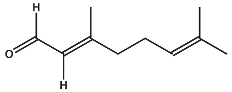
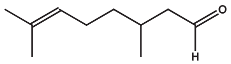
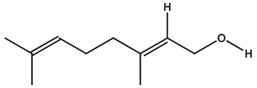
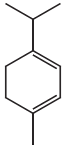
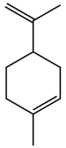
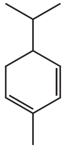
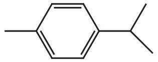
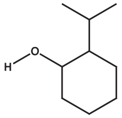
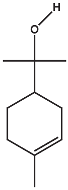
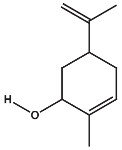
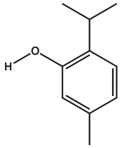
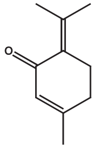
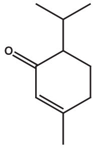
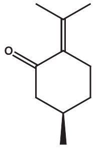
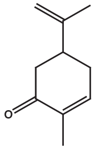
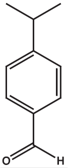
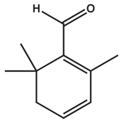
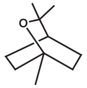
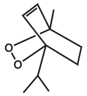
Monoterpenes are the most common in the group of true terpenes. Depending on their structure, they are divided into the following:

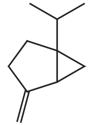
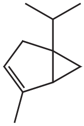
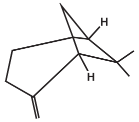
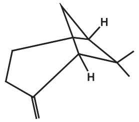
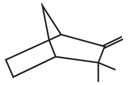
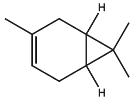
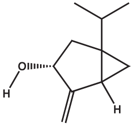
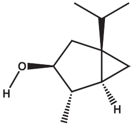
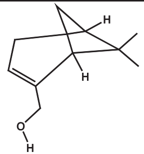
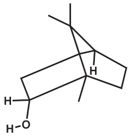
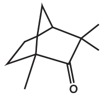
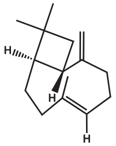
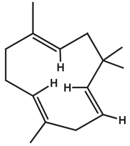
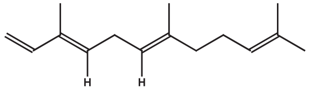
- Simple hydrocarbons (limonene, myrcene)
- Aldehydes (geranial)
- Alcohol (linalool, geraniol)
- Acids (geranoic acid)
- Esters (geranyl acetate)

Monoterpenes are divided into the following three groups:

- Acyclic
- Monocyclic
- Bicyclic

Table 1-67: Acyclic, monocyclic, and bicyclic monoterpenes

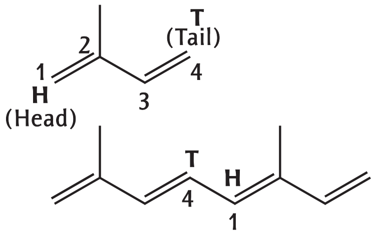
Hydrocarbons	Acyclic monoterpenes			
				
	Formula 1-171: Ocimene	Formula 1-172: Citral	Formula 1-173: Citronellal	Formula 1-174: Geranoil
	Monocyclic monoterpenes			
				
	Formula 1-175: α-Tepinen	Formula 1-176: Limonen	Formula 1-177: α-Phellandrene	Formula 1-178: p-Cymel
Alkochols, Fenols				
	Formula 1-179: Menthol	Formula 1-180: α-Terpineol	Formula 1-181: Carveol	Formula 1-182: Tymol
Ketones				
	Formula 1-183: Piperitone	Formula 1-184: Piperitenone	Formula 1-185: Pulegone	Formula 1-186: Karvon
Aldehydes, okisides, peroxides				
	Formula 1-187: Cuminal	Formula 1-188: Safran	Formula 1-189: 1,8-Cineol	Formula 1-190: Ascardiol

	Bicyclic terpenes			
Hydrocarbons				
	Formula 1-191: Sabinene	Formula 1-192: α-Thujene	Formula 1-193: α-Pinene	
				
	Formula 1-194: β-Pinene	Formula 1-195: Camphene	Formula 1-196: Λ^3-Carene	
Alcohols, ketones				
	Formula 1-197: Sabinol	Formula 1-198: Thujone		
				
	Formula 1-199: Myrtenol	Formula 1-200: Borneol	Formula 1-201: Fenchon	
Sesquiterpenes				
	Formula 1-202: β-Caryophyllen	Formula 1-203: α-Humulene	Formula 1-204: Farnesol	

Terpenes in the broader sense are divided into the following:

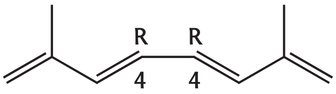
- Hemiterpenes, 5C
- Steroids, 27 C

Hemiterpenes are very rare in the plant world. Steroids are formed from triterpene (30 C) by the oxidative cleavage of 3 methyl groups. Theoretically, it can be said that they are formed by isoprene bonding. This is the so-called Ružička isoprene rule of asymmetric bonding H-T (Head-Tail) at position 1-4.



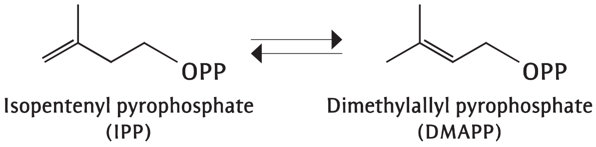
Scheme 1-24

Ružička bonding produces the precursors of monoterpene, sesquiterpene, diterpene, and sesterterpene. They can also be formed by symmetrical bonding, that is, by the 4-4 or R-R bonding to form the precursors of tri-and tetraterpenes

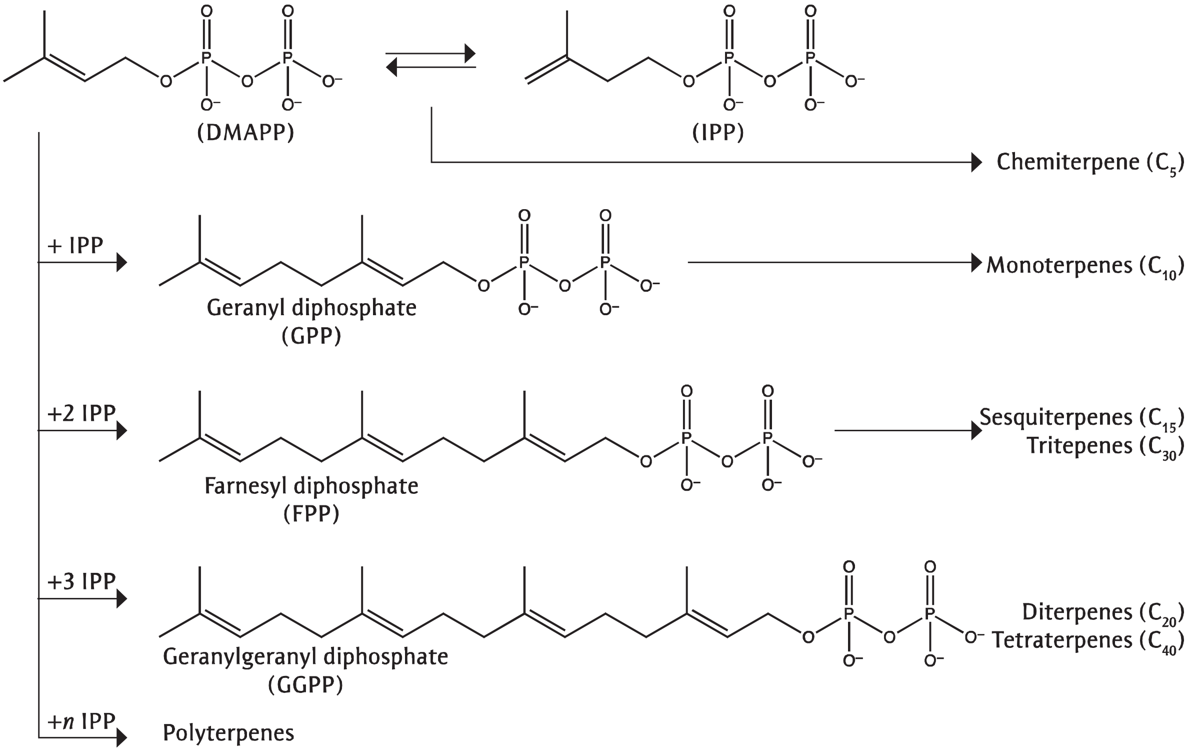


Scheme 1-25

They are practically formed by the coupling of active isoprene (C_5)



Scheme 1-26



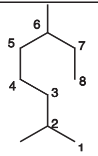
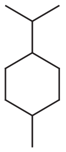
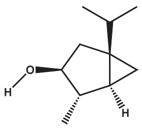
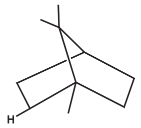
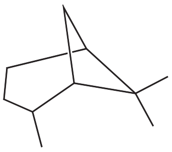
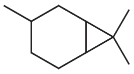
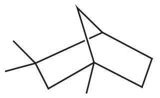
Scheme 1-27: Biosynthesis of active isoprene

Monoterpenes are divided into the following:

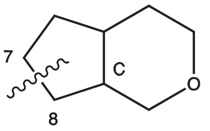
- Volatile
- Non-volatile

Volatile monoterpenes are constituents of essential oils, and non-volatile constituents of iridoids and secoiridoids. Volatile monoterpenes can be acyclic, monocyclic, and bicyclic. Volatile monoterpenes are listed in the table below:

Table 1-68: Structural formula of volatile monoterpenes

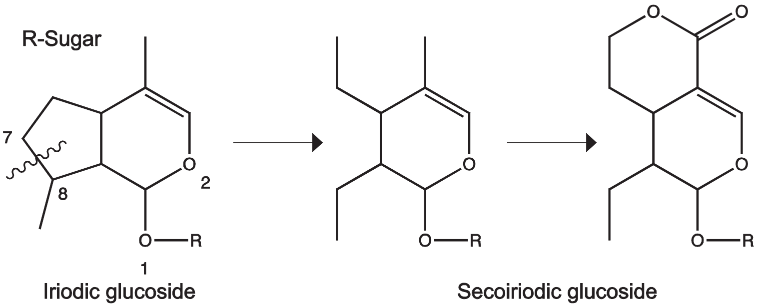
 Formula 1-205: 2,6-Dimethyl-octan	 Formula 1-206: Mentane	 Formula 1-207: Thujane	 Formula 1-208: Camphane	 Formula 1-209: Pinane	 Formula 1-210: Carane	 Formula 1-211: Fenchane

Non-volatile monoterpenes have an iridane skeleton. They contain at least two functional groups of oxygen.



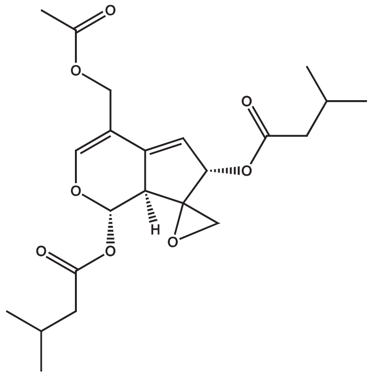
Formula 1-212: Iridane (cyclopenta (c)-pyran)

Secoiridoids are formed by opening (by oxidative degradation) the cyclopentane ring between C_7 and C_8.



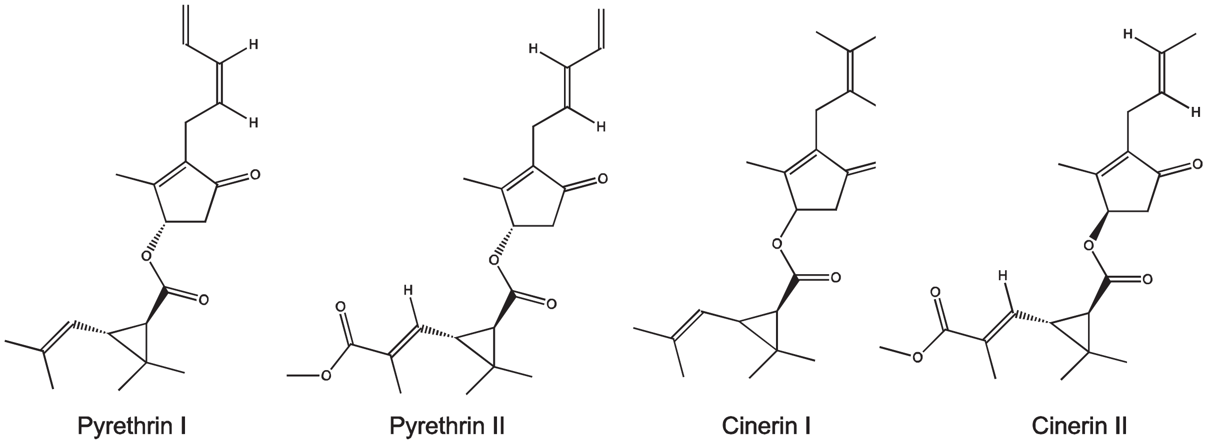
Scheme 1-28

Iridoid glycosides have a specific pharmacological effect; they are found in *Hapaophyti* roots, *Plantaginis lanceolata* and *Menyanthidis trifoliatae* leaves, and *Verbascum* flowers. Secoridoid glycosides are bitter substances. When they occur in the form of sweroside and swertiamarin, they are found in *Kao Gentianae* roots and *Centaurii* leaves. Secologanin is found in *Menyanthidis trifoliatae* leaves. Valepotriates are a special group of non-glycosylated iridoids. They are isolated from *Valeriane* roots.



Formula 1-213: Diene valepotriates

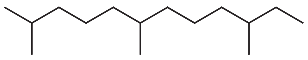
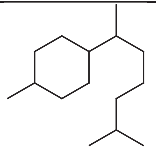
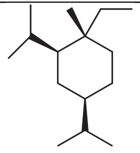
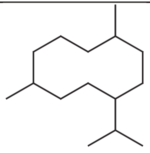
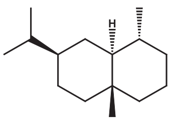
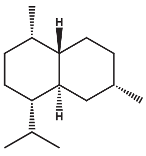
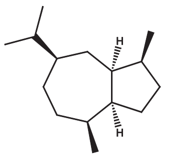
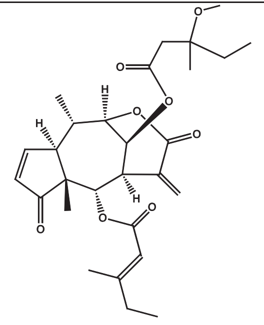
Irregular monoterpenes are formed by binding two DMAPP units. This produces chrysanthemic acid derivatives, pyrethrins, cinerins, and jasmolines, which are found in *Pyrethrum cinerariifolium* flowers.



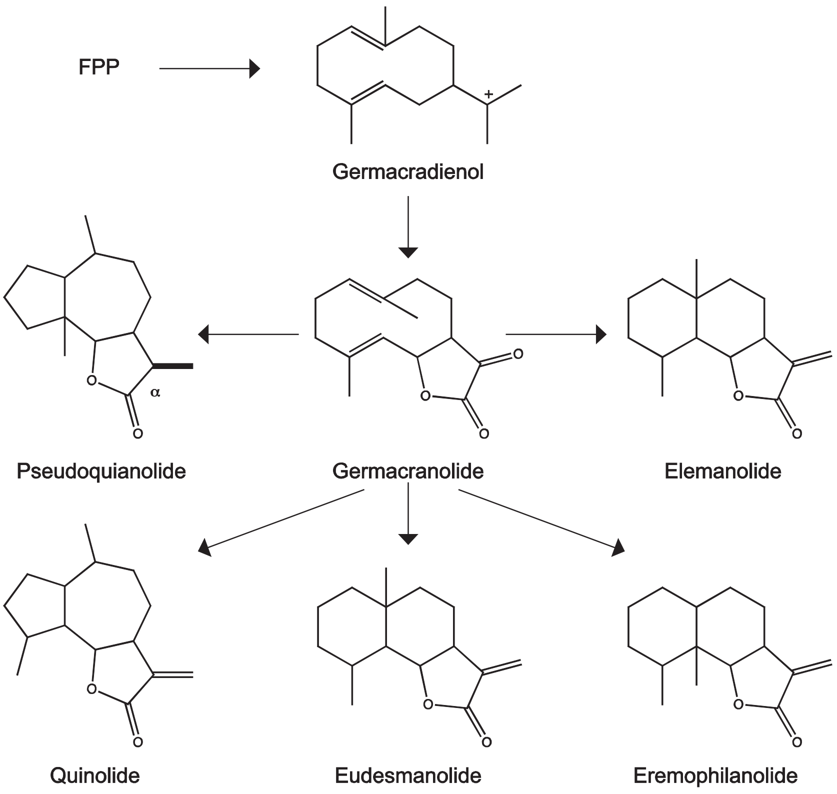
Scheme 1-29

Hemiterpenes are not true terpenes; they are formed from a single molecule of active isoprene. They are rarely found in nature, but can be found in hellebore rhizomes. There are volatile and non-volatile sesquiterpenes. Volatile sesquiterpenes are a part of essential oils, while non-volatile sesquiterpenes have a bitter taste and strong pharmacological activity (Wang *et al.* 2020). Volatile sesquiterpenes include farnesan, bisbolan, eleman, germacrane, eudesmane, cadinane, guaiene, and pseudo guaiene, whose structural formula can be seen in Table 1-69.

Table 1-69: Structural formula of volatile sesquiterpenes

 Formula 1-214: Farnesane	 Formula 1-215: Bisabolane	 Formula 1-216: Eleman	 Formula 1-217: Germacrane
 Formula 1-218: Eudesmane	 Formula 1-219: Kadian	 Formula 1-220: Guaiane	 Formula 1-221: Pseudoquaiane

Non-volatile sesquiterpenes (butyrolactones) are formed from germacranolides.



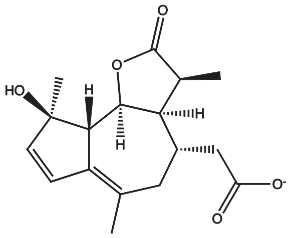
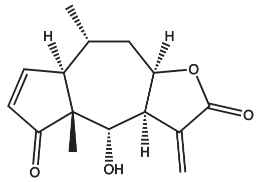
Scheme 1-30

Sesquiterpene lactones are found mainly in the *Asteraceae* family's plants and have the pharmacological effects listed in Table 1-70. This group of sesquiterpene lactones includes *matricin i helenalin*, which is found in *Matricaria recultita*, *Arnica montana*, and *Arnica hamissonis*.

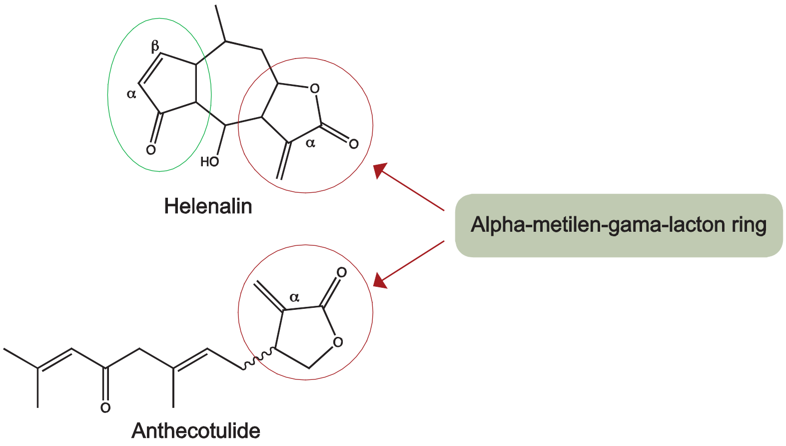
Table 1-70: Plants containing sesquiterpene lactones and their main pharmacological properties

Pharmacological effect	**Constituent**	**Plant**
Anti-inflammatory	Matricin, helenalin	*Matricaria recultita*, *Arnica montana*, *Arnica hamissonis*
Antimicrobial	Alantolactone	*Inula helenium*
Antimalarial	Artemisinin	*Artemisia annua*
Antimigrenous	Parthenolide	*Tanacetum parthenium*
Antiulcer	Dehydroleukodin	*Artemisia douglasiana*
Antirheumatic	Thapsigargin	*Thapsia garganica*

Table 1-71: Structural formula of sesquiterpene lactones

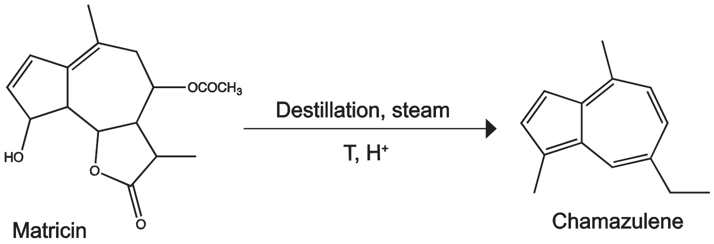
 Formula 1-222: Matricin	 Formula 1-223: Helenalin

Sesquiterpene lactones cause contact dermatitis and have an allergic potential. They have the α, β cyclopentenone ring and are present in *Laurus nobilis* plants belonging to the *Lauraceae* family.



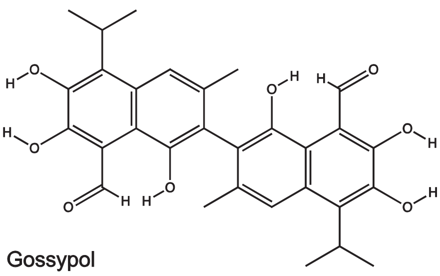
Scheme 1-31

Proazulenes are non-volatile and colourless sesquiterpene lactones, which are converted into azulenes during steam distillation. Azulenes are sesquiterpene hydrocarbons with 5 conjugated double bonds.



Scheme 1-32

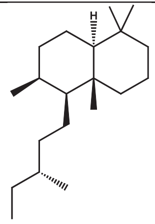
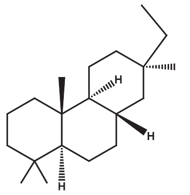
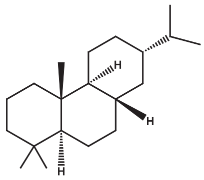
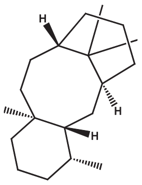
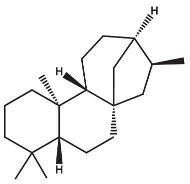
This also includes gossypol belonging to bisesquiterpenes, with some authors classifying it as a triterpene (C 30). It is found in cotton seeds (*Gossypium spp.*, fam. *Malvaceae*). It was used in China as a male contraceptive in the past, but this has been stopped because it has been proven to cause permanent sterility.



Scheme 1-33

Diterpenes can be volatile and non-volatile. Non-volatile ones can be bicyclic, tricyclic, and tetracyclic, and they are part of the milky sap of some plants. Essential oil constituents are volatile and rarely found in nature. The following non-volatile diterpenes are known: labdanum, abietane, cauran, primarane, and taxane.

Table 1-72: Structural formulas and names of non-volatile diterpenes

				
Formula 1-224: Labdane	Formula 1-225: Pimarane	Formula 1-226: Abitane	Formula 1-227: Taxane	Formula 1-228: Kaurane

The following diterpenes are known:

- Forskolin is found in the leaves of *Coleus forkohli* (*Lamiaceae*); it exerts antihypertensive and cardiotonic effects, and prevents platelet aggregation.
- Stevioside is found in the leaves of *Ginkgo biloba* (*Gingoaceae*); it stimulates the cerebral circulation and prevents platelet aggregation.
- Lactone of the abietane type is found in the root of *Salvia miltiorrhiza* (*Lamiaceae*); it acts as a sedative, cardiotonic, and bacteriostatic agent.
- Aconitin is found in the tubers of *Aconitum pentheri* (*Ranunculaceae*); it has antineuralgic effects.
- Taxol is found in plants of *Taxus spp.* (*Taxaceae*); it has cytostatic effects.

The following toxic diterpenes are known:

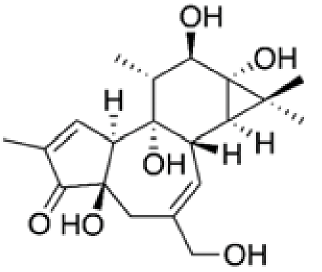
- Forbolesters are found in the milky sap of plants of *Euphorbia* spp. (*Euphorbiaceae*); they act as irritants and cause inflammation.
- Mezerein is found in plants of *Daphne spp.* (*Thymeleaceae*).
- Tetracyclic diterpenes are found in plants of *Rhododendron spp.* (*Ericaceae*).

Of the several types of substances that belong to diterpene esters, the following three major groups of diterpenes are the most important:

- Ingenol
- Phorbol (tigliane)
- Daphnan

Phorbol. Phorbol is a naturally occurring organic compound that belongs to diterpenes. It was isolated from the plant *Croton tiglium* in 1934 (Tseng *et al.* 1977). The structure of phorbol was determined by Hecker *et al.* (1967) and Pettersen *et al.* (1967). It is soluble in most polar solvents as well as in water. Phorbol esters have important biological properties; the most important is that they can act as tumour promoters via the activation of the protein kinase C enzyme (Blumberg, 1988).

Table 1-73: Physical and chemical properties of phorbol

CAS number	17673-25-5	 Formula 1-229: Phorbol
Molecular formula	$C_{28}H_{28}O_6$	
Molekular weight	364.44 g/mol	
Boiling point	250-251 ^{0}C	

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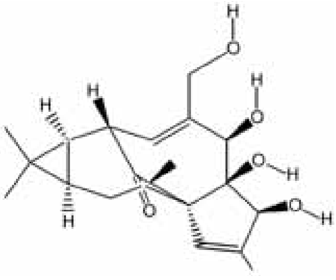
Phorbol esters are tetracyclic diterpenoids known for their tumour-promoting activity. Phorbol esters support the activity of diacyl glycerol (DAG); this is an activator of protein kinase C, which regulates a variety of signal transduction pathways in the metabolism and other cellular metabolic activities (Gunjan *et al.* 2007). This occurs in many plants of the *Euphorbiaceae* and *Thymelaeaceae* families. The biological activity of phorbol esters is highly specific and dependent on their structure. In low concentrations, they cause different toxicological effects in animals that use them for food. Some phorbol ester derivatives are known for their antimicrobial and antitumoural activities.

Igenol. Igenol is a tetracyclic diterpenoid, similar to phorbol in its three-dimensional structure. It has irritant and cocarcinogenic effects.

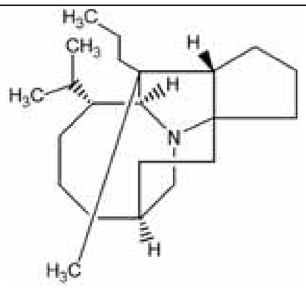
Table 1-74: Physical and chemical properties of ingenol

CAS number	30220-46-3	 Formula 1-230: Ingenol
Molecular formula	$C_{20}H_{28}O_5$	
Molecular weight	348.439 g/mol	

https://pubchem.ncbi.nlm.nih.gov/

Daphnan. Daphnan is the main compound in daphnan esters. In this group, huratoxin was first isolated; this was then followed by montanin, resinferatoxin, and thiniatoxin.

Table 1-75: Physical and chemical properties of daphnan

Molecular formula	$C_{22}H_{37}N$	 Formula 1-231: Daphnan
Molecular weight	315.545 g/mol	

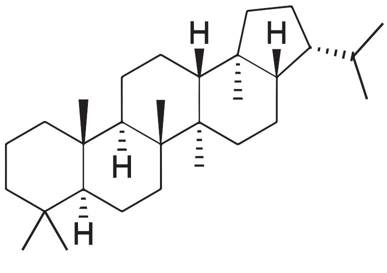
https://pubchem.ncbi.nlm.nih.gov/

There are tetracyclic and pentacyclic triterpenes in the triterpene group. As free agents, they are constituents of the resin and milky sap of plants, and, when glycosylated, they are tritepene saponins and glycosides.

Triterpenes are a class of chemical compounds consisting of three terpene units with the following molecular formula: $C_{30}H_{48}$. There is a large number of different triterpenes, as almost 200 structurally different compounds have found in natural sources (Xu *et al*. 2004). Triterpenes are relatively widespread in nature, with the exception of squalene, which is present in traces in all living organisms. Terpenoid alcohols, aldehydes, ketones, and acids that have a triterpene skeleton are more commonly found in living organisms, especially in plants. Most natural terpenoids are tetracyclic and pentacyclic structures. They are classified by the number of rings in a molecule, as shown in the Table below.

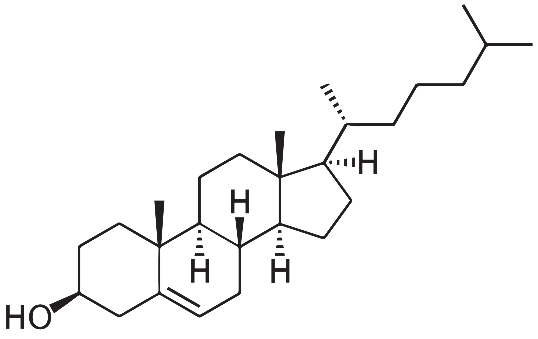
Number of rings	**Example**
0	Squalene
2	Polypodatetraene
3	Malabaricane
4	Lanostane
5	Hopane
6	Oleanane

Formula 1-232: Squalene, one of the most important triterpenes



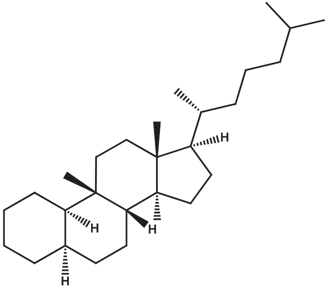
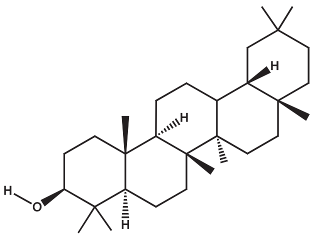
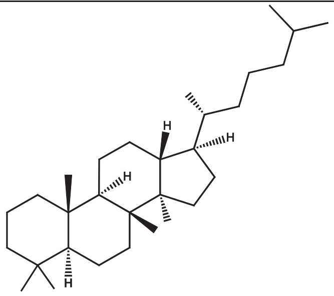
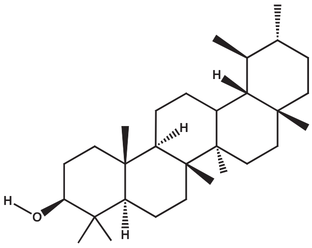
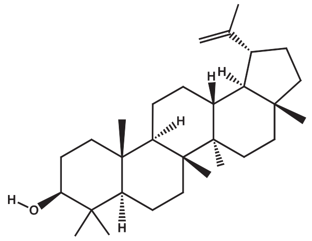
Formula 1-233: Hopane, an example of pentacyclic triterpenes

Triterpenes are hydrocarbons that do not have heteroatoms in their structure. Functional triterpenes are called triterpenoids, although this difference is not observed even in the scientific literature and so these names are used synonymously.



Formula 1-234: Cholesterol, one of the simplest and most important triterpenoids

Table 1-76: Names and structural formulas of tetracyclic and pentacyclic terpenes

Tetracyclic		**Pentacyclic**	
Type cucurbitane	 Formula 1-235	Type oleane	 Formula 1-236
Type dammarane	 Formula 1-237	Type ursane	 Formula 1-238
		Type lupane	 Formula 1-239

Steroids in plants are found as free (phytosterols), glycosylated (cardiotonic heterosides), and steroidal alkaloids (*Solanum* and *Veratrum* alkaloids). Tetraterpenes include carotenoids, which have yellow, orange, or red plant pigments that participate in the process of photosynthesis, and some of them are vitamin A provitamins. The following tetraterpenes are also known:

- Capsantin, capsorubin, found in *Capsicum annuum* (*Solanaceae*)
- Crocetin, crocin, found in plants of *Crocus spp.* (*Liliceae*)
- Fucoxanthin, found in plants of *Fucus spp.* (*Phaeophyceae*)
- Bixin or annatto, found in *Bixa orellana* (*Bixaceae*)

The following polyterpenes, which are found in the milky sap of some plants, are known:

- Gutta-percha, the milky sap of plants of the *Payena* and *Palaquium* (*Sapotaceae*) genera. It is used in patch making and dentistry, etc.
- Natural rubber, found in the milky sap of the rubber tree *Hevea brasiliensis* (*Euphorbiaceae*). Natural rubber contains 1.500–60.000 C_5 units. It is used in patch making and to obtain technical rubber by vulcanization.

Table 1-77: Terpenes ames of known terpenes

Name		
Abietene	Eugenol	Plastoquinone
Abietic acid	Ferruginolo	Presqualene pyrophosphate
Valerenic acid	Phytoene	Retinal
Anethole	Phytofluene	Retinol
Bornane	Phorbol	Simonellite (chemical compound)
Borneol	Geranyl pyrophosphate	Squalene 2,3-epoxide
Carvacrol	Geranilfarnesil pyrophosphate	Strigolactones
Carvone	Geranylgeranyl pyrophosphate	Terpinen-4-ol
Citral	Isopentenyl pyrophosphate	Thymol
Cucurbitacin	Madecasoside	Tocopherol
Deoxynivalenol	Menthol	T-2 toxin
Dimethylallyl pyrophosphate	Mircenolo	Trichothecene
Dolichol	Neotenina	Thujone
Eucalyptol		

Colophony

Colophony is used as an anti-slip agent; for example, it is used to coat the bows of different musical instruments and for soft soldering. It is also used in pharmacies. Colophony (Latin: colophonia, Greek: *Κολοφωνία,* colophony resin) is a dark yellow to light brown solid obtained by distillation, after the removal of volatile constituents from resin secretions from certain pine species. It is named after Colophon, a city in ancient Greece (today in the territory of Turkey). It is brittle, becomes sticky when heated, softens at 70–80 ^{O}C, and melts at 110–130 ^{O}C. It is soluble in organic solvents or bases and insoluble in water. It is used to produce paper, soap, lacquers, wood paints, printing ink, and as an anti-slip agent (lubricating bows, dance shoes, floors, and stages). Its chemical composition is very complex and depends on the production process, geographical area, and storage conditions. Depending on the production method, there are three types of colophony. It consists of about 90% acids and about 10% neutral substances. The principles underlying its allergic effects are not yet known. The oxidation products of abietic acids and dehydroabietic acids have been identified as allergens, but its neutral fractions also contain allergenic components (Downs and Sansom, 1999).

Resin extraction is the process of obtaining plant resins and balms from certain species of coniferous trees (pine, spruce, fir, and larch). Resin is extracted from the tree by making cuts on the trunk of various shapes and sizes, depending on the resin extraction technique (French, German, American). Coniferous trees that are 16 to 60 years old are used in resin extraction. The main products of resin extraction are monoterpenes and diterpenes which, after distillation, are separated as turpentine oils (turpentine). Distillation produces essential oils from young parts of the tree, branches, twigs, and needles.

Turpentine (German: terpentin, Latin: terbinthia, wood resin) includes resin secretions from over 100 species of coniferous trees. It consists of volatile turpentine oil and non-volatile resin acids and is used for the manufacture of paints and varnishes. The main constituent of turpentine oil is pinene, $C_{10}H_{16}$, a dicyclic terpene, from which camphor is derived. The oil is used as a solvent for fats, oils, resins, paints, and varnishes, as well as for the production of fragrances.

In the distant past, various types of natural resins and balms, waxes, plant extracts, bitumen, and other substances were used for the protection of wood and metal surfaces. In the Middle Ages, some types of oil paints and asphalt varnishes, etc. were known as wood and metal preservatives. Later, under the influence of eastern countries, coniferous oil began to be used for the impregnation of wood and ships. Turpentine oil was taken from the Arabs, and the so-called "rhus" lacquer from the Chinese. The Chinese obtained this lacquer from the sap of *Toxicoddendron vernicifluum* through an unknown method. The methods and procedures were kept secret and passed down from father to son. All these methods and procedures have been retained for the protection of surfaces throughout the Middle Ages. It was not until the 15th century that the Eyck brothers from the Netherlands used drying oil for the first time. This oil was known as early as the 10th century, but was not used for these purposes. The first production of protective oils began in the 17th century in the Netherlands and the production of varnishes and drying oil began in France in the 18th century. At the same time, pigment production technology started to be developed. The first inorganic pigment was made in 1704, which was followed by a whole range of pigments, such as lead bleach (1757), yellow and green paints (1809), ultramarine (1828), and zinc bleach (1850); after this, the process of synthesis of organic dyes began.

Terebentine (Turpentine)

Terebentine is an oil resin, which is yellow or brown in colour, depending on the origin of the tree from which it was obtained. After purification and distillation, terebentine is divided into two parts: one is colophony, which is solid and odourless, and the other is terebentine, which is liquid and with a scent. This is actually the residue after distillation from different pine species, but particularly maritime pine. The distillation is carried out at a temperature below 180^0C. It is a mixture of terpenes, acids, and alcohols. It is insoluble in water, absolute alcohol, and ether. It is poorly soluble in a mixture of water and alcohol. It is sensitive to light, mildly toxic, and highly flammable. It is a very good solvent for fats, oils, and waxes. It is used in many products (paints, varnishes, insecticides, and even perfumes or pharmaceuticals, such as creams and ointments). It contains about 60% of alpha-pinene. This is an irritant substance and precautions are required.

Table 1-78: Physical and chemichal properties of terebentine

CAS number	8006-64-2
Molecular formula	$C_{10}H_{16}$
Molecular weight	136.234 g/mol
Boiling point	154-170 ^{0}C
Solubility in water	20 mg/L
Density	0.86–0.87 g/cm^3
Ignition point	220 ^{0}C

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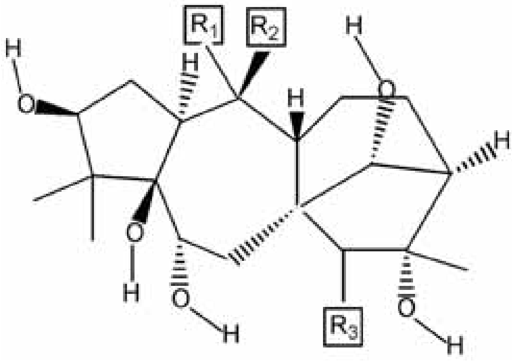
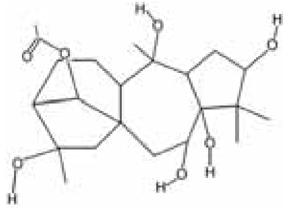
Grayanotoxins

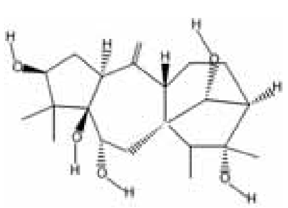
There are 18 diterpenoid components, which are isolated from plants in the grayanotoxins group (Li *et al.* 2013). The most famous of these is grayanotoxin I, which is also known as andromedotoxin, rhodotoxin, acetylandromedol, and asebotoxin. The general structure of these components is given in the below structural formula.



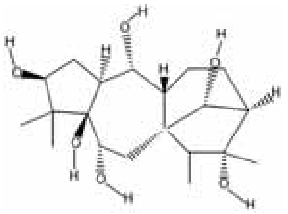
Formula 1-240: Grayanotoxin



Formula 1-241: Grayanotoxin I



Formula 1-242: Grayanotoxin II



Formula 1-243: Grayanotoxin III

Name	R_1	R_2	R_3
Grayanotoxin I	OH	CH_3	$COCH_3$
Grayanotoxin II	CH_2=	CH_2=	H
Grayanotoxin III	OH	CH_3	H

Table 1-79: Physical and chemical properties of grayanotoxin

Name	**Grayanotoxin I**	**Grayanotoxin II**	**Grayanotoxin III**
Chemical name	Acetylandromedol	Deacetylanhydro-andromedotoxin	Deacetylandromedotoxin
CAS number	4720-09-6	4678-44-8	4678-45-9
Molecular formula	$C_{22}H_{36}O_7$	$C_{20}H_{32}O_5$	$C_{20}H_{34}O_6$
Molecular weight	412.523 g/mol	352.471 g/mol	370.486 g/mol

https://pubchem.ncbi.nlm.nih.gov/

The activity of these compounds depends on their structure. Grayanotoxins have two types of receptors that open and close the sodium channels in the cell membranes. The hydroxyl group at position R_1 is responsible for their toxicity. The presence of the ester group at R_3 reduces the toxicity of such a compound, but increasing the chain of the ester group will increase its toxicity (Hikino *et al.* 1976). In toxicological experiments with rats, it was found that grayanotoxin III was the most toxic, followed by grayanotoxin I and grayanotoxin II.

Grayanotoxin I is a crystalline substance, which is soluble in warm water, alcohol, acetic acid and warm chloroform. It was isolated from bees by extraction with chloroform or chloroform-methanol (White and Riethof, 1959).

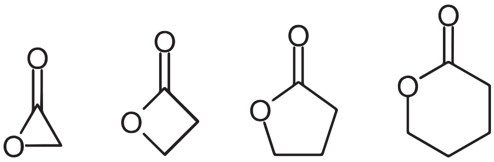
Dermatitis is known as "nettle rash"; in this condition, hives are caused by contact with azalea plants (Cleland, 1943; Agrup, 1969; Leach, 1982). Welts will appear after working with azalea plants that contain high concentrations of grayanotoxins, such as some azalea cultivars (Pride of Leonardsa) obtained by the hybridization of *Rhododendron fortunei* x *Rhododendron thomsonii* (Agrup, 1969; Agrup and Fregert, 1968; Fregert and Hjorth, 1968).

Grayanotoxins are found in many genera of the *Ericaceae* family. The most important genera of this family are *Kalmia*, *Ledum*, *Leucothoe*, *Menziesia*, *Pieris*, and *Rhododendron*. Indoor azaleas, *Rhododendron acidentale* and *Rhododendron molle*, as well as the hybrid *Rhododendron fortunei x Rhododendron thomsonii* have large amounts of grayanotoxin (Leach, 1982). By determining lethal doses for mice, it has been determined that the following species of the *Rhododendron* genus are also toxic: *Rhododendron fictolacteum*, *Rhododendron sinogrande*, and *Rhododendron thomsonnii*. Hybrids of some toxic species are more toxic than their parent species, while some are non-toxic (Carey *et al.* 1959).

LACTONES

In chemistry, lactone is a cyclic ester (Smith and March, 2007), which can be considered to be the condensation product of an alcohol group (-OH) and carboxylic acid (-COOH) in the same molecule. It has a characteristic ring consisting of two or more carbon atoms and one oxygen atom, with a ketone group=O on one of the carbons adjacent to the oxygen atom in the ring. Lactones are usually named after a precursor acid molecule (aceto=2 carbons, propio=3, butyro=4, valero=5, capro=6, etc.), with the lactone suffix and the Greek letter as a prefix, which indicate the number of carbons in the heterocyclic ring. The first carbon atom after the carbon in the-COOH group of the precursor compound is denoted by α, the second by β, the third by ϒ, and so on. Therefore, the prefixes also indicate the size of the lactone ring: α-lactone = three-membered ring, β-lactone = four-membered ring, and γ-lactone = five-membered ring, etc. “Olide” is another suffix used to indicate a lactone. It is used to denote classes of compounds, such as butenolide, macrolide, cardenolide, and bufadienolide.

Formula 1-244: β-propiolactone, formed from β-hydroxypropionic acid



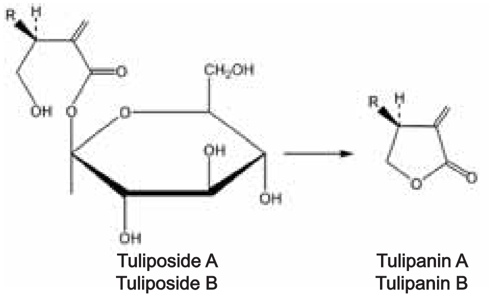
Scheme 1-34: Lactone nomenclature: α-acetolactone, Β-propiolactone, γ-butyrolactone, and δ-valerolactone

Sesquiterpene lactones

Sesquiterpene lactones represent one of the largest groups of natural products. So far, about 5,000 different structures have been discovered from natural sources and hundreds from synthetic ones (Milosavljević *et al.* 1999). A sesquiterpene lactone cnicin has a special place in this group of compounds, and it was first found in the *Cnicus benedictus* species, where its content ranges from 0.2 to 0.7% (Janaćković *et al*. 2003). These are compounds with high biological activity. They belong to the group of C_{15} terpenoids, that is, they are formed from three isoprene units. These are colourless substances, which often have a bitter taste and are lipophilic. They are mainly found in leaf tissues, where they make up about 5% of their dry weight (Heywood and Harborne, 1977). Sesquiterpene lactones are formed through the so-called mevalonic pathway, via the isoprene C_5 unit. Germacranolides are considered to be precursors for most types of sesquiterpene lactones: e.g., guaianolides, seco-germacranolides, and eudesmanolides. A common structural feature of sesquiterpene lactones is a γ-lactone ring. Although there are numerous structural variations of carbon skeletons in sesquiterpenes, the number of basic structural types is relatively small in sesquiterpene lactones. Most sesquiterpene lactones belong to the group of germacranolides, lactones whose lactone ring is fused to a ten-membered ring, and germacranolides are most likely formed by cyclization of (E, E)-farnesyl pyrophosphate, followed by a series of oxidative processes. Based on the carbon skeleton, lactones can be divided into the following types: germacranolides, guaianolides, pseudoguaianolides, eudesmanolides, eremophilanolides, and xanthanolides. The suffix "olide" corresponds to the lactone function. Structural modifications of the basic terpene ring include the introduction of an epoxide ring, hydroxyl groups, and esterification with carboxylic acids: e.g. acetic acid, isobutyric acid, etc. Esters of acids with 5-C atoms, such as tiglic and angelic acid, are very common. Some sesquiterpene lactones also contain a covalently bonded halogen atom. More than 90% of the lactones identified so far have been isolated from plants of the aster family, *Asteraceae*, which is one of the largest families of flowering plants, as it is comprised of about twenty-five thousand species. Individual plant species generally contain one type of skeleton with different oxidative variations. Many sesquiterpene lactones have a strong biological activity. Some lactones from the group of germacranolides, eudesmanolides, guaianolides, and pseudoguaianolides have antitumour and cytotoxic activities (Milosavljević *et al.* 1999). Some components have been proven to have antibacterial activity, while others are active against various micromycetes (Vajs *et al.* 1999). Also, some sesquiterpene lactones are significant allergens, which can sometimes cause contact dermatitis in humans. Some of them, such as artemisinin isolated from *Artemisia annua*, have an antimalarial activity (Lee, 2002). The species of the *Centaurea* (*Asteraceae*) genus are characterised by the presence of sesquiterpene lactones with 18 carbon atoms. The most commonly isolated lactones belong to the following classes: germacranolides, guaianolides, elemanolides, and eudesmanolides.

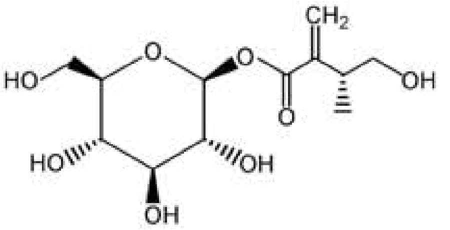
Tulipalin

These compounds are found in the bulbs of some species of the *Tulipa* genus. The tulipalin tuliposide is converted to tulipalin B (β-hydroxy-α-methylene-ϒ-butyrolactone). Tulipalin A is α-methylene-ϒ-butyrolactone. It was first isolated from tulip bulbs back in 1936 (Caulfeild, 1936). Lactones cause enzymes on the hands and nails to become brittle. Changes occur in the form of skin redness, swelling, itching, and a burning sensation, often with hyperpigmentation. The symptoms last for 2 to 3 days. The bulb contains 2.34% of tuliposide A and 1.5% of tuliposide B. Diagnosis is often erroneous (McCluskez *et al.* 2014). Similar symptoms are also caused by allyl isothiocyanates found in plants of the *Brassicaceae* (Cruciferae*)* family (Sasseville, 2009; Lerbaek *et al.* 2004). Tulipalin A is also found in the same parts, as well as its original component, tuliposide. They have antibiotic effects in plants (Bergman 1966; Bergman and Beijersbergen, 1968). In the German Federal Institute for Risk Assessment's (BFP) text on allergens, which covers 240 substances, both of these compounds are classified as Category B, because they have been proven to be contact allergens. They cause a cross reaction in humans (Schlede *et al.* 2003). Although there are many forms of dermatitis, their clinical presentation is similar (Sasseville, 2009).



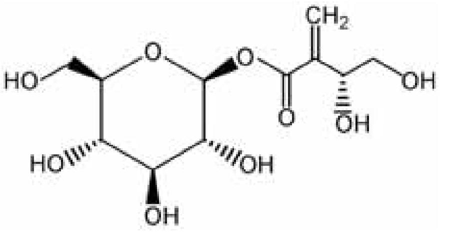
Scheme 1-35: Tuliposide and B transformation of Tulipanin A to B

Table 1-80: Physical and chemical properties of tuliposide A

CAS number	1980-30-5	 Formula 1-245: Tuliposide A
EC number	208-931-6	
Molecular formula	$C_{11}H_{18}O_8$	
Molecular weight	278.257 g/mol	

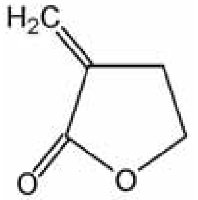
https://pubchem.ncbi.nlm.nih.gov/

Table 1-81: Physical and chemical properties of tuliposide B

CAS number	547-65-9	 Formula 1-246: Tuliposide B
EC number	208-931-6	
Molecular formula	$C_{11}H_{18}O_9$	
Molecular weight	294.256 g/mol	

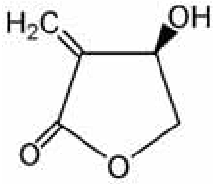
https://pubchem.ncbi.nlm.nih.gov/

Table 1-82. Physical and chemical properties of tulipanin A

CAS number	547-65-9	 Formula 1-247: Tulipanin A
EC number	208-931-6	
Molecular formula	$C_5H_6O_2$	
Molecular weight	98.101 g/mol	

https://pubchem.ncbi.nlm.nih.gov/

Table 1-83: Physical and chemical properties of tulipanin B

CAS number	38965-80-9	 Formula 1-248: Tulipanin B
Molecular formula	$C_5H_6O_3$	
Molecular weight	114.1 g/mol	

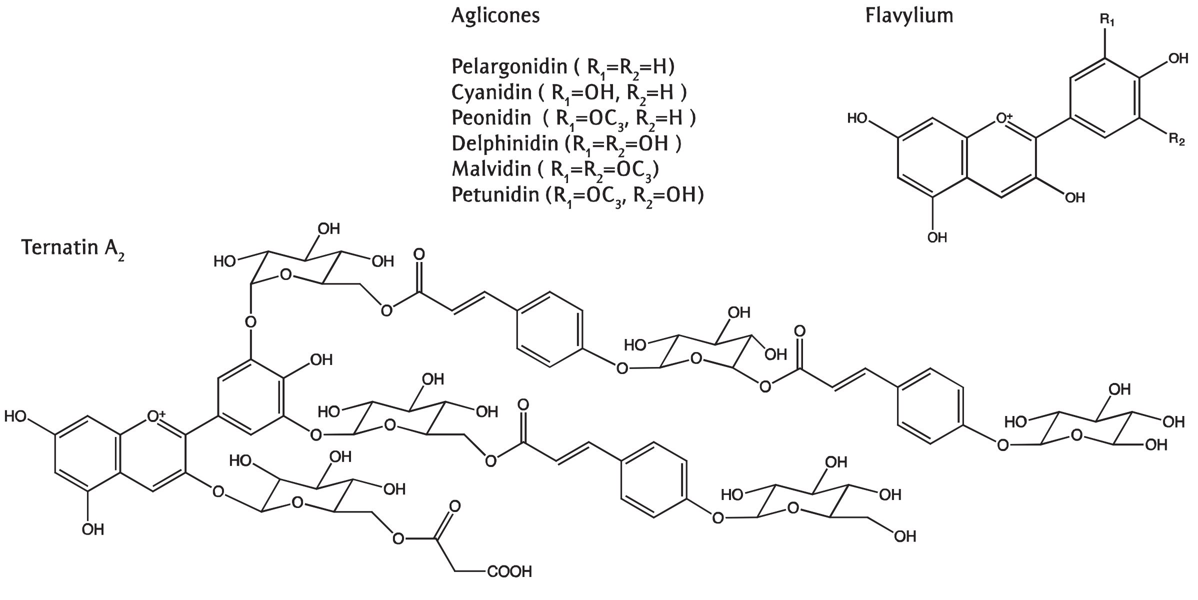
https://pubchem.ncbi.nlm.nih.gov/

Mansonone A

Mansonone A is a constituent of the tree *Mansonia altissima* (fam. Sterculiaceae), which is widespread in parts of Central West Africa. The dust from this tree has been reported to cause nausea, dizziness, and cardiotoxic effects, as well as allergic contact dermatitis. Mansonone is a sesquiterpenoid quinone (Schulz *et al*. 1979).

ANTHOCYANIDES AND ANTHOCYANINS

The term anthocyanin denotes heterosides, while anthocyanidins are aglycone components. Their name comes from the Greek words *anthos* (flower) and *kyanos* (blue). Anthocyanides are derivatives of 2-phenylbenzopyrilium cation (flavium cation). They have a flavonoid structure with a reduced central ϒ-pyrone cycle. At position C3, all anthocyanins have a hydroxyl group and most of them are penta-or hexa-substituted.



Scheme 1-36: Examples of the structure of anthocyanins and anthocianides

In addition to coloured anthocyanides, plants have non-coloured forms. These are leukoanthocyanides and their oligomers are proanthocyanides. Structurally they are derivatives of 3,4-flavandiols. These compounds can be polymerized and, in that state, they form tannins, while in the presence of acid they are easily oxidized and converted into the corresponding anthocyanides (Liu *et al.* 2018). Relatively small numbers of aglycone structures are found in nature, but there is a very large number of heterosides. Anthocyanins are mainly O-heterosides.

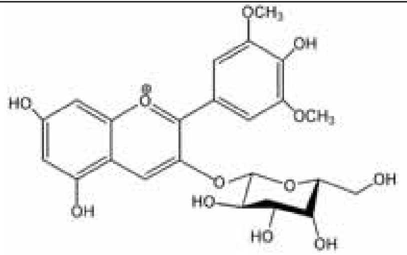
They are formed by binding sugars at C_3, C_5, and C_7. Anthocyanins are soluble in water, acetone and alcohols. Aglycones are soluble in non-polar solvents.

In cases of a change in pH, aqueous solutions of anthocyanins also change in terms of their structure and colour. The effects of anthocyanins are similar to those of other types of flavonoid heterosides. They also reduce permeability, while increasing the elasticity and intrinsic tone of the capillary wall. Such activity is conditioned by the inhibition of proteolytic enzymes and an increase in the amount of collagen and elastin in the blood vessel wall. Anthocyanins have a beneficial effect on the regeneration of visual purple (rhodopsin). Anthocyanin drugs, concentrated extracts, and individual compounds are used for the treatment of diseases resulting from venous circulation disorder, particularly retinal circulation disorders. In addition, anthocyanins are additives used to colour foods and cosmetic products.

Primulin

Primulin is anthocyanin. It is a malvidin 3-galactoside. It contains a benzthiazole ring and is a derivative of dehydrothiotoludine. It was isolated from *Primula sinensis* (Harborne and Sherratt, 1961). The first crystalline form of this pigment was obtained by Rose Scott-Moncrieff in 1930. It was actually the first pigment identified in crystalline anthocyanin (Cathie, 2016).

Table 1-84: Physical and chemical properties of primulin

CAS number	3013-37-2	 Formula 1-249: Primulin
Molecular formula	$C_{23}H_{25}ClO_{12}$, $C_{23}H_{25}O_{12}^{+}$	
Molecular weight	528.89 g/mol chloride, 493.43 g/mol	

https://pubchem.ncbi.nlm.nih.gov/

ALCOHOLS

Alcohols are organic compounds in which the hydroxyl functional group (-OH) is attached to a saturated carbon atom. The general formula for alcohol is R-OH. The carboxylic acids obtained by alcohol oxidation have a similar structure. The suffix "ol" is found in all chemical compounds of IUPAC names in which the hydroxyl group is of highest priority. According to the number of OH groups, alcohols are divided into the following:

- Monohydroxyl (one OH group)
- Dihydroxyl (two OH groups)
- Polyhydroxyl (three or more OH groups)

According to the way of carbon atom binding, alcohols are divided into the following:

- Aliphatic alcohols R-OH, in which R is an alkyl group
- Aromatic alcohols, AR-OH, in which AR is an aryl group

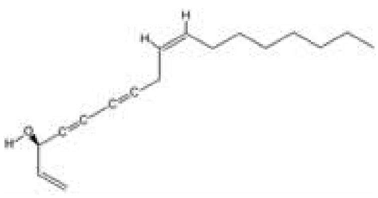
According to the position of the alkyl group, alcohols are divided into the following:

- Primary alcohols
- Secondary alcohols
- Tertiary alcohols

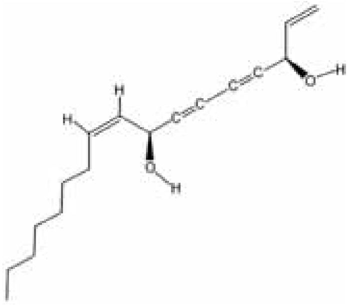
In a homologous series of primary alcohols, alcohols with smaller carbon atoms of up to four atoms are liquids, up to 11 atoms are oils, and higher alcohols are solids. Lower alcohols mix with water, while higher alcohols do not dissolve in water. They form esters with acids, and alkoxides with alkalis; they oxidize to aldehydes, ketones, and organic acids, that is, the oxidation of primary alcohols forms aldehydes and of secondary alcohols ketones.

Polyacetylenes

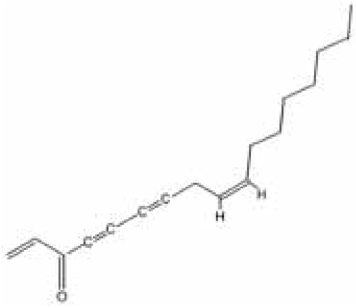
Natural polyacetylenes are compounds that have two or more triple bonds in their structure in an aliphatic order of 13 to 17 hydrocarbon atoms. The ring structure, such as thiophene, with a polyacetylene chain was also isolated from plants (alpha-tertienyl). More than 1,100 different acetylenes and their metabolites have been found in plants of the *Asteraceae* family. More than 1,400 different polyacetylenes and their components from higher plants have been isolated so far. They are widespread in plants of the *Apiaceae*, *Araliaceae*, and *Asteraceae* families. They are found in some species of 20 other families (Bohlmann *et al*., 1973; Hansen and Boll, 1986; Christensen and Lam, 1991 a, b). Polyacetylene compounds from plants of the *Asteraceae* family have cytotoxic, antimicrobial, anti-inflammatory, neurotoxic, phototoxic, and several other activities (Konovalov, 2014). Some of these substances are found in edible plants, especially in plants of the *Apiaceae* family, such as carrots, celery, and parsley. Many polyacetylene compounds are responsible for allergic reactions on the skin (Lars and Kirsten, 2006). Aliphatic C_{17}-polyacetylenes, such as falcarinol and falcarindiol, are also found in many plant species of these families. Many plants containing aliphatic C_{17}-polyacetylene cause allergic contact dermatitis (ACD, allergy of type IV) and irritate the skin (Hausen and Vieluf 2001). Falcarinol from the *Apiaceae* and *Araliaceae* plants has been found to cause the most severe allergic reactions on the skin (Hausen and Vieluf, 2001; Hausen *et al.* 1987; Machado *et al.* 2002; Murdoch and Dempster, 2000) when falcarindiol and falcarinon are present (Hansen *et al.* 1986). Polyacetylenes are volatile and degradable compounds, which exhibit toxicity from fresh plant parts. They are extremely reactive compounds.



Formula 1-250: Falcarinol



Formula 1-251: Falcarindiol



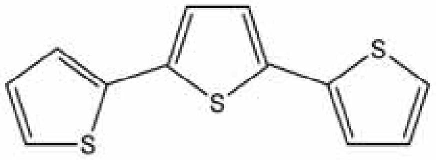
Formula 1-252: Falcarinon

Table 1-85: Physical and chemical properties of falcarinol, falcarindiol, and falcarinon

Falcarinol		Falcarindiol	Falcarinon
CAS number	21852-80-2	55297-87-5	4117-11-7
Molecular formula	$C_{17}H_{24}O$	$C_{17}H_{24}O$	$C_{17}H_{22}O$
Molecular weight	244.378 g/mol	260.377 g/mol	242.362 g/mol

https://pubchem.ncbi.nlm.nih.gov/

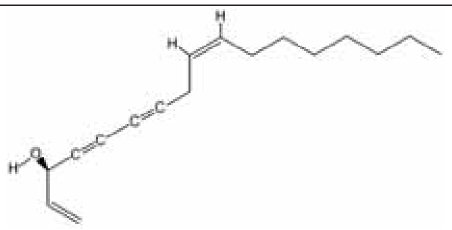
Table 1-86: Physical and chemical properties of alpha-tertienyl

CAS number	1081-34-1	 Formula 1-253: Alpha-tertienyl
Molecular formula	$C_{12}H_8S_3$	
Molecular weight	248.376 g/mol	

https://pubchem.ncbi.nlm.nih.gov/

Falcarinol. Falcarinol (carotatoxin) is a compound found in *Daucus carota*, *Panax ginseng*, and ivy. It is found in carrots in the amount of about 2 mg/kg (Crosbya and Aharonson, 1967). Falcarinol causes allergic and contact dermatitis (Machado *et al.* 2002). Falcarinol isolated from the *Scheffera arbicola* plant also causes allergic contact dermatitis. Experimental and chemical studies have found that ivy (*Hedera helix* susp. *helix*) contains three irritant components. Only two components, falcarinol and didehydrofalcarinol, are found in this plant throughout the year. Even in very low concentrations (0.03%), falcarinol causes severe reactions as it is a major allergen.

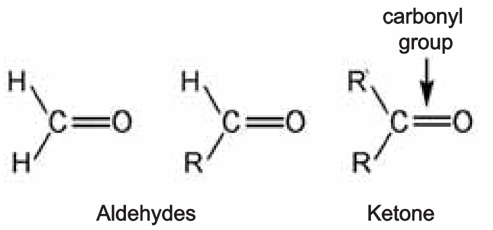
Table 1-87: Physical and chemical properties of falcarinol

CAS number	21852-80-2	 Formula 1-254: Falcarinol
Molecular formula	$C_{17}H_{24}O$	
Molecular weight	244.38 g/mol	

https://pubchem.ncbi.nlm.nih.gov/

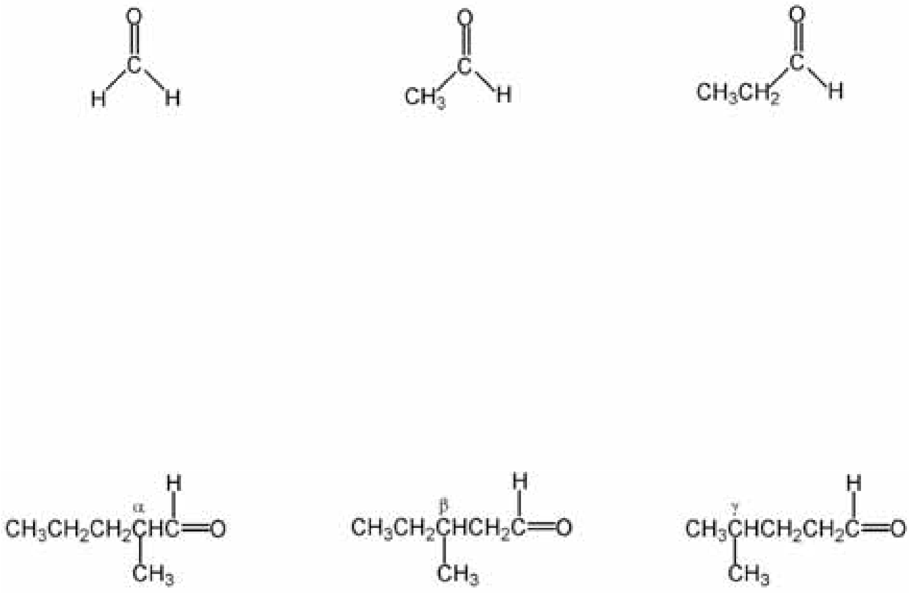
ALDEHYDES AND KETONES

Aldehydes and ketones are organic compounds which contain a carbonyl group in their structure. Aldehydes are compounds of the general formula RCHO, while the formula of ketones is RR'CO, in which R i R' are aliphatic or aromatic groups, except from HCHO, in which R=H.

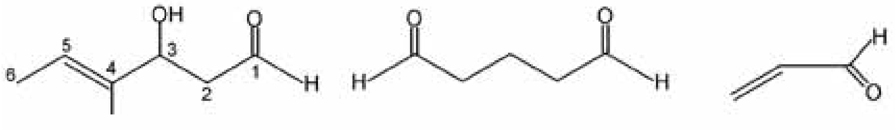


Scheme 1-37

The carbonyl group is responsible for the major physical and chemical properties of aldehydes and ketones. The trivial names of aldehydes are derived from the common name of the carboxylic acid, which is formed by the oxidation of the aldehyde in question and the substitution of the suffix "acid" with "aldehyde". The position of the substituent with respect to the aldehyde group is indicated by the Greek letters α, β, ϒ, etc. The position of a substituent with respect to the aldehyde group is indicated by numbers. According to the IUPAC nomenclature, aldehydes are treated as alkane derivaties: alkanals. Compounds where the CHO group is bonded directly to the ring are called carbaldehydes.

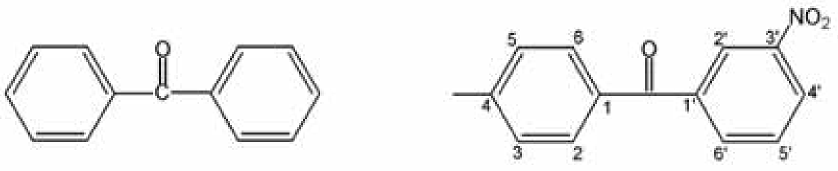


Scheme 1-39



Scheme 1-40

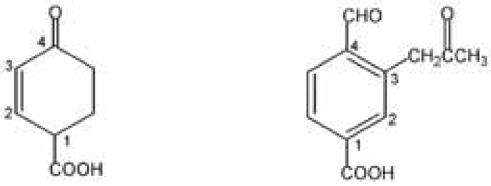
For ketones, the substituted groups, alkyl or aryl, are first written, and then the word ketone is added at the end. The names of phenyl ketones, in which the carbonyl group is directly attached to the benzene nucleus, end with the suffix, “fenon”. According to the IUPAC nomenclature, ketones are regarded as alkane derivatives: alkanones. Cyclic ketones are cycloalkanones.



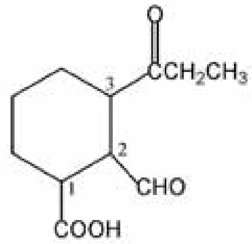
Scheme 1-41

Table 1-88: Examples of suffixes and prefixes in some compound classes

Compound class	**Suffix**	**Prefix**	**Example**
Karboxylic acids	-lic acid	carboxy-	Propanoic acid
Aldehydes	-al	oxo-	Propanal
Ketones	-on	oxso-	Propanone
Alcohols, phenols	-ol	hydroxy-	Propanol
Thiols	-thiol	mercapto-	Propanethiol
Amines	-amin	amino-	1-Propanamine
Ethers	-eter	alkoxsy-, oxsa-	Dimethyll-ether
Sulphides	-sulfide	alkylthio-, thia-	Dimethyl-sulfide
Alkenes	-en	alkenyl-	Propene
Alkynes	-in	alkynil-	Propine
Halogenes	-halogenid	halo-	2-Brompropan
Nitro	-	nitro-	2-Nitropropane
Alkanes	-an	alkyl-	Propane



Scheme 1-42



Scheme 1-43

Due to the carbonyl group, aldehydes and ketones are polar compounds and do not form intermolecular hydrogen bonds. Lower aldehydes and ketones are soluble in water and have a higher boiling point than non-polar compounds of the same molecular weight. They do not form intermolecular hydrogen bonds and have a lower boiling point than alcohols and carboxylic acids.

Table 1-89: Physical properties of aldehyde

Aldehyde	**Melting point, ^{0}C**	**Boiling point, ^{0}C**	**Solubility, g/100 g water**
Formaldehyde	-92	-21	v.r.v.
Acetaldehyde	-121	20	bes.
Propionaldehyde	-81	49	16
n-butyraldehyde	-99	76	7
n-caproaldehyde		131	s.r.
Phenylaldehyde		194	s.r.
Benzaldehyde	-26	178	0.3
Salicylaldehyde	2	197	1.7

https://pubchem.ncbi.nlm.nih.gov/

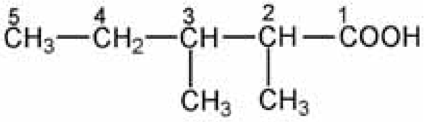
Table 1-90: Physical properties of ketones

Ketone	**Melting point, ^{0}C**	**Boiling point, ^{0}C**	**Solubility, g/100 g water**
Acetone	-94	56	bes
Ethyl-methyl-ketone	-86	80	26
2-pentanone	-78	102	6.3
3-pentanone	-41	101	5
2-hexanone	-35	150	2.0
3-hexanone		124	s.r.
Acetophenon	21	202	
Benzophenone	48	306	

https://pubchem.ncbi.nlm.nih.gov/

CARBOXYLIC ACID DERIVATIVES

Carboxylic acid derivatives are actually compounds derived from carboxylic acids. Carboxylic acids are also known as fatty acids, because they were first isolated from natural sources (fats and waxes). They were given names that indicated the place where they were found (e.g., formic, acetic, and butyric). IUPAC names are given to acids with more than 10 C atoms rather than common names. This is probably because acids with an even number of C atoms are found in fats, while acids with an odd number of C atoms are prepared synthetically. As with other homologous series, those acids having an isopropyl group at the end of a normal hydrocarbon sequence are given the prefix “iso”: e.g., isobutyric acid. IUPAC nomenclature prescribes that the names for acids are made from the name of the saturated hydrocarbon and the suffix, “ic”. Saturated cyclic acids are known as as cycloalkanecarboxylic acids.



$$\overset{5}{C}H_3-\overset{4}{C}H_2-\underset{CH_3}{\overset{3}{C}H}-\underset{CH_3}{\overset{2}{C}H}-\overset{1}{C}OOH$$

Formula 1-255: 2,3-dimethylpentanoic acid

Carboxylic acid derivatives can be formed by the substitution of the -OH group in the -COOH group, and by the substitution of H atoms in the radical. The first group includes the following:

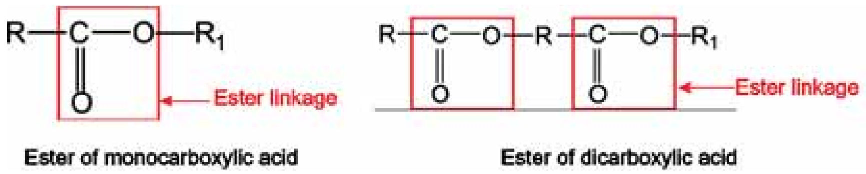
- Acid chlorides
- Acid amides
- Acid anhydrides
- Acid esters

The second group of carboxylic acid derivatives, which are formed by the substitution of H atoms in the acid radical, include the following:

- Halocarboxylic acids
- Oxycarboxylic acids
- Aminocarboxylic acids
- Ketocarboxylic acids

Acid chlorides or acyl chlorides are highly reactive compounds used in organic synthesis: their reactions with water form carboxylic acids, their reactions in alcohol produce esters, and their reactions with ammonia form acid amides. Carboxylic anhydrides contain two acyl residues bonded by an oxygen bridge. They are more reactive than carboxylic acids. Monocarboxylic acids produce acyclic anhydrides, while dicarboxylic acids form cyclic anhydrides. The word anhydride means without water. Anhydrides are formed by the removal of one molecule of water from two molecules of carboxylic acid. Carboxylic acid anhydrides have similar reactions to acid chlorides: they form carboxylic acids with water, esters with alcohols, and amides with ammonia.

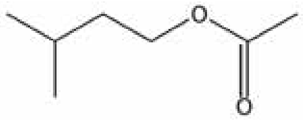
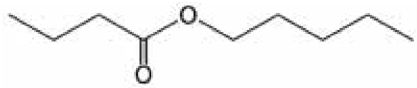
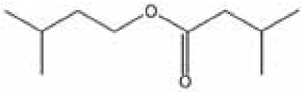
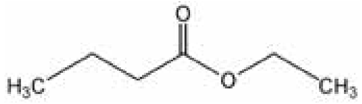
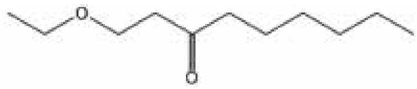
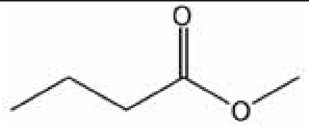
Carboxylic acid esters are formed by the substitution of -OH from the carboxylic group with an alkoxide residue. There are monocarboxylic and dicarboxylic acids containing two ester bonds (double esters).



Scheme 1-44

According to the IUPAC nomenclature, they are named after the acid or alcohol from which they are derived. The name of the alkyl group of alcohol is indicated first, followed by acid, except that the suffix “oate” is used: e.g. CH_3-O-CH_3 becomes methyl ethanoate or, according to the trivial nomenclature, methyl acetate or methyl ester of ethanoic (acetic) acid. Carboxylic acid esters are degraded into carboxylic acid and alcohol, while the reverse reaction from hydrolysis is known as esterification. Basic hydrolysis or saponification produces a carboxyl ion and alcohol. Hydrolysis is very slow. The compounds of the ester group are found in plant cells, and they create the aroma of fruits and flowers. Carboxylic acid esters are essential components of fats, oils, and waxes. The phosphate esters from sugar can be found in nucleic acids and phospholipids.

Table 1-91: Esters in different plants

Ester	Plant	Compound
Isopenthyl-acetate	Banana	 Formula 1-256
N-pentyl-butyrate	Apricot	 Formula 1-257
Isopentyl-isovalerate	Apple	 Formula 1-258
Ethyl-butyrate	Pear	 Formula 1-259
Ethyl-nonane	Flowers	 Formula 1-260
Methyl-butyrate	Pineapple	 Formula 1-261
Octyl-acetate	Orange	 Formula 1-262

Carboxylic acid amides are formed by the substitution of -OH from the carboxylic group with an amino group. Amides are amphoteric compounds. Hydrolysis produces the carboxylic acid from which the ammonia was formed. Carbonic acid diamide is carbamide. Substituted carboxylic acids are classified by the number of halogen atoms as follows:

- Monohalogen carboxylic acids
- Dihalogen carboxylic acids
- Trihalogen carboxylic acids
- Polyhalogen carboxylic acids

They are also classified according to the position of halogen relative to the carboxyl group:

- α-halogencarboxylic acids
- β-halogencarboxylic acids
- ϒ-halogencarboxylic acids.

Oxycarboxylic acids contain a hydroxyl group as a substituent in the radical, and they can be the following:

- Acyclic oxycarboxylic acids
- Cyclic oxycarboxylic acids

They can also be the following:

- Monocarboxyl monooxy
- Dicarboxyl dioxy
- Dicarboxyl monooxy
- Tricarboxyl monooxy acids

They can also be classified according to the position of the hydroxyl group, as follows:

- α-oxy
- β-oxy
- ϒ-oxy

Oxy acids are two-function compounds which, due to the presence of two functional groups, alcohol OH and carboxyl COOH, exhibit reactions with both alcohol and acid, as well as reactions that are characteristic of the presence and interaction of both functional groups. Dicarboxylic acid is tartaric acid, which is found in fruits, mostly grapes, and its salts are called tartarates. Tricarboxyl monooxy acid is citric acid, which is found in raspberries, gooseberries, grapes, and lemons, and its salts are called citrates.

Oxalates

Several types of oxalates have been found in plants. Oxalic acid is a product of cell metabolism and is found in some plant species. Soluble oxalic acid salts including sodium, potassium, ammonium, and acid potassium oxalate are found in many plants, including edible ones. Soluble salts are toxic and can lead to systemic poisoning (James, 1972). Plants with insoluble calcium oxalate are the most common cause of poisoning. In 1986, two genera of plants, *Dieffenbachia* and *Philodendron*, caused 7,000 cases of poisoning in the USA, or 8% of all plant poisoning (Litovitz *et al*. 1987). Calcium oxalate is oxalic acid calcium salt with the following chemical formula: CaC_2O_4. This is a compound which forms crystals in plants known as raphides. Many plants, from more than 1,000 genera, accumulate calcium oxalate in their organs. The accumulation of calcium oxalate is associated with the detoxification of calcium oxalate in the plant organism (Gary, 2009). Some plants, such as *Dieffenbachia*, species of the *Oxalis* genus, *Parthenocissus quinquefolia*, and *Arum italicum*, contain large amounts of calcium oxalate. Poorly soluble calcium oxalate is found in the roots, stems, and leaves of plants. Plants from the *Philodendron* genus contain large amounts of calcium oxalate; therefore, ingesting certain parts of these plants can cause poisoning symptoms.

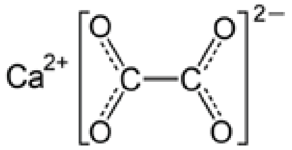
The following table gives information on plants containing oxalates based on the data from the literature.

Table 1-92: Overview of families and genera containing oxalates (Adapted from Morrison and Savage, 2003)

Family	**Genus**	**Oxalate form**	**Amount**
Agavaceae	*Agave*	Calcium oxalate	n/a
Amaranthaceae	*Amaranthus*	Potassium acid oxalate	0.74-1 %
Araceae	*Aglaonema*	Calcium oxalate	n/a
	Alocasia	Calcium oxalate	n/a
	Amorphophalus	Calcium oxalate	n/a
	Anthurium	Calcium oxalate	n/a
	Arisaema	Calcium oxalate	n/a
	Arum	Calcium oxalate	n/a
	Caladium	Calcium oxalate	n/a
	Colocasia	Calcium oxalate	n/a
	Dieffenbachia	Calcium oxalate	Stem 0.4 %.
	Epipremnum	Calcium oxalate	n/a
	Monstera	Calcium oxalate	n/a
	Philodendron	Calcium oxalate	0.7 %.
	Spathiphyllum	Calcium oxalate	n/a
	Syngonium	Calcium oxalate	n/a
	Xanthosoma	Calcium oxalate	n/a
	Zantedeschia	Calcium oxalate	n/a
Araliaceae	*Scheffera*	Unknown	0.9–1.5 %
Begoniaceae	*Begonia*	Calcium oxalate	n/a
Bromeliaceae	*Ananas*	Calcium oxalate	n/a
Caprifoliaceae	*Symphoricarpus*	Calcium oxalate	n/a
Chenopodiaceae	*Beta vulgaris*	Soluble oxalate	>10%
	Halogeton	Sodium oxalate	>10–34.5 %
	Sarcobatus	Sodium oxalate	>10%
Liliaceae	*Ornithogalum*	Calcium oxalate	n/a
Oxalidaceae	*Oxalis*	Potassium acid oxalate	7–0 %
Palmae	*Caryota*	Calcium oxalate	Fruits 0.05 %
Polygonaceae	*Setoria*	Ammonium oxalate	n/a
	Rheum	Potassium oxalate	0.28 %
	Rumex	Potassium acid oxalate	>10%
Rubiaceae	*Psychotria*	Calcium oxalate	n/a
Vitaceae	*Parthenocissus*	Soluble oxalate	n/a

n/a, not available

Table 1-93: Physical and chemical properties of calcium ethanedioate

CAS number	25454-23-3 anhydrous 5794-28-5 monohydrate	 Formula 1-263: Calcium ethanedioate
Molecular formula	CaC$_2$O$_4$	
Molecular weight	128.097 g/mol anhydrous 146.112 g/mol monohydrate	
Boiling point	200 ^{0}C, with decomposed (monohydrate)	
Solubility in water	0.67 mg/L (20 ^{0}C)	

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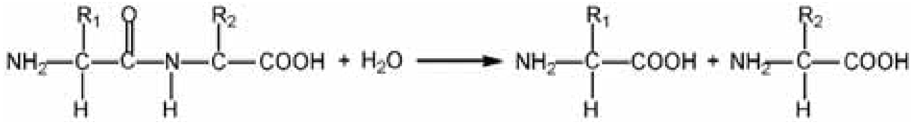
PROTEOLYTIC ENZYMES

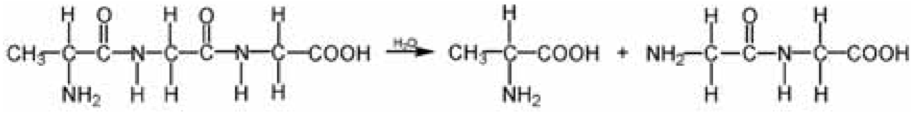
They belong to the hydrolytic enzymes group because they catalyse the hydrolysis of a peptide bond in a protein or peptide (Rawlings and Salvesen, 2013). The activity of these enzymes results in the complete hydrolysis of proteins to free amino acids.



Scheme 1-45

According to the action in the protein, proteolytic enzymes are divided into peptidases (exopeptidases) and proteinases (endopeptidases). Peptidases exhibit activity at the ends of protein molecules, which hydrolyse the peptide bond of terminal amino acids, in order to obtain solely free amino acids as a product. The hydrolysis of terminal amino acids is carried out sequentially: i.e. an amino acid is hydrolysed from the polypeptide by an amino acid. Peptidases are divided into aminopeptidases and carboxypeptidases.

Aminopeptidases are enzymes that require the presence of a free amino group at the NH$_2$ end of the polypeptide chain, which usually act on proteins and peptides (Taylor, 1993). Thus, the aminopeptidase enzyme has been found in animal tissues, which specifically hydrolyses tripeptides, such as L-alanyl-glycyl-glycine, thereby yielding L-alanine and L-glycyl-glycine as products.



Scheme 1-46

Carboxypeptidases require the presence of a free carboxyl group at the COOH-end of the polypeptide for hydrolytic action and they hydrolyse the last peptide bond in the polypeptide. Free amino acids are obtained as a product of complete reaction. There are two types of carboxypeptidase. Carboxypeptidase A, whose activity requires the presence of zinc ion (Zn^{2+}), which is an integral part of the enzyme's active centre and is required to catalyse the hydrolysis of a peptide bond (Casiday and Frey, 1998). This enzyme hydrolyses the peptide bond at the COOH-end of the polypeptide, regardless of the type of terminal amino acid, although it is most active in case of aromatic amino acids (Phe, Tyr, Trp). Carboxypeptidase B is specific for peptide bonds that form arginine (Arg), lysine (Lys), or histidine (Hys) at the COOH-end of the polypeptide.

The main proteolytic enzyme of the stomach is pepsin, which is synthesised in mucosal cells in inactive form in a proenzyme known as pepsinogen. It is stable at a neutral pH, but quickly converts to pepsin in the acidic environment of the stomach juice (the optimum pH for the activity of pepsin is 2). Pepsin can be activated by pepsinogen in an autocatalysis process involving the release of a 44 amino acid polypeptide from the NH_2 end of pepsinogen. This polypeptide acts as a pepsin inhibitor.

Pepsin hydrolyses the peptide bond between the amino groups of aromatic amino acids, most commonly tyrosine, and the carboxyl group of the adjacent amino acid. In addition, it hydrolyses the bond between the amino group of glutamic acid and the carboxyl group of leucine. The reaction products are oligopeptides of different lengths. The movement of partially degraded proteins from the stomach to the duodenum leads to hydrolysis with trypsin and chymotrypsin.

Trypsin is an enzyme that is synthesised in the pancreas in an inactive form of trypsinogen and, as such, it is secreted into the duodenum, together with the alkaline juice of the pancreas, in order to neutralise the acidic environment and activate trypsin, whose optimal activity requires a pH of 8. Trypsinogen is autocatalytically activated into trypsin by trypsin activity alone; also, the intestinal enzyme enterokinase can specifically activate trypsinogen and convert it to trypsin (Shah and Mital, 2018). Trypsinogen is formed from a single polypeptide chain, and the activation process involves the hydrolysis of a peptide bond, whereby one hexapeptide (Val-/Asp/4-Lys) is carried out from the NH_2 end of trypsinogen. Trypsin hydrolyses the peptide bond between the carboxylic group of basic amino acids (Lys, Arg, His) and the amino group of the adjacent amino acid.

Chymotrypsin is synthesised in the pancreas in the inactive form of chymotrypsinogen, which is a polypeptide chain of 245 amino acids and is completely catalytically inactive. Activation of chymotrypsinogen is slightly more complex than the activation of pepsinogen and trypsinogen (Appel, 1986).

Chymotrypsinogen is activated in a fully active enzyme π- chymotrypsin when trypsin hydrolyses the peptide bond between arginine at position 15 and isoleucine at position 16 in the polypeptide (Berg *et al.* 2002). The formation of α-chymotrypsin, which is an active, stable form of chymotrypsin, is related to the excision of two dipeptides. The first is Ser-Arg (positions 14 and 15), and the second is Thr-Asp (positions 147 and 148) in the π-chymotrypsin polypeptide chain. Due to the disulphide bonds (covalent bonds between sulphur atoms of two cysteines; there are five in a molecule), the three newly formed polypeptides remain bound to each other. This activation changes the conformation of chymotrypsinogen, resulting in the formation of an active centre of chymotrypsin, which consists of histidine, serine, and asparagine. Chymotrypsin performs hydrolysis on proteins at the site of the peptide bond involving the carboxyl group of aromatic acid, primarily phenylalanine or tyrosine, and the amino group of the adjacent amino acids. The highest activity is exhibited in the hydrolysis of the peptide bond formed by the carboxyl group of tyrosine and the amino group of glycine.

Inactive forms of enzymes are proenzymes. If the enzymes are synthesised in the active form, this would result in the hydrolysis of proteins in the cells synthesising them (pancreatic cells and gastric mucous cells). This is why proenzymes that are activated after excretion are synthesised. The pancreas, for example, is multi-protected from the activity of the trypsin and chymotrypsin that it synthesises. First, both enzymes are synthesised in an inactive form in the acinar cells of the exocrine pancreas. In addition, they are packed in special granules, which are wrapped in a membrane that represents a barrier between the cell content and proenzymes.

Namely, the acute disease pancreatitis is characterised by disruption of the protective mechanisms of the pancreas, leading to premature activation of proteolytic enzymes: i.e. their activation in the pancreas, which creates pancreatic proteolysis.

Diallyl disulphide

Diallyl disulphide is an organic compound containing 6 carbon atoms and with a molecular weight of 146,274 Da.

Table 1-94: Physical and chemical properties of diallyl disulphide

CAS number	2179-57-9	 Formula 1-264: Diallyl disulphide
EC number	218-548-6	
Molecular formula	$C_6H_{10}S_2$	
Molecular weight	146.27 g/mol	

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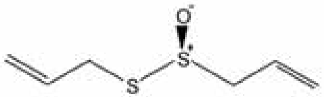
Allicin or alliin

As early as 1944, an oily, colourless, and volatile substance called allicin was isolated from garlic by distillation with water and alcohol under reduced pressure (Chester and Baile, 1944). Experiments have found that an aqueous solution of allicin has a strong bactericidal activity against some microorganisms. For example, even in a dilution of 1: 85,000 to 1: 125,000, allicin has antibacterial activity against Gram-positive and Gram-negative microorganisms, such as *Staphilococcus* and *Streptococcus*, which are inducers of typhoid, dysentery, and cholera. Its structure was determined in 1947. In the same year, a new compound called alliin, which has the form of crystalline needles and is odourless, was isolated from garlic and cloves (Borlinghaus et al. 2014). Alliin also has antibacterial properties, but its activity requires the aliinase to be fermented from fresh garlic in order to exhibit antibacterial activity against *Streptococcus piogenes*, as well as inducers of typhoid, tuberculosis, and dysentery. When garlic is chopped, the alliin lyase enzyme converts alliin to allicin, which is responsible for its smell. Allicin has a functional group characteristic of thiosulphinate, RS(O)SR, which is not present unless an onion is chopped. Allicin is unstable and decomposes in 16 hours at 23^0C. Allicin is an oily, yellowish liquid with a unique smell. It is actually a sulphenic acid thioester, which is also known as thiosulphinate (Nikolić *et al.* 2004). Its biological activity is related to its antioxidant activity and its reaction with protein-containing thiols (Focke *et al.* 1990). In addition to its remedial effects on normalising the balance of lipoproteins and reducing blood pressure, it can have toxic effects in larger amounts, and it can cause dermatoses in some people.

Table 1-95: Physical and chemical properties of allicin

CAS number	539-86-6	 Formula 1-265: Allicin
EC number	208-727-7	
Molecular formula	$C_6H_{10}OS_2$	
Molecular weight	162.26 g/mol	
Density	1.112 g/cm^3	
Melting point	<25^0 C	
Boiling point	decomposed	

https://pubchem.ncbi.nlm.nih.gov/

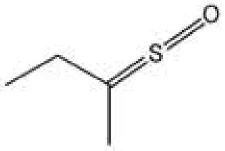
Many *Allium* plant species have irritant and allergenic effects. This comes from the sulphur, which is contained by amino acids in intact plants. There is very little difference between S-(1-propenyl)-L- cysteine sulphoxide and S-(2-propenyl)-L-cysteine sulphoxide or alliin. Diallyl sulphide, allyl propyl sulphide, and allicin have smaller molecular masses than garlic allergen.

Table 1-96: Properties of allyl propyl disulphide

CAS number	2179-59-1	 Formula 1-266: Allyl propyl disulphide
EC number	218-550-1	
Molecular formula	$C_6H_{12}S_2$	
Molecular weight	148.282 g/mol	
Boiling point	66-68 ^{0}C	

https://pubchem.ncbi.nlm.nih.gov/

Table 1-97: Physical and chemical properties of thiopropanal S-oxide

CAS number	32157-29-2	 Formula 1-267: Thiopropanal S-oxide
Molecular formula	C_3H_6OS	
Molecular weight	90.14 g/mol	

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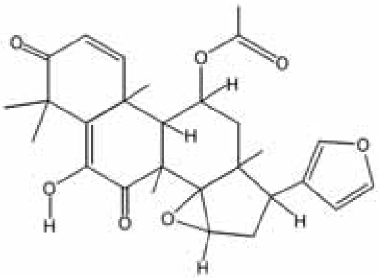
Bromelin or Bromelain

Bromelin is a mixture of proteolytic enzymes extracted from pineapple (*Ananas comosus*). It is found in pineapple trees and its fruit *(*Ketnawaa *et al.* 2012*)*. It has been used in Central and South America for centuries as a remedy for digestive problems and inflammation. It can cause allergies in people. Bromelin was first isolated from pineapple by Venetian chemist Ricente Marcano in 1891. This term was originally used for any protease isolated from *Bromeliaceae* family plants. Today, it is used as a meat tenderiser (meat softening powder). The optimum temperature for enzyme activity needs to last for few minutes. After one hour at a temperature of 50^{0}C, 83 % of the enzyme is degraded and, at a temperature of 40^{0}C, its activity is 100% retained (Hale *et al.* 2005). The enzyme can retain its activity for at least one week at room temperature (Jutamongkon and Charoenrein, 2010)

OTHER COMPOUNDS

Anthothecol

Table 1-98: Physical and chemical properties of anthothecol

CAS number	10410-83-0	 Formula 1-268: Anthothecol
Molecular formula	$C_{28}H_{32}O_7$	
Molecular weight	480.557 g/mol	

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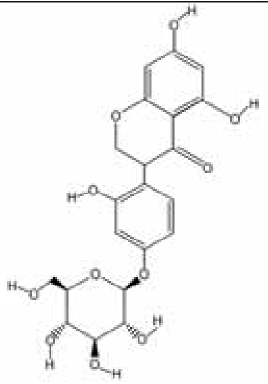
Dalbergion

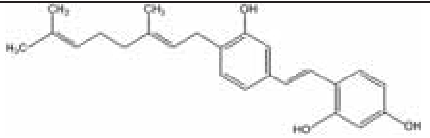
Table 1-99: Physical and chemical properties of dalbergion

CAS number	160206-04-2	 Formula 1-269: Dalbergion
Molecular formula	$C_{21}H_{22}O_{11}$	
Molecular weight	450.396 g/mol	

https://pubchem.ncbi.nlm.nih.gov/

Chlorophorin

Table 1-100: Physical and chemical properties of chlorophorin

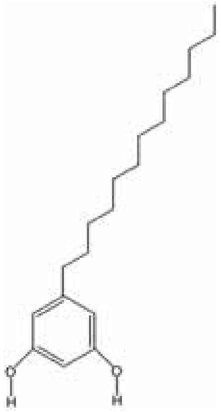
CAS number	534-41-7	 Formula 1-270: Chlorophorin
Molecular formula	$C_{24}H_{28}O_4$	
Molecular weight	380.484 g/mol	

https://pubchem.ncbi.nlm.nih.gov/

It causes allergic contact dermatitis (Kanerva *et al*. 2001).

Grevillol

Table 1-101: Physical and chemical properties of Grevillol

CAS number	5259-01-8	 Formula 1-271: Grevillol
Molecular formula	$C_{19}H_{32}O_2$	
Molecular weight	292.463 g/mol	

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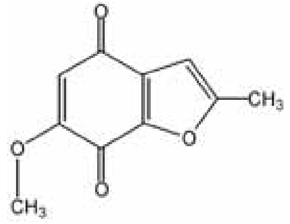
It causes allergic reactions on the skin (category 1) and severe eye damage (category 1) (Hoffman et al. 1985).

Acamelin

Acamelin is found in the Australian plant, *Acaciai melanoxylon*; it is used for commercial purposes. In 1925, it was found that its constituents are harmful to health. It belongs to the furanoquinones group.

Table 1-102: Physical and chemical properties of acamelin

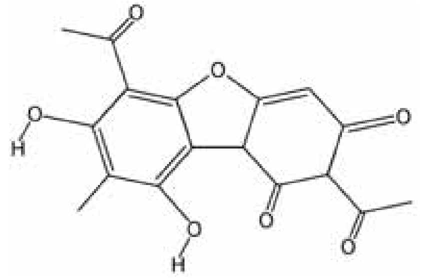
CAS number	74161-27-6	 Formula 1-272: Acamelin
Molecular formula	$C_{10}H_8O_4$	
Molecular weight	192.17 g/mol	

https://pubchem.ncbi.nlm.nih.gov/

Usnic acid

In folk medicine, the use of lichen has a long history. The *Pseudoevernia furfuracea* species was probably used in ancient Egypt (17th or 18th century BC). Hippocrates recommended the use of *Usnea barbata* to treat certain diseases. In the Middle Ages, some lichen species, such as *Lobaria pulmonaria*, *Parmelia sulcata*, and *Peltigera canina*, were valued by medical practitioners in Europe. The use of lichen in traditional medicine has been preserved to this day to a small extent. Some lichens, such as *Cetraria islandica*, are still used in scientific medicine. Due to its vitamin C content, *Cetraria cucullata* is used to suppress avitaminoses, while substances with antibiotic effects have been found in some lichen species. One of them is yellow pigment, which is usnic acid; this is a broad-spectrum antibiotic that is now widely used in many commercial products and it is effective at treating inflammatory processes and flesh wounds (Savić, 1995).

Table 1-103: Physical and chemical properties of usnic acid

CAS number	125-46-2	
Molecular formula	$C_{18}H_{16}O_7$	
Molecular weight	344,32	
Melting point	200 ^{0}C	
Boiling point	594.8 ^{0}C (na 760 mm Hg)	
Density	1.49 g/cm^3	Formula 1-273: Usnic acid

https://pubchem.ncbi.nlm.nih.gov/

Recent research shows that, in addition to aromatic herbs, lichens are a significant raw material for food, pharmaceutical, cosmetic, animal feed, spice, perfume, paint, and other industries. It is known that lichens are able to survive and adapt to a wide variety of habitats due to their slow metabolism and production of biologically active compounds (Cocchietto *et al.* 2002). A detailed overview of the sources of medicinal substances in different lichen species can be found in recent literature (Shukla *et al.* 2010). *Usnea barbata* or old man's beard (Old Man's Beard, Beard Lichen, Treemoss) belongs to the *Parmeliaceae* family and grows on trees and branches of various woody and conifer species. This lichen is a combination of two types of organisms, fungus (*Ascomycota*) and algae (*Chlorophyta*), which live in symbiosis. This lichen is difficult to define because of its extreme morphological variability. It grows in the northern hemisphere of Asia, Europe, and North America. Due to the continuous decrease in its number of habitats, it is a protected species in Germany and Nepal. Today, in Germany, raw materials for the industrial production of *Usnea barbata* are imported from Indonesia. Usnea has been used in Chinese medicine, contemporary homeopathy, and traditional medicine around the world for 3000 years (Simović, 2003). *Usnea barbata* has been approved in the German commission's monographs for the treatment of mild inflammations in the mucous membranes of the mouth and throat. In recent literature, it is considered that *Usnea barbata*'s wide range of biological effects, such as antibacterial, antifungal, antiviral, analgesic, antipyretic and cytotoxic activity, are due to the presence of usnic acid (Ingolfsdottir, 2002). This is also found in species from the following genera: *Alectoria*, *Cladonia*, *Lecanora*, *Ramalina*, and *Evernia*. Usnic acid [2,6-diacetyl-7,9-dihydroxy-8,9b-dimethyl-1,3 (2H,9bH)-dibenzo-furandione] ($C_{18}H_{16}O_7$, CAS number: 125-46-2), which was isolated in 1844, is one of the most studied secondary metabolites in the lichen species, as it has commercial applications in the production of pharmaceuticals, fragrances, and in ecology (in the control of insects and other pests) (Bazin *et al.* 2008, Ingólfsdóttir 2002). As a pure substance, it is added to creams, toothpastes, mouthwashes, deodorants, and sunscreens as an active substance or a preservative. Usnic acid has an extremely strong antibacterial effect on Gram-positive bacteria, including strains of methicillin-resistant *S. aureus* (MRSA) and clinical isolates of the *Enterococcus* species (Cocchietto *et al.* 2002; Wenqiang *et al.* 2007). In recent literature (Wenqiang *et al.* 2007), usnic acid's strong antibacterial activity has been observed against Gram-positive and Gram-negative bacteria (*Clostridium perfringens*, *Propionibacterium acnes*, *Bacteroides fragilis*, *Bacteroides vulgatus*, *Peptococcus magnus*, *Fusobacterium nucleatum*, *Prevotella intermedia*, *Veillonella parvula*, and *Porphyromonas gingivalis*), as well as *Malassezia furfur* yeast. Allergies are rare and uncommon (Kanerva *et al.* 2000).

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PART TWO

THE BASIC TRAITS OF PLANTS: CAUSATIVE AGENTS OF DERMATOSES

VASKRSIJA JANJIC AND GORICA DJELIC

Family *Agavaceae*

Agave americana L.
SENTRY PLANT

Genus name. Originates from the Greek word “agauos” meaning “illustrious”, “notably or brilliantly outstanding”, and “magnificent”.

Morphological description. It is a succulent plant and although it is called the century plant, it typically only lives up to 30 years. It only flowers once and dies afterwards. It has 30 to 40 leaves, arranged in a rosette, which are greenish blue in colour. They are fleshy with toothed margins, and a long and sharp spine at the tip. They can be up to 2 m long and 25 cm wide. The flowers are grouped into a complex (panicle) cluster. The length of the inflorescence axis can be up to 12 m and it develops over the course of approximately 10 years. Its radially symmetrical flowers are bisexual. The funnel shaped perigonium consists of six petals, which are greenish yellow in colour with six lobes at the tip. There are six stamens. The syncarpous gynoecium consists of three carpels. The fruit is an elongated capsule with small flat black seeds.

Habitat. It grows in open habitats and on rocks; it is also able to bind soil.

Distribution. It is native to America’s tropical regions, and has been introduced into the remaining parts of the world, including Europe (in the 16th century), Canary Islands, southern China, southern Africa, Australia, and New Zealand. It is grown in Serbia as an ornamental plant.

Variability. There are two subspecies and two varieties within this species:

- ○ *Agave Americana* subsp. *americana*
- ○ *Agave Americana* subsp. *protamericana*
- ○ *Agave Americana* var. *expasa*
- ○ *Agave Americana* var. *oaxacensis*

Main constituents with toxic and dermatological effects. Fresh sap from the leaf contains calcium oxalate raphides that cause erythema, urticaria, and oedema in humans if they reach the skin (Ricks *et al*. 1999). Kerner *et al.* (1973) indicated that the sap from *Agave americana* plants causes acute eczematous dermatitis. The sap of this plant has irritating properties due to calcium oxalate crystals, oxalic acid, and saponins (Bouaziz *et al.* 2014). The dermatitis pathogenesis is related to the high velocity of sputtering sap when the plant is cut with a chainsaw (Lazur’evskii *et al.* 1975). Oxalate crystals and saponins, which are released by the mechanical action of the chainsaw, sputter onto and are then absorbed by the skin. Dermatitis caused by the sap from *Agave americana* plants does not include phototoxic and photoallergic reactions. The mechanism of dermatitis incidence depends on the amount of the sap. Cherpelis and Fenske (2000) identified a new form of dermatitis with the evidence of leukocytoblastic vasculitis. These authors suggest that when oxalic acid crystals are absorbed by the skin, it could result in damage to the vascular organs.

Figure 2-1 (left): *Agava americana* (photo, Vaskrsija Janjic);
Figure 2-2 (right): *Agava americana* L. (photo, Gorica Djelić)

Figure 2-3 (left): *Agava americana* (photo, Vaskrsija Janjic);
Figure 2-4 (right): *Agava americana* L. (pixabay.com)

Figure 2-5: *Agava americana* L. (pixabay.com)

Family *Alstroemeriaceae*

Alstroemeria spp.
PERUVIAN LILY

Genus name. The genus was named after Clas Alströmer, a Swedish baron, who was a close friend of Carl Linnaeus.

Morphological description. Plants from the genus *Alstroemeria* are commonly known as Peruvian lily or lily of the Incas. This is a genus of flowering plants in the family *Alstroemeriaceae*. The family consists of four genera (*Alstroemeria, Bomarea*, *Luzuriaga*, and *Schickendatziella*), which consists of approximately 650 plants. Plants propagate from bulbs. They have fertile and sterile stems that reach 1.5 m in height. The plants have an alternate leaf arrangement. The undersides of the lower petioles face upwards. The leaves are variable in shape and they are not serrated. Each flower has six petals of up to 5 cm long. The flowers are in many shades of red, orange, purple, green, and white with various stripes. There are six stamens, while the stigma has three lobes. The fruit is a capsule with three valves.

Habitat. The majority of its varieties are grown in home gardens. These plants require at least six hours of sunlight, while bulbs endure temperatures of -5ºC.

Distribution. They originate from South America, and have been naturalised in the United States, Mexico, Australia, New Zealand, and the Canary Islands. All of its species originate from two different centres: Chile and eastern Brazil. The species from Brazil are summer-growing plants, while those from Chile are winter-growing.

Variability. There are over 122 species belonging to this genus, some of which are cultivated and some appear as weed plants (e.g., *Alstroemeria pulchella* and *Alstroemeria aurea* in Australia). Many hybrids and at least 190 varieties have been developed. The following varieties have gained the Royal Horticultural Society's Award for Garden Merit:

- Apollo
- Coronet
- Friendship
- Orange Gem
- Orange Glory
- Yellow Friendship

Main constituents with toxic and dermatological effects. Different types of skin irritation result from a reaction to the tulipalin contained in plants from the genus *Alstromeria*. Eczema and erythema immediately appear on the fingertips and then spread to the hands. *Alstromeria* contain glucoside 6-tuliposide A, which is converted to tulipalin A. According to some authors, *Alstroemeria lightu* plants contain 1–2 % tuliposides (Hausen *et al.* 1983; Bjorkner, 1982; Marks, 1988). An extract made from its petals will contain 40.2 ng/100 g tuliposides (0.04 %). Tulipalin A (α-ethylene-γ-butyrolactone) and (+) tulipalin B (β-hydroxy-α-ethylene-γ-butyrolactone) are known allergens that cause various forms of dermatitis. Plants from this genus cause eczema and urticaria on sensitive people's skin. There are certain variations in reactions depending on the type and the species of *Alstroemeria*. It seems that the methylene group in the alpha position of the tulipalin structure is required for allergenic activity.

Figure 2-6: *Alstroemeria* spp (pixabay.com; flowers)

Figure 2-7: *Alstroemeria* spp (pixabay.com)

Family *Anacardiaceae*

Toxicodendron diversilobum (Torr. & A. Gray) Greene

PACIFIC POISON OAK

Genus name. Originates from the Greek words "toxikos" meaning "poison" and "arrows were dipped into poisons ", and "dendron" meaning "tree".

Species name. Derived from the Latin word "diversilobum" meaning "many shaped lobes".

Morphological description. It is a deciduous shrub that grows up to 9 m with a climbing vine of up 30 m. The pinnately veined leaves are usually divided into three leaflets up to 10 cm long, with lobed edges that resemble the leaves of a true oak (*Quercus* sp). The odd leaflet can be positioned on a longer petiole. The leaves are green in spring and red in autumn. White radially symmetrical, bisexual flowers are clustered into terminally arranged panicles. There are five sepals, five petals, and five stamens. The fruit is a drupe. It blossoms from March to June.

Habitat. When it grows in open habitats it is a shrub, but under shady conditions (mixed coniferous forests) it is a climbing vine. It thrives at an elevation of 1.650 m in wetlands.

Distribution. *Toxicodendron diversilobum* (Torr. & A. Gray) Greene is native to the west coast of the USA and Canada. The following species also grow on the American continent:

- *Toxicodendron radicans* in the USA
- *Toxicodendron vernix* along the bank of the Mississippi
- *Toxicodendron pubescens* (syn *Rhus toxicarium*) in the USA
- *Toxicodendron rydbergii* (syn *Rhus rydbergii*) in northern and western regions of the USA and in Canada
- *Toxicodendron striatum* (syn *Rhus striata*) in South America

The species of the genus that grow in Asia are as follows:

- *Toxicodendron acuminatum* in China, India, and Nepal
- *Toxicodendron potaninii* (syn *Rhus potaninii*) in central China
- *Toxicodendron succedaneum* (syn *Rhus succedanea*) in India
- *Toxicodendron sylvestre* (syn *Rhus sylvestris*), in China, Japan, Korea, and Taiwan
- *Toxicodendron vernicifluum* (syn *Rhus verniciflua*) in China and Japan

Variability. No lower taxonomic units have been established within this species.

Main constituents with toxic and dermatological effects. Representatives of the genus *Toxicodendron* (such as *Toxicodendron adicans* Kuntze, *Toxicodendron diversilobum* Greene, *Toxicodendron toxicarium* Gillis, and *Toxicodendron striatum* Kuntze) contain urushiol in their vegetative and reproductive organs, which causes an allergic reaction in approximately 85% of North America's inhabitants, if they come into contact with the Pacific poison oak (Craig *et al.* 1978). At least 25% of these people have an extremely strong reaction. However, this type of dermatitis is not very common in Europe. Usually, the leaves are responsible for contact dermatitis. However, even fallen leaves can cause a skin reaction (Hogan, 2008). On skin contact, *Toxicodendron diversilobum* first causes itching, and then it evolves into dermatitis with inflammation, colourless bumps, and severe itching (Gladman, 2006).

Figure 2-8: *Toxicodendron diversilobium* (Torr. & A. Gray) Greene (http://commons.wikimedia.org)

Figure 2-9: *Toxicodendron diversilobum* (Torr & A. Gray) Greene (https://commons.wikimedia.orgwikiFilePoisonOak_wb_biggerLeaves.jpg)

Family *Apiaceae*

Anethum graveolens L.

DILL

Genus name. Originates from the Greek word “aemi “ meaning “to exhale”, due to its strong odour.

Species name. Originates from the Latin word “graveolens” meaning “strong-smelling”.

Morphological description. An annual herbaceous aromatic plant with a thin spindle-shaped root and an erect, hollow, ridged stem that branches in the upper part. The stem can grow up to 130 cm. The 2–4 pinnate leaves are alternately arranged. The lower leaves have long petioles, while the upper ones are sessile. The flowers are clustered into compound umbel. There is neither an involucre or an involucel. The flowers are bisexual and radially symmetrical with five sepals, five petals, five stamens, and two carpels. The fruit is a mericarp with five filiform ridges. It blooms in July and August.

Habitat. It grows in forests and brushwood in lower and hilly regions.

Distribution. It is native to Central Asia, and cultivated in other parts of the world.

Variability. There are one subspecies and two varieties within the *Anethum graveolens* species:

- *Anethum graveolens* L. subsp. *sowa*
- *Anethum graveolens* L. var. *hortorum*
- *Anethum graveolens* L. var. *graveolens*

Main constituents with toxic and dermatological effects. Phytochemical analysis has shown that dill plants contain alkaloids, terpenoids, flavonoids, saponins, steroids, and tannins. 20 to 60 aromatic compounds were found in dill essential oil, while 12 compounds, which constitute 96.8% of the oil, were identified (Rana and Blazquez, 2014.). The main compounds were α-phellandrene (31.8%), apiole (15.3%), dill ether (13.2%), limonene (11.8%), geraniol (10.6%), and p-cymene (5.3%) (Blazquez and Amparo, 2014). The principal components of oil are α-phellandrene, limonene, and anetofuran/dill ether in the leaf; α-phellandrene, limonene and anetofuran/dill ether in the flower; and cis-carvone and limonene in the seed (Radulescu *et al.* 2010.). When it comes into contact with skin exposed to ultraviolet light, it causes photodermatitis.

Figure 2-10 (left): *Anethum graveolens* L. (photo, Vaskrsija Janjic);
Figure 2-11 (right): *Anethum graveolens* L. (pixabay.com; Anethum-87106)

Figure 2-12: *Anethum graveolens* L. (pixabay.com; dill-261044)

Figure 2-13: *Anethum graveolens* L. (pixabay.com; dill-756192)

Figure 2-14: *Anethum graveolens* L. (pixabay.com; dill-4382098)

Figure 2-15: *Anethum graveolens* L. (pixabay.com; anethum-4744673)

Figure 2-16: *Anethum graveolens* L. (pixabay.com; dill-2826422)

Angelica archangelica L.
GARDEN ANGELICA

Genus name. Originates from the Greek word “angolos” or “aggelos” meaning “angel”, as it is a plant with exceptional medicinal properties.

Morphological description. It is a perennial aromatic plant of up to 3 m in height. The rhizome is turnip-shaped, and its adventitious roots contain yellow latex. The stem is robust and branched, with dark red parenchyma. Three-pinnate leaves are up to 90 cm long and are sheathed at the base of the petioles. The leaves on the upper part of the stem are in a widened sheath. The flowers are clustered into a compound umbel with no involucre, and the involucel is made of a large number of leaflets. The flowers are radially symmetrical, bisexual, and self-pollinated. The sepals are small and its five petals are greenish in colour. There are five stamens and two carpels. The fruit is mericarp, and the seeds have five ridges. The flowering period is during July and August.

Habitat. It grows in water-logged habitats with abundant moisture, along rivers, in brushwood, light forests, and embankments. It thrives in shady and semi-shady places.

Distribution. It is native to northern and central Europe (Russia, Finland, Sweden, Norway, Denmark, Germany, Greenland, Faeroe Islands, and Iceland). It is a protected species in Iceland.

Variability. This species has no lower taxonomic units.

Main constituents with toxic and dermatological effects. Garden angelica roots contain oestrogen, 1% essential oil, coumarins, furocoumarins (osthol, angelicin, osthenol, bergapten, imperatorin, isoimeperatorin, xanthotoxol, and xantothoxin), flavonoids, sitosterol, bitter compounds (bitters), glucose, sucrose, saccharine, and different acids (angelic, citric, fumaric, lauric, myristic, palmitic, stearic, oleic, and linoleic). The seed is rich in fatty oils (furocoumarin), while the leaves contain tannins and bitter compounds (Lewis *et al*. 2007). The principal constituent of the oil is phellandrene: α-phellandrene and β-phellandrene are cyclic monoterpenes (Sowndhararajan *et al.* 2017). Furocoumarin increases skin photosensitivity and can cause dermatitis. This component is responsible for causing phytophotodermatitis in humans.

Figure 2-17: *Angelica archangelica* L. (https://commons.wikimedia.orgwikiFileAngelica_archangelica_RF.jpg)

Figure 2-18: *Angelica archangelica* L. (pixabay.com; garden-angelica-3505262_1280)

Figure 2-19: *Angelica archangelica* L. (pixabay.com; angelica-archangelica-3175408)

Anthriscus sylvestris (L.) Hoff.
COW PARSLEY

Genus name. Originates from either the Greek word "antherix" meaning "thin stem", because the stem is slender, or from "anthos" meaning "flower" and "rhyscos" meaning "hedgerow", as it often grows in hedgerows.

Species name. Originates from the word "sylvestris" meaning "sylvestrian" because it grows in forests.

Morphological description. This is a biennial herbaceous plant with a turnip-shape root. The ribbed stem is erect, thin, hollow, and reach up to 200 cm in height. The 2-3 pinnate leaves are alternately arranged. The lower leaves have petioles, whereas the higher ones are sessile leaves. The flowers are clustered into a compound umbel. There is no involucre, while the involucel is composed of 5–8 broad-lanceolate leaflets. The flowers are bisexual and radially symmetrical. The calyx is less developed. The corolla is composed of five small obovate greenish-yellowish petals. There are five stamens and two carpels. The fruit is a 10 mm long elongated lanceolate mericarp. The flowering period is from April to July.

Habitat. It grows in wet and sunny places, on soils rich in nitrogen, and on the edge of forests.

Distribution. It is native to Europe, west Asia, and north Africa. It has been introduced to America. It is cultivated.

Variability. There are seven subspecies and three varieties within *Anthriscus sylvestris*:

- *Anthriscus sylvestris* subsp. *fumarioides*
- *Anthriscus sylvestris* subsp. *faurei*
- *Anthriscus sylvestris* subsp. *nemorosa* C. Y. Wu & F. T. Pu
- *Anthriscus sylvestris* subsp. *alpina*
- *Anthriscus sylvestris* subsp. *candollei*
- *Anthriscus sylvestris* subsp. *alpestris*
- *Anthriscus sylvestris* subsp. *nitida*
- *Anthriscus sylvestris* var. *sylvestris*
- *Anthriscus sylvestris* var. *angustisecta*
- *Anthriscus sylvestris* var. *gracilis*

Main constituents with toxic and dermatological effects. The cow parsley plant contains smaller amounts of essential oil (0.3% in the fresh plant and 0.9% in seeds). The chemical compounds in cow parsley are as follows: lignans (nemerosin, yatein, and deoxypodophyllotoxin), flavonoids (apiin, apigenin, quercetin, and rutin), coumarins, sucrose, linolenic, linoleic, oleic, palmitic, and stearic acid, etc. The concentration of flavonoids in the leaves is many times higher than in the roots.

Milovanović *et al*. (1996) isolated not only known substances, such as stigmasterol, o-cresol and p-cresol, but also p-cymene, eugenol, and pentacyclic terpenes from purified extracts of above-ground plant parts. The same authors also established that the species does not contain photoactive furocoumarins. Olaru *et al*. (2015) pointed out that the roots contain Z-β-ocimene, α-pinene, coumarins (scopoletin, isoscopoletin, bergaptene), lignans (anthricin, anthriscusin, nemorosin), deoxypodophyllotoxin, podophylltoxin, yatein, and anhydropodorhizol. The leaves contain monoterpenes (β-phellandrene, β-myrcene, sabinene, Z-β-ocimene), while the flowers and leaves contain the following phytochemical components: benzyl alcohol, 2-phenyl ethanol, eugenol, soligenol, (Z)-3 hexenol, α-pinene-7-ol acetate, and β-farnesene (Berger, 2007). It causes photodermatitis on contact with skin and in the presence of light.

Figure 2-20: *Anthriscus sylvestris* (pixabay.com; cow-parsley-116313_1280)

Figure 2-21: *Anthriscus sylvestris* (L.) Hoff (photo, Gorica Djelic)

Figure 2-22 (left): *Anthriscus sylvestris* (L.) Hoff. (photo, Gorica Djelic);
Figure 2-23 (right): *Anthriscus sylvestris* (L.) Hoff. (photo, Gorica Djelic)

Apium graveolens L.
CELERY

Genus name. Originates from the Latin word “apium” meaning “celery”.

Species name. Originates from the Latin word “graveolens” meaning “strong smelling”.

Morphological description. Celery is a biennial aromatic plant. A spindle-shaped rhizome and rosulate leaves develop during the first year. The pinnate leaves are developed on long succulent petioles. During the second year, the root lignifies (it is fleshy in cultivated species) and the ribbed, branched stem grows up to 100 cm. Alternate, almost sessile, leaves are divided into three segments. A compound umbel has 6–12 rays of unequal length and there is no involucre or involucel. The flowers are small, bisexual, and radially symmetrical. There are five coalescent sepals, five petals, five stamens, and the gynaecium of two carpels. The fruit is a mericarp and the seeds are semi-circular. It blossoms from June to September.

Habitat. It grows on saline soils, wet meadows, and marshy areas.

Distribution. Celery belongs to the Mediterranean floral element. It is native to Europe and northern Africa, and it is cultivated all over the world.

Variability. *Apium graveolens* var. *rapaceum* is the variety most often grown in Europe, while *Apium graveolens* var. *secalinum* is cultivated in eastern Asia and the Mediterranean region. Cultivated varieties differ in the colour of their leaves, production region (temperate of subtropical regions), and height (tall, medium, and dwarf). Celery was grown by the ancient Greeks and Egyptians. It has been cultivated in China since the 6th century.

Main constituents with toxic and dermatological effects. Celery seeds contain carbohydrates, flavonoids, alkaloides, steroids, glycosides, furanons (celerin, bergapten, apiumoside, apiumetin, apigravrin, osthenol, isopimpinellin, isoimeperatorin, celereosides 5- and 8-hydroxy methoxypsoralen), apigenin, isoquercitrin, and tannins.

Celery seeds, stems, and leaves contain sesquiterpene alcohol, fatty acids, salinine, limonene, p-pinene, camphene, α-thuyene, α-pinene, p-phellendrene, p-cymene, i-terpinene, sabinene terpinolene, myristicic acid, linoleic acid, petroselinic acid, palmitoleic acid, palmitic acid, oleic acid, myristoleic acid, stearin acid, santalol, β-eudesmol, α-eudesmol, sedanenolide, and 3-n-butyl phthalide. The major constituents of celery seed oil are limonene (approximately 60%), selinene (10%), furocoumarins, furocoumarin glycosides, and their flavonoids (Wesam *et al.* 2015a; Wesam *et al.* 2015b). The leaves contain the following furocoumarins: psoralen, bergapten, cantotoxin, and isopimpinellin.

Celery roots/tubers contain phenolic derivatives (such as caffeic acid, ferulic acid, and p-coumarin derivatives), coumarin, scopoletin, methoxsalen (8-methoxypsoralen), 5-methoxypsoralen, and profilin (Api G_1) (Kootti and Daraei, 2017; Al-Snafi, 2014). When it comes into contact with skin, it may cause dermatitis (phytophotodermatitis) primarily due to its psoralen (furocoumarin) content (Ermertcan *et al*. 2007).

Figure 2-24: *Apium graveolens* (photo, Vaskrsija Janjic)

Figure 2-25: *Apium graveolens* L. (pixabay.com; celery-2552297)

Figure 2-26: *Apium graveolens* (photo, Vaskrsija Janjic)

Figure 2-27. *Apium graveolens* L. (pixabay.com; celery-3654966)

Conium maculatum L.
BRITISH HEMLOCK

Genus name. Derived from the Greek word “koneion” meaning “to whirl or spin”, in reference to vertigo, which is one of its toxic symptoms.

Species name. Originates from the Latin word “maculates” meaning “with spots”, “speckled”, and “mottled”.

Morphological description. Hemlock is an annual or biennial plant with a foetid smell. During the second year, its stems are developed from the leaf rosette. The stem is erect, glabrous, hollow with bluish coating, and has reddish spots towards its base. The lower leaves are 3-pinnate and leaf segments are ovate, acuminate, runcinate, triangular, and petiolate. The upper leaves are smaller without petioles. The white flowers are clustered into compound umbels. The fruit is a mericarp, which is approximately 2.5 mm long with wavy ribs (Gutman and Djelić, 2018). It blossoms in June and July.

Habitat. It typically grows on waste ground, disturbed sites-boundary strips, alongside fences, along roads, fallows, garbage dumps, in the vicinity of settlements, in fields, and in gardens.

Distribution. Hemlock is native across Europe, Asia, northern Africa, America, and New Zealand. It belongs to the Eurasian floral element.

Variability. One subspecies and one variety are known within this species:

- *Conium maculatum* subsp. *Viride*
- *Conium maculatum* var. *viride*

Main constituents with toxic and dermatological effects. Hemlock is a poisonous plant, especially, its stems, leaves, flowers, and fruits, although only in the later stages of development and growth. The plant has a very unpleasant mousy odour. The alkaloid content varies across its parts and amounts to 0–0.6%, 0.03–0.18%, 0.9–0.24%, 0.73–98%, and 1.05–3.06% in its stems, leaves, flowers, and immature fruits, and mature/ripe fruits, respectively (McGovern and Barkley 1998).

The entire plant and seeds contain several piperidine alkaloids, such as coniine, γ coniceine, N-methyl coniine, conhydrine, and pseudoconhydrine. Coniceine and coniine are the principal poisonous constituents. These alkaloids are neurotoxic and teratogenic. The chemical structure of coniine is similar to that of nicotine. It disturbs the function of the central nervous system by acting on the acetylcholine receptors (Schep *et al.* 2009). Large ingestions can be toxic to humans and animals. When the plant ages, N-methyl coniine becomes the main toxic constituent. Toxicity reduces when the plant is dried, which indicates that the toxic constituents are unstable and that they decompose during storage (Vetter, 2004.). The acute toxicity of hemlock alkaloids is categorised in the following order: γ- coniceine is the most toxic, followed by coniine, N-methyl coniine, conhydrine, λ-coniceine, and pseudoconhydrine. Hemlock's toxic substances are not only dangerous if ingested but also on contact with the skin, because the alkaloids excreted from its sap cause allergic dermatitis.

Symptoms of poisoning appear almost immediately after ingesting material from the plant. They depress the central nervous system depression, which leads to paralysis of the respiratory muscles, causing coma and death. The remaining symptoms are increased salvia, impaired movement and coordination, a slow heart rate, respiratory distress, hearing impairment, and increased body temperature, etc. In cases of poisoning, it is necessary to induce vomiting and gastric lavage. Tannin may be used as an antidote to bind the non-absorbed portion of the alkaloid.

Figure 2-28: *Conium maculatum* L. (photo, Gorica Djelic)

Figure 2-29: *Conium maculatum* L. (photo, Gorica Djelic)

Figure 2-30: *Conium maculatum* L. (photo, Gorica Djelic)

Daucus carota L.
CARROT

Genus name. Originates from the Greek word “dauci” meaning “carrot-like”.

Species name. Originates from the Latin word “carota” meaning “carrot”.

Morphological description. It is a biennial herbaceous plant with spindly (more turnip-shaped in cultivated species) thickened taproot which is orange to yellow in colour. The rosulate leaves develop during its first year. The leaves on the long petioles are finely divided. The stem (develops during the second year) is erect, ribbed, and branched; it reaches up to 150 cm in height. The higher leaves are sessile with tunicate sheaths. The compound umbels have rays covered with coarse hairs. The involucre is composed of a large number of tripinnate leaflets. The involucel is made of a great number of leaflets. The flowers are bisexual and radially symmetrical. There are five sepals, with poorly pronounced coalesced teeth. There are five white yellowish petals. The fruit is a 2–3 mm long mericarp. The flowering time is from April to September.

Habitat. The plant is tolerant to various types of soil. It also thrives on sandy sites and is semi-sciophilous.

Distribution. It is native to temperate regions in Europe, southwest Asia, and northern Africa. It is cultivated all over the world.

Variability. There are two subspecies within the genus *Daucus*:

- *Daucus carota* subsp. *carota*-indigenous
- *Daucus carota* subsp. *sativus*-cultivated

Main constituents with toxic and dermatological effects. Ksouri *et al*. (2015) determined that essential oil from carrot leaves and seeds contains the following: α-thujene, α-pinene, camphene, sabinene, β-pinene, β-myrcene, α-terpinene, p-cymene, limonene, β-phellendrene, ocimene, γ-terpinene, terpinolene, linalol, verbenol, terpinen, geraniol, α-longipinene, α-capaen, geranyl acetate, β-bourbonene, β-elemene, β-caryophyllene, α-transbergamotene, β-damascone, α-humulene (E, E), γ-muurolen, germacrene, β-himachalene, isoshybunone, bicyclogermacrene, β-bisobolene, dihydroisolongifolene, γ-cadinene, himachalene, α-calacorone, germacrenene β, spathulenol, caryophyllene oxide, cubenol 1-epi, cederone, asorone (Z), asorone, α-bisobolol, selin-11-en-4-alpha-ol, cedrenol, and curcumenol. The concentration of polyacetylenes in the carrot root differs across the varieties and ranges from 20 to 100 mg/kg (Baranska *et al*. 2005).

In sensitive people, skin contact with the carrot’s foliage (particularly wet foliage) and sap can cause photodermatitis when in the presence of sunlight. Photosensitive people can even obtain an exact reproduction of the leaf by placing it on the skin and exposing it to sunlight. Falcarinol is one of its principal phototoxic components. It is also present in many other plants, especially in English ivy (*Hedera helix*). Polyacetylene compounds, including falcarinol, cause eczema or more extensive reactions with urticaria and vesiculation. Falcarinol is a rapidly decomposing volatile substance, just like other polyacetylenes.

Figure 2-31 (left): *Daucus carota* L. (photo, Gorica Djelic);
Figure 2-32 (right): *Daucus carota* L. (pixabay.com; carrot-2743498)

Figure 2-33: *Daucus carota* L. (pixabay.com; daucus-carota-84742)

Figure 2-34: *Daucus carota* L. (pixabay.com; flower-3655076_1280)

Figure 2-35: *Daucus carota* L. (pixabay.com; umbel-4741164_1280)

Foeniculum vulgare Mill.
FENNEL

Genus name. Derived from the Latin word “foenum” meaning “hay”, because the wilted leaves look like hay.

Species name. Derived from the Latin word “vulgaris” meaning “common”, “everyday”, “ordinary”, and “vulgar”.

Morphological description. Fennel is a perennial aromatic plant with a whitish rhizome. The stem is hollow, round, striated, and branched; it grows up to 2.5 m. The leaves are alternately arranged; the lower ones with petioles, while the higher ones only have sheaths, which are 3–6 cm long, broaden and envelop the stem. Three-four pinnate compound leaves grow up to 40 cm. The leaf segments are threadlike. The florescences (compound umbels) are large with many rays (up to 25) of various lengths. Neither the involucre nor the involucel is developed. The five-sepal flowers are radially symmetrical, bisexual, small, and yellow. The fruit is a mericarp.

Distribution. It is indigenous to the Mediterranean region and south western Asia, but it has been widely naturalised and cultivated in the Northern, Eastern, and Western hemispheres, especially in Asia, North America, and Europe. It is a cultivated species.

Variability. There are two varieties of *Foeniculum vulgare*:

- *Foeniculum vulgare* var. *dulce* Mill.
- *Foeniculum vulgare* var. *vulgare* Mill.

Main constituents with toxic and dermatological effects. There are five major groups of chemical compounds responsible for contact dermatitis in fennel: α-methylene-γ-butyrolactones, quinones, phenol derivatives, terpenes, and miscellaneous structures (disulphides, isothiocyanates, and polyacetylenic derivatives) (Rozas-Muñoz *et al.* 2012 32 compounds were identified in the fruit’s essential oil, with the highest percentages belonging to t-anethole, α-pinene, D-limonene (terpentine), α-fenchone, and fenchol (Shahmokhtar and Armand, 2017). Furthermore, anethol and limonene are mainly present in the oil from the fennel leaf. Anisaldehyde, phenyl acetate, and phenon are also present (Chowdhury *et al.* 2010).

Approximately 20 fatty acids were identified: capric, undecanonic, lauric, myristic, myristoleic, palmitic, stearic, oleic, linoleic, α-linoleic, and arachidonic. Barros et al. (2010) concluded that polyunsaturated fatty acids are the major group of fatty acids present in all fennel parts. The highest concentrations of ω-3 fatty acids were established in the leaves (i.e. inflorescence). The ω-6 to ω-3 fatty acids ratio plays an important role in the human diet. The highest levels of ω-3 fatty acids are found in the leaves. Foeniculoside is a glucoside determined in the fruit (Ono *et al.* 1995).

Figure 2-36 (left): *Foeniculum vulgare* Mill (photo, Vaskrsija Janjic);
Figure 2-37 (right): *Foeniculum vulgare* Mill. (pixabay.com; fennel-3650486_960_720)

Figure 2-38: *Foeniculum vulgare* Mill. (pixabay.com; nature-3564229_1280)

Figure 2-39: *Foeniculum vulgare* Mill. (pixabay.com; fennel-3633536_1280)

Figure 2-40. *Foeniculum vulgare* Mill. (pixabay.com; same-3427929_1280)

Heracleum mantegazzianum (Sommier & Levier)
GIANT HOGWEED

Genus name. Derived from the Greek word “herákleion”, after the mythological hero Hercules, which refers to its strong growth.

Species name. This refers to Paolo Mantegazza (1831–1910), an Italian traveller and anthropologist (Gledhill 2008).

Morphological description. Giant hogweed is a giant, monocarpic, perennial, herbaceous plant from the *Apiaceae* family. It is native to the western Caucasus. It was brought to Great Britain in the 19th century as an ornamental plant and from there it has spread to other regions in western Europe, the USA, and Canada. It grows to heights of 2 to 5 m. The stem is bright green in colour with broad reddish-purple spots and protuberant coarse white hairs, particularly at the base of the petioles. The stem is hollow, 3–8 cm in diameter. Pinnately and deeply lobed leaves are large, about 1–1.5 m wide (MacDonals and Anderson, 2012; Stace, 2010). The flowers are clustered in umbrella-shaped inflorescences called compound umbels. The inflorescences are white or greenish white, radially symmetrical, and can be up to 100 cm in diameter (Stace, 2010). The plant blooms in mid-summer during June and July. The fruit is a schizorcarp. The seeds are yellow in colour with brown lines, with a wide base and broad ridges. One plant produces about 20,000 seeds, although this number can vary from 10,000 to 50,000 (Gucker, 2009). The seeds are dispersed by the wind (anemochory) and may be viable for over five years (Gucker, 2009). During winter, the above-ground parts of the plant dry out, leaving dry stems with umbels and seeds. The seeds germinate in spring and a new plant is developed, whose leaves sprout from the overwintering roots.

Habitat. It grows along roads, on meadows, brushwood, in dense humid forests, on forest edges, and on rocky hillsides. It is an invasive species.

Distribution. Giant hogweed is widespread throughout western and northern Europe, northern-western USA, and southern Canada. In 1817 in Great Britain, it was grown for the first time at Kew Botanic Gardens in London. It was first observed growing wild in in the vicinity of Cambridge in 1828. Giant hogweed was delisted by the Royal Horticultural Society of Great Britain in 2002.

Variability. There are 148 species within the *Heracleum* genus. Its species are similar to each other, but no lower taxonomic units have been established within *Heracleum mantegazzianum*.

Main constituents with toxic and dermatological effects. Many species from the *Heracleum* genus are poisonous and have a strong dermatological effect on humans. Approximately 36 species of this genus contain furocoumarins, whereas 25 contain derivatives of psoralen, bergapten, and methoxsalen. Giant hogweed is the most toxic species and causes the strongest phytodermatological effects in humans; it creates blisters and scars on the skin. These effects occur due to the presence of the furocoumarins in its leaves, roots, stems, flowers, and fruits. The concentration of furocoumarins is the highest, medium, and the lowest in fruits, leaves, and the basal part of stems, respectively. Psoralen is most abundant in leaves, whereas bergapten is most abundant in its fruit and the basal part of its stems. The maximum, medium, and the minimum content of furocoumarins occur in the leaves in June, August, and November, respectively (Pira *et al.* 1989). Seventeen different furocoumarins were isolated from its various organs (Hattendorf *et al.* 2007). Furthermore, the following coumarins were found in its sap: angelicin, bergapten, imperatorin, isobergapten, isopimpinellin, marmesin, osthol, pangelin, pimpinellin, psoralen, sphondin, umbelliferone, and methoxsalen (Malikov and Saidhodzahaev, 2004; Jakubska-Busse *et al.* 2013). The sap is considered to be at its most poisonous when the plant is in the flowering stage. Its sap is phototoxic and causes phytophotodermatitis, as well as severe skin inflammation, when it comes into contact with skin that is then exposed to sunlight (Camm *et al.* 1976; Mitchell and Rook, 1979; Patocka and Cupalova, 2017; Gadner, 2018). The skin reaction will increase with moisture (e.g. sweating) and heat. The phototoxic reaction occurs as early as 15 minutes after contact with the sap. Photosensitivity is maximal between 30 minutes and two hours after contact with the sap, and it may last for several days (Booy *et al* 2005; McDonalds and Anderson, 2012). The sap can also cause temporary or permanent blindness if introduced into eyes. When working with this plant it is necessary to wear protective clothing and goggles. Hands should be thoroughly washed with soap and cold water, and exposure to sunlight should be avoided for at least 48 hours (Nelsen *et al.* 2005).

Figure 2-41 (left): *Heracleum mantegazzianum* L. (photo, Vaskrsija Janjic);
Figure 2-42 (right): *Heracleum mantegazzianum* L. (pixabay.com; giant-hogweed-1492294)

Figure 2-43: *Heracleum mantegazzianum* L. (pixabay.com; hogweed-1508579)

Figure 2-44 (left): *Heracleum mantegazzianum* L. (pixabay.com; cow-parsnip-1764033);
Figure 2-45 (right): *Heracleum mantegazzianum* L. (pixabay.com; giant-hogweed-391133)

Heracleum sphondylium L.
HOGWEED

Genus name. Derived from the Greek word “herákleion”, which refers to the mythological hero, Hercules, because of its huge growth and its curative properties.

Species name. Originates from the word “sphondylium” meaning “vertebrates”, which refers to the shape of the segmented stem because looks like a spine.

Morphological description. Hogweed is a perennial herbaceous plant with a spindle-shaped rhizome, which is branched, yellow on the outside, and white in the central part. The rhizomes contain a yellowish sap in spring. The segmented, hollow, branched stem with bristly hairs grows up to 150 cm. The basal leaves are simple and large (60 cm in length) with long petioles, whereas the higher ones are serrate sessile leaves finely divided into five lobed segments. The compound umbels are approximately 20 cm in diameter with 10–30 rays whose lower part is covered with hairs. The involucre is usually absent. The involucel is composed of a great number of lanceolate leaflets covered with hairs. The flowers are bisexual and radially symmetrical. There are five coalescent sepals. The sepals are not fused at the tip and in the shape of short teeth. There are five obcordate petals that are white, greenish, or red in colour. There are five stamens, and the gynaecium consists of two carpels. Obovate fruit is a 10 mm long mericarp. Approximately 4-mm stigma remains on the fruit. Hogweed blossoms from June to September.

Habitat. It grows in moderately humid habitats, on nitrogen-rich soils, in the bush, dense humid forests, along forest edges, and in regions up to 2000 m altitude.

Distribution. Hogweed belongs to the Eurasian floral element. It grows all over Europe (except Iceland), western and northern Asia, and in the western parts of northern Africa.

Variability. There are 15 subspecies and four varieties with the *Heracleum sphondylium* species:

- *Heracleumsphondylium* subsp. *algeriense* (Coss. ex Batt. & Trab.) Dobignard
- *Heracleumsphondylium* subsp. *alpinum* (L.) Bonnier & Layens
- *Heracleumsphondylium* subsp. *aurasiacum* (Maire) Dobignard
- *Heracleumsphondylium* subsp. *embergeri* Maire
- *Heracleumsphondylium* subsp. *granatense* (Boiss.) Briq.
- *Heracleumsphondylium* subsp. *montanum* (Schleich. ex Gaudin) Briq.
- *Heracleumsphondylium* subsp. *orsinii* (Guss.) H. Neumayer
- *Heracleumsphondylium* subsp. *pyrenaicum* (Lam.) Bonnier & Layens
- *Heracleumsphondylium* subsp. s*ibiricum* (L.) Simonk.
- *Heracleumsphondylium* subsp. s*uaveolens* (Litard. & Maire) Dobignard
- *Heracleumsphondylium* subsp. *ternatum* (Velen.) Brummitt
- *Heracleumsphondylium* subsp. *transsilvanicum* (Schur) Brummitt
- *Heracleumsphondylium* subsp. *trifoliolatum* (Blanch.) Kerguélen
- *Heracleumsphondylium* subsp. *trifoliolatum* (Blanch.) Kerguélen
- *Heracleumsphondylium* subsp. *verticillatum* (Pančić) Brummitt
- *Heracleumsphondylium* var. *tsaurugisanense* (Honda) H. Ohba
- H*eracleumsphondylium* var. *akasimontanum* (Koidz.) H. Ohba
- *Heracleumsphondylium* var. *lanatum* (Michx.) Dorn
- *Heracleumsphondylium* var. *nipponicum* (Kitag.) H. Ohba

Main constituents with toxic and dermatological effects. The *Heracleum* genus has broad pharmacological activities, including anti-inflammatory, antimicrobial, anticholinesterase, antioxidant, antiviral, cytotoxic, and anticancer. A total of 94 compounds were isolated from plants from the *Heracleum* genus, and almost all of them exhibited vital biological activities. Moreover, approximately 50 compounds were identified as major components in their essential oils (Özek *et al.* 2005; Iscan *et al.* 2004). The genus is rich in several types of bioactive coumarins compounds with high potential activity.

Octyl acetate, octyl butanoate, and octyl hexanoate occur in this species of the genus *Heracleum* (Maggi *et al.* 2014). Essential oils (mainly aliphatic esters and monoterpenes) with a wide range of biological activities can be found in various parts of these plants. In particular, this species exhibits phytophotodermatitis if a person is exposed to its sap and sunlight. Furanocoumarins (bergapten, cantotoxin, 5-methoxypsoralen, sphondin, and pimpinellin) are the phototoxic components of *Heracleum sphondylium* with dermatological effects (Nielsen, 1970). Matejić *et al.* (2016) stated that the dominant constituents in *Heracleum sphondylium* oil were curcumenes (13.42%), β-sesquiphellandrene (11.91%), and p-bisabolene (10.11%). Maggi *et al.* (2014) found large amounts of rutin in leaves and flowers, quercitrin and quercetin in flowers, and phenolic acid, ferulic acid, and chlorogenic acid in roots. Phytophotodermatoses caused by contact with *Heracleum sphondylium* L. were described in the 1960s (Van Dijk and Berrens, 1964; Pathak *et al.* 1962).

Figure 2-46 (left): *Herasleum sphondylium* L (photo, Vaskrsija Janjic);
Figure 2-47 (right): *Heracleum sphondylium* L. (pixabay.com; heracleum-sphondylium-846546)

Figure 2-48 (left): *Heracleum sphondylium* L. (hogweed-4801743);
Figure 2-49 (right): *Heracleum sphondylium* L. (pixabay.com; hogweed-3016259)

Figure 2-50: *Heracleum sphondylium* L. (pixabay.com; nature-1798552)

Notobubon galbanum (L.) Magee
BLISTER BUSH

Genus name. Derived from the Greek word “noto” meaning “southern”, referring to its southern African origin and the word “bubon”, because many *Notobubon* species were once a member of the *Bubon* genus.

Species name. Originates from the word “galbanum”, which indicates that it was erroneously classified into the species from which one of the oldest recorded medicines, Galbanum, was obtained.

Morphological description. Blister bush is a large, aromatic, perennial, and herbaceous plant that grows up to 2.5 m. Its compound serrated leaves are alternately arranged and consist of occasionally three-lobed leaflets. The umbels have a large number of rays and are up to 15 cm in diameter. The involucre is composed of 3–6 lanceolate leaflets. Yellow flowers on short pedicels are radially symmetrical. The fruit is a mericarp that separates into two-seed segments. It blossoms from October to February.

Habitat. Blister bush is found in shady and dump areas of the hilly and mountainous regions.

Distribution. South Africa.

Variability. No lower taxonomic units have been established within this species.

Main constituents with toxic and dermatological effects. Furanocumarins, xanthotoxin, psoralen, and bergapten are found in the plant. Finkelstein *et al.* (1993) isolated xanthotoxin from *Notobubon galbanum* leaves and pointed out that its phototoxicity depended on the intensity of solar radiation or seasonal variation in xanthotoxin concentrations, and that the lack of the response in an individual was undoubtedly due to incomplete or superficial contact with a leaf and/or insufficient exposure to the sunlight. The fruit contains phenolic compounds and coumarins (Modi *et al.* 2009).

Figure 2-51: *Notobubon galbanum* L. (https://en.wikipedia.orgwikiNotobubon_galbanum#mediaFilePeucedanum_galbanum_Blister_bush_Table_mt_)

Figure 2-52: *Notobubon galbanum* L.
(https://commons.wikimedia.orgwikiFilePeucedanum_galbanum_Blister_bush_Table_mt.JPG)

Pastinaca sativa L.
PARSNIP

Genus name. Derived from the Latin word "pastus" meaning "food", because it is grown to be eaten.

Species name. Originates from the Latin word "sativus" meaning "planted", "sown", "grown", and "cultivated".

Morphological description. Parsnip is a biennial plant with a whitish taproot. The hollow, branched stem develops up to 30–150 cm during the second year. The lower leaves have short stalks and broad sheaths. The leaf blades are simply pinnate; the lobes are sessile and the terminal lobes have three segments. The upper leaves are reduced to sheaths. The flowers are clustered into the compound umbel, which is terminally positioned with 5–20 rays. There is no involucre or involucel. The flowers are bisexual and radially symmetrical. There are five yellow petals and five stamens. The fruit is a mericarp. The seeds are dark yellow and ellipsoid with narrow wings. The flowering period is during July and August.

Habitat. It grows in dry and moderately moist habitats, embankments, and rocks.

Distribution. Parsnip is native to Europe, the Caucasus, and Siberia, while it is cultivated in the remaining part of the world.

Variability. There are five subspecies and six varieties within the *Pastinaca sativa* species:

- *Pastinaca sativa* subsp. *183ivaricate* (Desf.) Rouy & Camus
- *Pastinaca sativa* subsp. *Pratensis* (Pers.) Čelak.
- *Pastinaca sativa* subsp. *Sylvestris* (Mill.) Rouy & Camus
- *Pastinaca sativa* subsp. *Umbrosa* (Steven, ex DC.) Bondar. Ex O.N. Korovina

- *Pastinaca sativa* subsp. *Urens* (Req. ex Godr.) Čelak.
- *Pastinaca sativa* var. *brevis* Alef.
- *Pastinaca sativa* var. *edulis DC.*
- *Pasinaca sativa* var. *hortensis* Ehrh. Ex Hoffm.
- *Pastinaca sativa* var. *longa* Alef.
- *Pastinaca sativa* var. *pratensis* Pers.
- *Pastinaca sativa* var. *siamensis* Roem. & Schult. Ex Alef.

There are another two subspecies in Serbia's flora:

- *Pastinaca sativa* L. subsp. *Eu-sativa*
- *Pastinaca sativa* L. subsp. *urens*

Main constituents with toxic and dermatological effects. Parsnip stem and leaves contain toxic substances—furanocoumarina, bergopten, isopimpinellin, xanthotoxin, imperatorin, and sphondin (Robertson, 2013; Berenbaum *et al.* 1986)—just like the rest of the *Apiaceae* family. Symptoms caused by parsnip are similar to those caused by *Toxicodendron radicans*: redness and inflammation of the skin, which can persist for up to two years. Its photosensitive chemical compounds cause phytophotdermatitis on contact with the skin. The root's essential oil contains a high percentage of myristicin (Anon., 2013)

Figure 2-53: *Pastinaca sativa* L. pixabay.com; (the-garden-parsnip-2392749)

Figure 2-54: *Pastinaca sativa* L. (pixabay.com; pastinaca-sativa-844439)

Figure 2-55: *Pastinaca sativa* L. (pixabay.com; parsnips-2111592)

Petroselinum crispus L.
PARSLEY

Genus name. Derived from the Greek word “petros” meaning “rock”, “stone”, and “selinon”, which is the ancient name for some umbelliferaes (*Apiaceae*, *Umbelliferae*).

Species name. It originates from the Latin name “crispus” meaning “curled” and “curly-haired”.

Morphological description. Parsley is a biennial herbaceous aromatic plant that only develops rosulate leaves during its first year, and then it grows a stem in the second year. The rosulate leaves are 2–3 pinnate with a leaf stalk. The upper sessile leaves have tunicate sheaths. The compound umbels are positioned on a long stem, with no involucre, and the involucel is made of 6–8 leaflets. The flowers are bisexual and unisexual (male). The seeds have thin ridges of 2.5–3 mm in length. It blossoms in June and July. Parsley is low in calories, but is extremely rich in minerals and vitamins, which classifies it as a high-quality food and which means that it is used in medicinal products. After dog rose and bilberry, parsley leaves contain the most vitamin C, as much as 170 mg of vitamin per 100 g. It is also rich in provitamin A, B complex vitamins, and the rare B_{12} (which is important for the formation of red blood cells).

Habitat. It grows in dry, light habitats.

Distribution. Parsley belongs to the Mediterranean floral element. It is native to southern Europe and northern Africa, but it is cultivated in the remaining parts of the world.

Variability. There are no lower taxonomic units within this species.

Main constituents with toxic and dermatological effects. Parsley plants contain flavonoids (apigenin, apigenin-7-O-glucoside or cosmosiin, and apiin) and coumarins (2’’, 3’’-dihydroxyfuranocoumarin) (Chaves *et al.* 2011). Marín *et al.* (2016) found 24 components in parsley essential oils, notably the following: α-thujene, α-pinene, camphene, β-pinene, α-phellandrene, myristicin, elemicin, allyl tetramethoxy benzene, and apiol. It is likely that coumarins are responsible for the occurrence of dermatitis in sensitive people.

Figure 2-56 (left): *Petroselinum crispum* L. (pixabay.com);
Figure 2-57 (right): *Petroselinum crispum* L. (pixabay.com; parsley-428720)

Figure 2-58: *Petroselinum crispum* (photo, Gorica Djelic)

Figure 2-59: *Petroselinum crispum* L. (pixabay.com; parsley-4077577)

Family *Apocynaceae*

Nerium oleander L.

OLEANDER

Genus name. Derived from the ancient Greek word “noros” meaning “likes moisture” and “water”.

Morphological description. Oleander grows in the form of a low tree or a shrub. The stem is upright, glabrous, and reaches up to 5 m in height. The leaf arrangement is verticillate (usually three), and the leaves are evergreen, with a coriaceous and narrow lanceolate. The flowers are quite large and sweet-scented, with pedicels clustered into terminal racemose inflorescences. The funnel shaped calyx has five lobes. The corolla is pink and occasionally white or another colour. Its lobes are rounded with entire or slightly serrated margins. The corolla mouth is crowned with five divided leaflets. The stamens are fused to the corolla tube. The fruit is made of two follicles up to 15 cm long, with pronounced longitudinal ribs. The seed is oblong and covered with hairs, which are long at their ends. It blossoms from June to September.

Habitat. Oleander is widely grown as an ornamental plant, which has to be protected from low temperatures during winter. It also grows in natural habitats, usually along streams and rivers, and on slightly wet to arid soils.

Distribution. It is widely distributed as a cultivated plant. It is native to the Mediterranean region and the Middle East.

Variability. One oleander subspecies is known:

- *Nerium oleander* subsp. *oleander*

Main constituents with toxic and dermatological effects. Oleander is a poisonous plant, because some of its compounds have a toxic effect on animals when consumed in large amounts (Blum and Reiders, 1987). These compounds include oleandrin and oleandrigenin, which are known as cardiac glycosides. The leaf contains glycosides. The main glycosides are as follows:

1) Oleandrin (0.08–0.15 %): hydrolysis of oleandrin produces aglycone, oleandrigenin, and a sugar, oleandrosis.

2) Desacetyloleandrin, which, when hydrolysed, produces gitoxigenin and oleandrosis.
3) Adynerin which hydrolysis into diginose and adynerigenin (Kumar et al. 2013).

In addition, the leaves, bark, and flowers contain nerigoside, digitoxigenin, nerium, saponins, rutin, and kaempferol 3-rhamno-glucoside. Oleander glycosides resemble cardiac glycosides in terms of their chemical structure and biological activities. However, they differ in their toxic and extracardiac effects. The poisonous compounds contained in oleander cause disorders in the gastrointestinal system and central nervous system, hyperkalemia, ventricular arrhythmia, and, rarely, death in animals. The gastrointestinal symptoms include nausea and vomiting, abdominal pain, diarrhoea, and colic in horses. Effects on the central nervous system appear in the form of sleepiness, tremors, convulsions, and collapse (Wasfi *et al*. 2008). Pellet *et al.* (2015) indicate that oleander (that is, the glycosides and saponins that it contains) cause irritant dermatitis on contact with the skin. Oleander glycosides are used for inadequate blood flow and arrhythmia. In China and Russia, oleandrin has been used for many years as a cardiotoxic glycoside for suicidal and therapeutic purposes. It is rapidly absorbed and does not have pronounced cumulative properties. Nerolin preparations are produced in the form of tables and solutions.

Figure 2-60: *Nerium oleander* L. (pixabay.com; oleander-58691)

Figure 2-61 (left): *Nerium oleander* L. (pixabay.com; oleander-1169808);
Figure 2-62 (right): *Nerium oleander* L. (pixabay.com; oleander-1521525)

Figure 2-63: *Nerium oleander* L. (photo, Gorica Djelic)

Figure 2-64: *Nerium oleander* L. (photo, Gorica Djelic)

Family *Araceae*

Alocasia macrorrhiza (L.) G. Don

GIANT TARO

Genus name. Derived from two Greek words, “a” meaning “without” and “*Cocolocasia*”, which is the name of the closely allied genus from which it had been separated.

Species name. Derived from two Greek words, “macro” meaning “large” and “rrhiza” meaning root, which refers to the plant’s rhizomes.

Morphological description. Giant taro is a perennial rhizomatous plant. The cordate leaves are simple, with a broad leaf blade that reaches up to 90 cm in length. The unisexual flowers are clustered into inflorescence, which is a spadix subtended by a leafy spathe. The female flowers are positioned in the lower part of the inflorescence, while the sterile male flowers are above them. The male flowers have staminodia instead of stamens. Fertile male flowers are placed above the sterile male flowers. The fruit is a berry.

Habitat. Giant taro naturally occurs in wet tropical forests. In our country, it is grown as an indoor ornamental plant.

Distribution. Southeast Asia, Australia, Oceania, and South America.

Variability. Giant taro is cultivated and has numerous varieties: “Laufola”, “Fiasega”, “Faitama”, and “Niu Kini”.

Main constituents with toxic and dermatological effects. The whole plant exhibits dermatological effects because its sap contains calcium oxalate (Lin *et al*. 1998). Furthermore, the plant contains indole alkaloids, flavonoids, cyanogenic glycosides, and some organic acids (maleic, oxalic, and succinic acids). The young plant is relatively harmless, while the adult plant can cause serious dermatoses. The milky sap can cause eye irritation upon contact with eyes and, if the leaves are consumed, irritability, redness, inflammation of mucous membranes and tongue, and sometimes death may occur. There is certain data in the literature regarding child deaths after ingesting a certain amount of this plant’s roots or stems. Delirium and death occur within six hours. The following species from this genus can cause the same effects:

- *Alocasia denudata* Engl.: Perry and Metzger, (1980) state that if the powdered plant is mixed with bamboo hairs and rubbed into the skin it may cause severe itching and sometimes death.
- *Alocasia cucullata* G. Don (syn. *Alocasia cucullata* Schott, *Arum cucullatum* L.),
- *Alocasia sanderiana* Hort.
- *Alocasia denudata* Engl.
- *Alocasia indica* Schott
- *Alocasia portei* Becc. & Engl. (syn. *Schizocasia portei* Schott)

Figure 2-65: *Alocasia macrorhiza* (L.) G. Don. (pixabay.com)

Figure 2-66: *Alocasia macrorrhisa* (L.) G. Don. (pixabay.com)

Figure 2-67: *Alocasia macrorrhiza* (L.) G. Don. (pixabay.com)

Arum italicum Mill
ITALIAN ARUM

Genus name. Derived from the Greek word “aros” meaning “useful”, because it was used as a medicinal plant.

Species name. Originates from the word “italicum”, because it is native to Italy.

Morphological description. Italian arum is a perennial, herbaceous plant, which grows up to 40 cm. It has simple leaves with long stalks that become broader at the base and grow into sheathe. The leaf blade is lanceolate. Unisexual flowers with a verticillate arrangement along the spadix are female in the lower part of the inflorescence and male in the upper part. Sterile flowers are located between the male and female flowers. The spatha envelops the whole inflorescence. The fruit is an orange red berry. The plant blossoms in April and May.

Habitat. It grows in shady locations on soil rich in organic matter with the acid to neutral pH reactions (6.5–7.0).

Distribution. It is native to the Mediterranean region (southern Europe, northern Africa, and the Middle East), as well as the Canary Islands. Italian arum sporadically grows in Serbia. It is naturalised in Argentina and northern America.

Variability. There are one subspecies and two varieties within this species:

- *Arum italicum* subsp. *italicum*
- *Arum italicum* subsp. *italicum var. marmoratum*
- *Arum italicum* var. *pictum*

Main constituents with toxic and dermatological effects. All parts of the plant are poisonous, and contain calcium oxalate, saponins, and cyanogenic glycosides (Barabé *et al* 2004; Robertson, 2009). Calcium oxalate crystals irritate the skin and mouth on contact or if they are consumed (Francis and Southcott, 1967). Calcium oxalate crystals cause skin reactions within minutes when they come into contact with people who are sensitive to them. Ingesting certain parts of the plant can cause death.

Figure 2-68: *Arum italicum* Mill (photo, Gorica Djelic)

Figure 2-69: *Arum italicum* (https://commons.wikimedia.orgwikiFileAronfrucht3962)

Arum maculatum L.
CUCKOO-PINT

Genus name. Originates from the ancient Greek names for this genus “aron” or “aros” meaning “useful”, because it was used as a medicinal plant, while the Latin “arum” is perhaps derived from the Arabic name for this plant, “ar”.

Species name. Derived from the Latin name “maculates” meaning “with spots”, “speckled”, and “mottled”.

Morphological description. Cuckoo-pint is a perennial plant with a cylindrical rhizome. Two to three basal lanceolate leaves are 7 cm long, with a long leaf stalk, which broadens at the base into a sheathe. The spatha is pale green on the outside and yellow on the inside, with purple on both the margins and the lower parts. The inflorescence is composed of female and male flowers (the inflorescence with female flowers is 3–4 times longer than that of the male). The upper part of the inflorescence axis is purple, and occasionally yellow. The fruit is a berry, which is orange red in colour. The plant blossoms in April.

Habitat. Cuckoo-pint often occurs in deep hums soils on various geological substrata. It grows in different forest communities up to the subalpine regions.

Distribution. Cuckoo-pint is widespread in central and northern Europe, the Balkan peninsula, the Caucasus, and in central and southern Asia.

Variability. There are several subspecies, varieties, and forms of *Arum maculatum* in the world, including the following:

- *Arum maculatum* subsp. *pyrenaeum*
- *Arum maculatum* var. *flavescens*
- *Arum maculatum* var. *heldreichii*
- *Arum maculatum* var. *immaculatum*

- *Arum maculatum* var. *karpati*
- *Arum maculatum* var. *malyi*
- *Arum maculatum* var. *tetrelii*
- *Arum maculatum* var. *vulgare*
- *Arum maculatum* var. *zelenbori*
- *Arum maculatum* f. *flavescens*
- *Arum maculatum* f. *immaculatum*
- *Arum maculatum* f. *roseum*
- *Arum maculatum* f. *scolopendriforme*
- *Arum maculatum* f. *spathulatum*
- *Arum maculatum* f. *tetrelii*

There are two forms of *Arum maculatum* in Serbia:

- *Arum maculatum* f. *maculatum*
- *Arum maculatum* f. *tetrelli*

Main constituents with toxic and dermatological effects. Cuckoo-pint is a poisonous plant and it is especially dangerous for children. The berries have an attractive appearance and sweet taste. The above-ground parts can cause inflammation and swelling of the mouth and lips. The poisonous parts of the plant (berries, leaves, and flowers) contain saponins, aroin, aroidin, aronin, and aion (substances of unknown chemical structures), which cause toxicological effects and even death (Brown, 2000). It is proven that aroin, which is cuckoo-pint's principal poisonous substance, is destroyed by drying and through heat treatments. The needle-shaped crystals of calcium oxalate in berries irritate the skin, mouth, tongue, and throat. The acrid taste coupled with a pricking sensation in the mouth prevents the consummation of large amounts of this plant, which means that poisoning is rare and accidental (Stahl and Kaittenbach, 1965; Govaerts and Frodin, 2002).

In contrast to the poisonous parts of the plant, its dried rhizomes are made up of about 70% starch; this means that they were used for human consumption in earlier periods and during wars. It is known that Serbian soldiers used to cook and eat its rhizomes during the First World War and the retreat across Albania. Other species from this genus (*Arum italicum*, *Arum orientale*, and *Arum petteri*) have similar properties in terms of the composition of their toxic compounds. This means that it might be possible to use their rhizomes in the diet during times of major food shortages, natural disasters, and wars.

Figure 2-70 (left): Arum maculatum L. (photo, Gorica Djelić);
Figure 2-71 (right): *Arum maculatum* (photo, Gorica Djelic)

Figure 2-72: *Arum maculatum* L. (pixabay.com; aerosol-1260780); Figure 2-73: *Arum maculatum* L. (photo, Gorica Djelic)

Figure 2-74: *Arum maculatum* L. (photo, Gorica Djelic); Figure 2-75: *Arum maculatum* L. (pixabay.com; arum-maculatum-848722)

Dieffenbachia spp.
DUMB CANE

Genus name. Heinrich Wilhelm Schott, director of the Botanical Gardens in Vienna, named the plant in honour of his head gardener, Joseph Dieffenbach (1796–1863).

Morphological description. Dumb cane is a perennial herbaceous plant with an erect stem. The stem bears large, simple, alternately arranged leaves with pale spots and flecks. The flowers are unisexual, as well as clustered into the spike inflorescence with spathe and spadix. Female flowers are positioned at the base of the inflorescence, while the males are found on the top of the inflorescence. Pollination occurs via insects.

Ecological conditions. Dumb cane is an indoor plant outside of the tropical regions. It prefers moderate light and the temperature of 15–18°C. Although the plants can survive at 10°C for a short period, they may lose their lower leaves. The maximum summer temperature tolerated by dumb cane is 24°C, but the percentage of air humidity has to be significantly increased.

Distribution. It is native to tropical forests of South America. The genus *Dieffenbachia* encompasses 135 species.

Main constituents with toxic and dermatological effects. The whole plant is poisonous, particularly leaves and fruits (Oloyede *et al.* 2012). The primary dermatological effects result from calcium oxalate, but also from a proteolytic enzyme dumbcain. Calcium oxalate has been localised in idioblasts. One idioblast can contain 100–200 raphides. The proteolytic enzyme dumbcaine has been found in the leaves of some species (*Dieffenbachia seguine*, *Dieffenbachia amoena*, and *Dieffenbachia maculata*), but also in the stem sap of *Dieffenbachia eqositica*. In fact, according to the literature, the nature of dumb cane's irritating effect is controversial. Contact with the plant occurs through the release of raphides, which then penetrate into the skin and facilitate histamine release from mastocytes. Saponins, cyanogenic glycosides, proteolytic enzymes, and alkaloids are likely to contribute the occurrence of vesicles and erythema on the skin (Sakai *et al.* 1984). If the sap gets into someone's eyes, severe pain and spasm will occur, because a large number of calcium oxalate crystal will have penetrated the cornea (Sakai *et al*. 1984).

Figure 2-76: *Dieffenbachia* spp. (photo, Gorica Djelic)

Figure 2-77: *Dieffenbachia* spp. (pixabay.com; dieffenbachia-2825214_1280)

Philodendron spp.
PHILADNDRON

Genus name. The name of this genus is derived from the Greek words “philo” meaning “love, affection” and “dendron” meaning “tree”.

Morphological description. According to the number of species (489), the *Philodendron* genus is the second largest member of the *Araceae* family. Species from this genus have both aerial and underground roots. They are creeping plants, with articulate stems, and aerial roots that originate from nodes. Aerial roots have two purposes: to attach the plant to a support and to absorb water and nutrients. The leathery leaves are large, have leaf stalks, and are alternately arranged. The margin of the juvenile leaves is entire, but it is deeply incised in adult leaves (Mclntire et al 1990). Variability in the shape and the size of leaves is pronounced in plants from the same species.

Habitat. Plants thrive in tropical forests, swamps, and on river banks. They are found even over 2000 m above sea level (Croat *et al.* 2007).

Distribution. It is native to tropical regions of Americas and the West Indies, and it is cultivated as a house plant in the remaining parts of the world.

Variability. Philodendrons can be epiphytes (grow on other plants and/or trees), hemiepiphytes, and terrestrial plants (Croat, 1985). Certain epiphytic species have a symbiotic relationship with ants (Yu, 1994). Ants build anthills next to philodendron roots, as they support their nests. They also use the philodendron’s nectar as food, while the plants also obtain nutrients from ant nests (Gauthier *et al.* 2008). A primary hemiepiphyte philodendron starts life high up in a canopy of trees where its seeds germinate and embryos start growing into epiphytic plants. Once it reaches a sufficient size and age, it will form aerial roots that grow toward the ground. When the ground is reached, the roots will obtain nutrients directly from the soil (Orihuela and Waechter, 2010). Secondary hemiepiphytes are philodendron species that develop on the ground, and grow elongated internodes along the ground until they reach a tree to climb. After this, they become epiphytes loosing underground roots.

There are three subgenera of the *Philodendron* genus:

- *Meconostigma*
- *Pteromischum*
- *Philodendron*

Main constituents with toxic and dermatological effects. Philodendrons can contain as much as 0.7% of oxalates in the form of calcium oxalate crystals, such as raphides (Pillay, 2013). The presence of oxalate crystals can cause local irritations, oedema, and dysphagia. Cases of mild dermatitis with symptoms including vesiculation and erythema due to contact with leaves have been reported. It is believed that the chemical derivative, alkenyl resorcinol, is responsible for the contact dermatitis in some people (Frohne and Pfänder, 2005). Resorcinol is one of the major natural phenols found in many plant oils, but it occurs in the greatest amounts in *Argania spinosa*, which grows in Morocco. The major implications are caused by the following species: *Philodendron cordatum*, *Philodendron selloum*, *Philodendron speciosum*, and *Philodendron scandens oxycardium*. If it is introduced to the eyes, philodendron sap may cause conjunctivitis. These plants are highly toxic to cats.

Figure 2-78 (left): *Philodendron* spp. (pixabay.com; leaves-375611);
Figure 2-79 (right): *Philodendron* spp. (pixabay.com; philodendron leaf-93702_1280)

Figure 2-80: *Philodendron* spp. (pixabay.com; philodendronplant-3356944_1280)

Figure 2-81: *Philodendron* spp. (pixabay.com; philodendron-406841)

Figure 2-82: *Philodendron* spp. (pixabay.com; tribe-93699)

Hedera helix L.
ENGLISH IVY

Genus name. Derived from the Greek word "hedra" meaning "substrate" or "ground", because the plant's aerial roots attach it to the ground. It is also said that the name originates from the Celtic word "hedea" meaning "cord", as the stem looks a bit like one.

Species name. Derived from the Latin name "helix" meaning "twist", "turn", and "spiral-shaped", because it wraps around the trunk.

Morphological description. English ivy is a woody climbing plant that grows up vertical surfaces or creeps over ground using its aerial roots. The young shoots are covered with stellate hairs and later become glabrous. Leathery spirally arranged leaves are dark green, glossy, and glabrous on the upper surface, whereas they are yellowish green on the lower surface. The juvenile leaves have grey stellate hairs. The leaves have different shapes (heterophylly). They can be round to ovoid, three-to five-lobed, narrow or broad, rhombic, or even asymmetrical. The flowers are clustered into umbels. They are usually bisexual with a poorly developed calyx. The petals are greenish. The fruit is a round berry and, when mature, it is bluish black and to 1 cm in diameter. English ivy grows slowly and lives for a long time. Its flowering period is from September to October.

Habitat. It often grows in various forest communities and from lowlands to highlands, especially in thermophilic and xeric oak forests and mesophilic beech, beech-fir, and other forests. It is cultivated in gardens as well as in pots.

Distribution. English ivy is distributed in central and southern Europe, the Crimea, the Caucasus, and reaches as far as the Baltic sea. It belongs to sub-Atlantic-sub-Mediterranean floral element.

Variability. The following three subspecies of *Hedera helix* are known:

- *Hedera helix* subsp. *helix*
- *Hedera helix* subsp. *poetarum*
- *Hedera helix* subsp. *rhizomatfera*

Main constituents with toxic and dermatological effects. English ivy is a very poisonous plant, because its leaves, flowers, and twigs contain spanonins, hederin, oestrogen, some organic acids (malic acid and formic acid), pectins, tannis, and cholesterin. It is thought that small amounts of hederin widen blood vessels, while the greater amounts narrow them and slow the heart rate (Kalish *et al*. 1994). This plant is used in traditional medicine to treat bile, for easier expectoration, for the regulation of menstruation, to treat jaundice, to treat catarrh on lungs, stomach, and intestines, and to manages diseases of urinary organs and hypertension, etc. The plant is quite poisonous; therefore, attention needs to be paid when using it in traditional medicine. In cases of poisoning, vomiting and gastric lavage should be induced. The plant can cause a skin allergy (Jøhnke and Bjarnason, 1994; Boyle and Harman, 2006.). Irritations and contact dermatitis are thought to be caused by its polyacetylene compounds. The plant leaves contain falcarinol and didehydro-falcarinol, especially during winter. Relatively small amounts of these compounds can also be found during summer. The ratio of these compounds in ivy leaves varies from 10:1 to 2:1. Hederin, which is also isolated from *Hederahelix* plants, is a strong irritant, particularly to mucous membranes of the nose and mouth. A dose of below 10 mg causes death within hours, which is accompanied by hypotension and bradycardia.

Figure 2-83: *Hedera helix* (photo, Vaskrsija Janjic); Figure 2-84: *Hedera helix* L. (photo, Gorica Djelić)

Figure 2-85 (left): *Hedera helix* L. (photo, Gorica Djelic);
Figure 2-86 (right): *Hedera helix* L. (inflorescences-60354)

Figure 2-87 (left): *Hedera helix* L. (pixabay.com; ivy-1191154);
Figure 2-88 (right): *Hedera helix* L. (photo, Vaskrsija Janjic)

Figure 2-89 (left): *Hedera helix* L. (photo, Vaskrsija Janjic);
Figure 2-90 (right): *Hedera helix* L. (pixabay.com; ivy-324261)

Family *Aristolochiaceae*

Asarum europeum L.
ASARABACCA

Genus name. Originates from the Greek prefix “a” meaning “without” and the word “saron” meaning “branch” and “broom”, because it is an unbranched plant.

Species name. Derived from the Latin word “europaeus” meaning “European”.

Morphological description. It is a 4–10 cm tall perennial plant. The underground stem (rhizome) is short and articulate. The aboveground stem bears leaves at its base. Reniform leaves have long hairy petioles, entire margins, and a glossy upper surface. Their scent resembles freshly ground pepper and they are used as such. The actinomorphous, bisexual, and solitary flowers are terminally arranged. The bell-shaped perigonium is greenish on the outside and red-brown on the inside. There are 12 stamens, and a six-celled ovary. The plant has a capsule-like fruits that open irregularly. The seeds are elongated. Pollination is performed by snails (malacophily), while seed dispersal is performed by ants (myrmecochory). The flowering period is from March to May.

Habitat. Asarabacca grows in mesophilic forests (forests with common oak and European ash, sessile oak, European hornbeam, beech forests, deciduous-coniferous forests and coniferous forests), from lowlands up to the subalpine belt.

Distribution. Asarabacca is widespread in Europe, southern Russia, Asia Minor, and Siberia. It belongs to the sub-Central European floral element.

Variability. There are two subspecies:

- *Asarum europaeum* ssp. *caucasicum* (the Southeastern Alps)
- *Asarum europaeum* ssp. *italicum* (central and northern Italy, Skopska Crna Gora).

Main constituents with toxic and dermatological effects. Asarabacca contains about 1.2% of essential oil with asarone, camphor, mucilage, tannin, resin, sugar, bitter compounds, and organic acids (Wilczewska *et al*. 2008). All of the asarabacca’s parts have an acrid taste. Asarone causes poisoning. There are two isomers of asarone: α (or *trans*) and β (or *cis*). Essential oil from the asarabacca’s root contains 50% asarone (Lewis et al. 2017). The symptoms of asorone poisoning include a prolonged vomiting that sometimes lasts more than 15 hours.

Figure 2-91: *Asarum europeum* L. (photo, Gorica Djelić)

Figure 2-92: *Asarum europeum* L. (photo, Gorica Djelić)

Figure 2-93: *Asarum europeum* L. (photo, Gorica Djelic)

Asarum canadense L.
CANADIAN WILD GINGER

Genus name. Originates from the word "asaron": a name that can be found in *De Materia Medica* by Pedanios Dioscorides.

Species name. Derived from the word "canadense", which refers to the species' origins, Canada.

Morphological description. Canadian wild ginger is a perennial aromatic plant, which grows up to 15 cm in height, and has an articulate rhizome. Its leaves with long petioles are densely covered with white hairs. Its reniform leaf blades have entire margins. The flowers are bisexual, radially symmetrical, and solitary with pedicels of up to 3 cm in length. The bell-shaped perigonium is distinctly hairy on the lower part, purple on the outside, and whitish on the inside, with three pointed lobes. There are 12 stamens and a six-celled ovary. The fruit is a six-celled pod. The seeds are elongated, and dispersal is performed by ants (myrmecochory). The plant blossoms in May and June.

Habitat. It grows in mesophilic forests in shady sites.

Distribution. It is native to Canada and the USA.

Variability. No lower taxonomic units have been established within this species.

Main constituents with toxic and dermatological effects. The whole plant contains essential oil. The rhizome essential oil contains the following: (Z)-3-hexen-1-ol, trans-pinocarveol, (Z)-isoelemicin, oplopanon, methyleugenol, linalyl acetate, -pinene, bornyl acetate, aristolone, geraniol, linalool, limonene (0.8), elemicin, 2,3,4,5-tetramethoxyallylbenzene, 2, 4-dimethoxycinnamaldehyde, and β-sitosterol (Bauer *et al.* 1967). Aristolochic acid has carcinogenic and nephrotoxic effects.

Figure 2-94: *Asarum canadensis* L. (pixabay.com; wild-ginger-2211966)

Figure 2-95: *Asarum canadensis* L. (pixabay.com; leaf-2141235)

Family *Asparagaceae*

Convallaria majalis L.

LILY OF THE VALLEY

Genus name. Originates from the Latin word "convallis" meaning "valley" or "the flower of the valley".

Species name. Originates from the Latin word "majalis" menaing "of the month of May".

Morphological description. Lily of the valley is a perennial and highly poisonous woodland angiospermous plant that is native to the cool temperate northern hemisphere in Asia and Europe. It grows up to 10–20 cm in height and has a thin, creeping, and branched shoot. Each year, the plant usually produces 2 to 3 oblong elliptical leaves with long petioles and long sheathes. The stem is leafless (leaves grow from the ground) with the loose raceme at the top. The flowers (5–8) are up to 1 cm long, white in colour, fragrant, face one side, and are bent on short pedicels. The fruit is quite red globular berry with 2–7 seeds. The flowering period is in May and June.

Habitat. Plants grow in small oases in light and mostly deciduous forests and brushes, close to forests, in highland meadows, and from lowland to highland regions. This plant is also grown in gardens.

Distribution. Lily of the valley occurs almost all over Europe, except for the Arctic region and certain parts of southern Europe. There are varieties of lily of the valley, *Convallaria majalis* var. *manschurica*, that grow in Japan and in regions of the eastern Asia, as well as *Convallaria majalis* var. *montana* which grows in eastern parts of the USA.

Variability. There are several subspecies, varieties, and forms within this species (Chase et al., 2009; Vandepitte et al., 2013):

- *Convallaria majalis subsp. prolificans*
- *Convallaria majalis* subsp. *tetraploidiae*
- *Convallaria majalis* subsp. *transcaucasia*
- *Convallaria majalis* var. *bracteosa*
- *Convallaria majalis* var. *laminaris*
- *Convallaria majalis* var. *latifolia*
- *Convallaria majalis* var. *prolificans*
- *Convallaria majalis* var. *rosea*
- *Convallaria majalis* var. *rubra*
- *Convallaria majalis* var. *transcaucasia*
- *Convallaria majalis* var. *variegata*
- *Convallaria majalis* f. *abchasia*
- *Convallaria majalis* f. *angustifolia*
- *Convallaria majalis* f. *laminaris*
- *Convallaria majalis* f. *latifrons*
- *Convallaria majalis* f. *latior*
- *Convallaria majalis* f. *mappii*
- *Convallaria majalis* f. *picta*
- *Convallaria majalis* f. *prolificans*

There are three varieties of lily of the valley that are not included in its species or subspecies. For example,

- *Convallaria majalis* var. *keiskei*, which originates from China and Japan with red fruits and bowl-shape flowers (Ohara et al. 2006).
- *Convallaria majalis* var. *majalis*, which originates from Eurasia with white midribs on the flowers.
- *Convallaria majalis* var. *montana*, which originates from the USA, with green tinged flowers.

Furthermore, *Convallaria transcaucasica* is recognised as a distinct species; it was formerly known as *Convallaria japonica*, and today it is classified as *Ophiopogon japonicus*.

Main constituents with toxic and dermatological effects. Due to its pronounced scent, *Covalvaria majalis* is often grown in gardens. Diverse species and varieties are grown, including those with double flowers, rose-coloured flowers, and multicoloured leaves:

- *Covalvaria majalis* "Albostriata" with white stripes on its leaves.
- *Covalvaria majalis* "Green Tapestry", "Haldon Grange", "Hardwick Hall", "Hofheim", "Marcel", "Variegata", "Vic Pawlowski's Gold" and other multicoloured species.
- *Covalvaria majalis* "Berlin Giant" and *C. majalis* "Géant de Fortin" (syn. "Fortin's Giant"), which has a wide-ranging habitat.
- *Covalvaria majalis* "Flore Pleno" with double flowers.
- *Covalvaria majalis* "Rosea", which is sometimes found under the name of *C. majalis* var. *rosea*, due to its pink flowers.

All parts of the plant are poisonous, but particularly its flowers and fruits, which are red berries that attract children. Glycosides are major toxic substances that the heart, but the plants also contain a number of saponins that have a local irritant activity (Mitchell and Rock, 1979). The glycoside convallamarin has similar, but milder and less cumulative, effects than the glycosides found in foxgloves (*Digitalis* L.). This plant contains over 38 cardiac glycosides (cardenolides) including corglycon, convallarin, convallotoxin, convalloside, lokundjoside, cannagenol-3-*O*-α-L-rhamnoside, and cannagenol-3-*O*-β-D-allomethyloside. More recently, convallatoxin has been isolated. The flowers contain 0.30.4% of these glycosides (Joy *et al.*

1998). Convallarin and convallaric acid are the most important saponins and they are most abundant in fresh plants. The fruits and seeds do not contain saponins. Moreover, the leaves and flowers contain essential oil. Although deadly, the plant has been used as a folk remedy in moderate amounts. The scent of lily of the valley, particularly that of the bourgeonal, attracts mammals. Studies show that, in high concentrations, bourgeonal imitates the role of progesterone and simulates chemotaxic processes. It is interesting that lily of the valley has been used in bridal bouquets. Its flower is also called Our Lady's tears or Mary's tears as, according to the Christian legends, it sprang from the Virgin Mary's tears during Jesus' crucifixion.

Figure 2-96 (left): *Convallaria majalis* L. (photo, Gorica Djelić);
Figure 2-97 (right): *Convallaria majalis* L. (pixabay.com; lily-of-the-valley-2256899)

Figure 2-98: *Convallaria majalis* L. (pixabay.com; lily-of-the-valley-1415809)

Hyacinthus orientalis L.
COMMON HYACINTH

Genus name. Originates from the Greek word “hyakinthos”, which is the name of a young man admired and accidentally killed by Apollo, who caused a hyacinth to grow from his blood.

Species name. Derived from the Latin name “orientalis” meaning “of the east” and “from the Orient”.

Morphological description. Hyacinth is a perennial plant with a large globoid bulb; it is 5–8 cm in diameter. Its leaves are flat or grooved, strap-shaped, 20–25 cm long, and 1–2 cm wide. The thick flower pedicel is 20–30 cm long. The flowers are clustered into long, ovoid to cylindrical racemes. Its pedicels are shorter than its flowers. The flowers come in shades of blue, pink, or white. The perigonium leaflets are fused into a tube. The filaments are short, as they are only about 2 mm long. The fruit is a round capsule. The flowering period is in March and April.

Habitat. Hyacinth is grown as an ornamental plant. There are numerous forms and hybrids of cultivated hyacinth that differ in their flower colour, as well as their flowering periods.

Distribution. Hyacinth is found in Iran, Iraq, Syria, Asia Minor, and Greece; it is a subspontaneous plant in Croatia (Dalmatia).

Main constituents with toxic and dermatological effects. Many authors classify hyacinth into a group of poisonous plants. Poisonous constituents, whose nature and composition are still unknown, are found in all parts of the plant. The bulb is the most poisonous part of the plant (Śmigielska et al. 2014). Hyacinth is also considered to be in the allergenic plant group, because all of its constituents cause allergies in sensitive people. Their flowers, leaves, stems, bulbs, and sap can cause allergic reactions. This plant contains alkaloids (phenanthridine), of which lycorine is the best known. Its flowers, stems, and leaves contain high concentrations of lycorine (Nelson *et al*. 2014). Its flowers and other parts cause rhinitis and asthma in sensitive people. Although hyacinth is classified as a poisonous plant, additional studies are needed to identify its poisonous constituents, determine the dynamics of its synthesis, the arrangement of its organism, and its toxicological effects on various organisms, including humans.

Figure 2-99 (left): *Hiacynthus orientalis* L. (photo, Gorica Djelić);
Figure 2-100 (right): *Hiacynthus orientalis* L. (photo, Gorica Djelić)

Figure 2-101 (left): *Hiacynthus orientalis* L. (photo Gorica Djelić);
Figure 2-102 (right): *Hyacinthus orientalis* L. (pixabay.com; garden-hyacinth-49793)

Figure 2-103: *Hyacinthus orientalis* L. (pixabay.com; garden-hyacinth-49796)

Figure 2-104: *Hyacinthus orientalis* L. (pixabay.com; hyacinth-4770926)

Polygonatum odoratum (Mill.) Druce
SCENTED SOLOMON'S SEAL

Genus name. Derived from the Greek words, "ploys" meaning "many" and "gony" meaning "knees", in reference to the plant's numerous, jointed stems.

Species name. Derived from the Latin word "odoratus" meaning "fragrant" and "perfumed".

Morphological description. Solomon's seal is a perennial plant with a long rhizome. The glabrous, upright, or arching stem is 10–50 cm tall. Alternate leaves arranged in two rows are elliptical-ovate, almost sessile, with green upper surfaces and green-grey lower surfaces. One to two flowers are usually clustered in leaf axils in the middle part of the stem. The arched pedicels are almost 2 cm long. Its fragrant flowers are approximately 2 cm long. The perianth is white with greenish lobes. Its filaments are smooth and flat. The fruit is a blue-red spherical berry, which is 8–12 mm in diameter. The seeds are yellowish in colour. Solomon's seal flowers in May and June.

Habitat. It grows in light coniferous and deciduous forests, in shrubberies, on rocks, and meadows, from lowlands up to the subalpine belt.

Distribution. Solomon's seal is widespread in Europe, Siberia, and the Himalayas. It belongs to the sub-south-Siberian floral element.

Variability. Four varieties are recognised:

- *Polygonatum odoratum* var. *maximowiczii*
- *Polygonatum odoratum* var. *odoratum*
- *Polygonatum odoratum* var. *pluriflorum*
- *Polygonatum odoratum* var. *212hunbergia*

Main constituents with toxic and dermatological effects. The aboveground plant parts, especially the berries, are poisonous. They contain cardiac glycosides that are volatile, particularly under high temperature. The rhizomes contain methylated homoisoflavonones and triterpenoids (Wang *et al.* 2009). Its oil contains aldehydes, such as decanal (28%), dodecanal (44%), and alcohol decanal (11%). Furthermore, its oil contains the following sesquiterpenes: α-humulene and β-caryophyllene (approximately 15%). These constituents are responsible for the occurrence of dermatitis in sensitive people (Starkenmann *et al.* 2006). The young shoots can be used as food if boiled, as they are rich in vitamin C. Solomon's seal rhizomes can also be used as food if cooked, because they are rich in starch. American Indians used to use this plant's rhizomes to make bread. It is believed that the plant contains some substances with antidiabetic activities. When consumed, its berries and mature plants cause nausea, vomiting, diarrhoea, visual disturbances, hallucinations, and heart failure. Solomon's seal berries are similar to blueberries. In cases of poisoning, gastric lavage should be performed and cleansing preparations should be undertaken.

Figure 2-105: *Polygonatum odoratum* (Mill.) Druce. (photo, Gorica Djelic)

Figure 2-106: *Polygonatum odoratum* (Mill) Druce. (pixabay.com; polygonatum-odoratum-338936)

Figure 2-107: *Polygonatum odoratum* (Mill.) Druce. (photo, Gorica Djelic)

Figure 2-108: *Polygonuatum odoratum* (Mill.) Druce. (photo, Gorica Djelic)

Family *Asteraceae*

Achillea millefolium L.
COMMON YARROW

Genus name. "Achillea", the plant may have been named after the Greek hero Achilles who healed Telephus.

Species name. "Millefolium" meaning "million leaves", because its leaves are divided into a great number of parts.

Serbian common name. "Haiduk's grass": the plant has been named after the haiduks: legendary outlaws who opposed Turkish rule in Serbia and who always carried this plant in a cloth bag to heal their wounds.

Morphological description. Yarrow is a perennial, herbaceous plant with a spreading rhizomatous growth. The aboveground stem is erect and covered with sparse floccose hairs. Its bipinnate or tripinnate leaves are alternately arranged. Its lowers are radially symmetrical (tubular or disc florets) and zygomorphic (ligulate or ray florets); they are clustered into the capitulum inflorescence, which is 3–5 m in diameter. Ligulate flowers (5) are on the inflorescence periphery, whereas tubular flowers occupy the middle part of the inflorescence. The involucre is ovoid. The plant blossoms from June to August. Achene-like fruits are glabrous and reach up to 2 mm in length.

Habitat. It grows in arid and moderately moist sites, as well as along roads, railroads, rocky places, and meadows.

Distribution. It belongs to the Eurasian floral element, and grows in Europe, Siberia, the western Himalayas, the Caucasus, and up to northern Persia. It has been introduced to North America, New Zealand, and southern Australia. It is also found in Serbia.

Variability. There are eight subspecies and five varieties within the *Achillea millefolium* species:

- *Achillea millefolium* subsp. *collina*
- *Achillea millefolium* subsp. *pannonica,*
- *Achillea millefolium* subsp. *chitralensis*
- *Achillea millefolium* subsp. *sudetica*
- *Achillea millefolium* subsp. *millefolium*
- *Achillea millefolium* subsp. *millefolium* var. *millefolium*
- *Achillea millefolium* subsp. *millefolium* var. *borealis*
- *Achillea millefolium* subsp. *millefolium* var. *rubra*
- *Achillea millefolium* var. *alpicola*
- *Achillea millefolium* var. *californica*
- *Achillea millefolium* var. *occidentalis*
- *Achillea millefolium* var. *pacifica*
- *Achillea millefolium* var. *puberula*

Main constituents with toxic and dermatological effects. The aboveground plant part is frequently used, whereas its inflorescences or leaf are used less often. The drug contains 0.2–1% of essential oil with azulene, whose percentage is up to 25% depending on the geographical origin of the plant (Anon., 2001). The herb is used as a bitter aromatic to improve appetite. It also acts as a mild haemostatic and spasmolytic agents. Furthermore, it expresses antiphlogistic effects when externally used. It is of great use in gastrointestinal disorders (inflammation, diarrhoea, insufficient secretion, lazy bowels, etc.), in female diseases/disorders (irregular and painful cycles), hypertension of known origin, and as an antithrombic agent (in cerebral and cardiac thrombosis). It calms mucous membrane and skin inflammation (Hausen, 1996). It also helps with epithelisation, heals wounds and purulent processes, helps constrict blood vessels, and stops bleeding.

Several cases of increased sensitivity to yarrow-based preparations have been reported (Hausen and Vieluf, 1997). The principal constituents of essential oil are germacrene-D, eugenol, and p-cymene. The sesquiterpene lactones found in yarrow are causative agents of allergic contact dermatitis (Hausbn *et al*. 1991). Alpha-peroxyachifolide causes dermatitis and is the most important of these lactones.

Figure 2-109 (left): *Achillea millefolium* L. (photo, Vaskrsija Janjic);
Figure 2-110 (right): *Achillea millefolium* L. (photo, Vaskrsija Janjic)

Figure 2-111 (left): *Achillea millefolium* L. (pixabay.com; achillea-millefolium-844587);
Figure 2-112 (right): *Achillea millefolium* L. (pixabay.com; achillea-millefolium-1340686)

Figure 2-113: *Achillea millefolium* L. (photo, Vaskrsija Janjic)

Anthemis arvensis L.
CORN CHAMOMILE

Genus name. Derived from the Greek word “anthemon” meaning “flower”, because this genus’ species have many flowers with a long flowering period.

Species name. Originates from the Latin word “arvensis” meaning “field”, which points to the site where the plant grows.

Morphological description. Corn chamomile is an annual plant with a spindle-shaped root and erect slightly ridged stem of about 50 cm high. Two-pinnate leaves are alternately arranged. The stems and leaves are covered with sparse floccose hairs. The flowers are clustered into solitary capitula. The receptacles are not hollow. The involucral bracts are arranged into several rows as roof tiles. White ligulate florets are on the inflorescence periphery, whereas yellow tubular florets are in the middle of the inflorescence. The flowering time is from June to September. The fruit is achene 3 mm long.

Habitat. It grows on loose soils poor in calcium, in sunny and semi-shady meadows, tilled fields, alongside roads, and glades in thermophilic oak forests.

Distribution. It belongs to the Central European floral element. It is native to Europe, Asia and northern Africa. The species has been introduced to America, Australia, and New Zealand.

Variability. There are four subspecies of the species *Anthemis arvensis*:

- *Anthemis arvensis* subsp. *arvensis*
- *Anthemis arvensis* subsp. *cyllenea* (Halácsy) R. Fern.
- *Anthemis arvensis* subsp. *incrassata* (Loisel.) Nyman
- *Anthemis arvensis* subsp. *sphacelata* (C. Presl) R. Fern.

Main constituents with toxic and dermatological effects. The plant contains α-bisabolol, bisbolol oxides A and B, farnesene, sesquiterpene lactones (including the blue compound chamazulene), and acetylene derivative (Frohne and Pfander, 2005). The phenolic compounds found in the flowers encompass hydroxycinnamic acid derivatives, caffeic acid, and flavonoids (apigenin, luteolin and hamemelloside).

This species mainly causes contact dermatitis due to its sesquiterpene lactones (Denisow-Pietrzyk *et al.* 2019). The largest quantities are found in the flowers, then the leaves and the smallest amounts are detected in the stems. Plants collected in spring causes more severe dermatitis than those harvested in autumn. The allergen contains aldehydes or ketones.

However, the acetylation does not cause any changes, which leads to the conclusion that this allergen does not have an alcohol group (Fernández de Corres *et al*. 1989).

Figure 2-114: *Anthemis arvensis* L. (photo, Vaskrsija Janjic)

Figure 2-115: *Anthemis arvensis* L. (photo, Vaskrsija Janjic)

Figure 2-116: *Anthemis arvensis* L. (photo, Vaskrsija Janjic)

Figure 2-117: *Anthemis arvensis* L. (pixabay.com; anthemis-arvensis-846595)

Anthemis cotula L.
STINKING CHAMOMILE

Genus name. Derived from the Greek word “anthemon” meaning “flower”, in reference to this genus’ many flower heads.

Species name. Derived from the Greek word “kotule” meaning “a small cap”, which refers to a hollow at the base of the 218mplexicaule leaves.

Morphological description. Stinking chamomile is an annual plant with an unpleasant odour. The upright, branching stem can reach up to 61 cm in height. The two-pinnate leaves are alternately arranged. Each stem is topped with a single flower head of 1.2–2.6 cm in diameter. Its ligulate flowers are sterile, whereas the tubular ones are bisexual. The pappi are not developed. The fruit is an achene with no pappus.

Habitat. It grows in open xerothermic habitats and on clay soils with a neutral pH.

Distribution. It belongs to the Central European floral element. It is native to Europe, Asia, and northern Africa. The species has been introduced to America, South Africa, and Oceania.

Variability. No lower taxonomic units have been established within this species.

Main constituents with toxic and dermatological effects. The whole plant contains the sap that can cause allergies on contact with the skin. It contains the following: n-nonadecane, cedran, α-farnesene, eicosane, benzyil salicylate, aromadendrene, and sesquiterpene lactones. Sesquiterpene lactones cause blisters on the skin and severe forms of dermatitis after prolonged contact with flower heads (Robert and O'Malley, 1990). In addition to contact dermatitis, they cause vomiting, diarrhoea, anorexia, and allergic reactions.

Figure 2-118: *Anthemis cotula* L.
(https://commons.wikimedia.orgwikiFileAnthemis_cotula_L._(AM_AK330561-1)

Figure 2-119: *Anthemis cotula* L. (pixabay.com)

Arctium lappa L.
GREATER BURDOCK

Genus name. Derived from the Greek word “arktos” meaning “bear”, due to the floccose hairs found in species of this genus.

Species name. Lappa is derived from the Greek word “labein” meaning “to take” or “to grab” (because of the hooks on the fruit that adhere to clothes or animal fur/wool).

Morphological description. Greater burdock is a biennial herbaceous plant that reaches up to 2 m in height. It has a spindle-shaped, branched root up to 1 m in length. The erect stem is covered with floccose hairs. The alternating, simple, cordiform, and large leaves have long petioles. The lower leaves are the largest with blades of up to 50 cm and petioles that can be longer than 30 cm. The flowers are radially symmetrical, bisexual, and tubular with five lobs. They are purple-red and grouped into globular capitula and united in clusters. The involucre is made of many bracts, each with a hook on its tip. The plant blossoms from July to September. The fruits are achenes, which are approximately 7 mm long with short pappi.

Habitat. It grows on soils rich in nitrogen, in open habitats, along roadsides, garbage dumps, and unmaintained sites around houses.

Distribution. It is native to Europe from Scandinavia to the Mediterranean region, in Russia, the Middle East, India, China, Taiwan, and Japan.

Variability. There is one species, with two varieties and two forms within this species:

- *Arctium lappa subsp. Majus*
- *Arctium lappa* L. var. *herkules*
- *Arctium lappa* var. *edule* (Sieb. Ex Miq.) Mansf.
- *Arctium lappa* f. *lappa*
- *Arctium lappa* f. *purpurascens*

Main constituents with toxic and dermatological effects. The plant contains polysaccharides (e.g. inulin), arctigenin, diarctigenin, arctiin, sesquiterpene lactones (arctiopicrine), phenolic compounds, triterpene, phytosteroids, and tannins. Arctiopicrine is an allergen that is responsible for the allergic contact dermatitis caused by greater burdock (Adams and O'Malley, 1990). Rodriguez *et al*. (1995) point out that allergic contact dermatitis occurs due to contact with greater burdock. The root of this plant contains sulphurous acetylene compounds, guaianolide-type constituents, and polyacetylenes, whereas the seeds contain arctigenin, arctiin, and butyrolactone lignans.

Figure 2-120: *Arctium lappa* L. (photo, Gorica Djelic)

Figure 2-121: *Arctium lappa* L. (pixabay.com; great-burdock-3560745)

Figure 2-122: *Arctium lappa* L. (pixabay.com; arctium-lappa-855515)

Figure 2-123: *Arctium lappa* L. (photo, Gorica Djelic)

Chrysanthemum corymbosum L.
CORYMBFLOWER TANSY

Genus name. Derived from the Greek word "chrysos" meaning "gold", and "anthemon" meaning "flower".

Species name. Derived from the Greek word "korymbos" meaning "corymbiform, corymbose, cluster of flowers"

Morphological description. Corymbflower tansy is a perennial plant with a gnarled and cylindrical rhizome. The erect stem grows from 40 to 120 cm. Its impair-pinnate, runcinate leaves are arranged alternately. The lower leaves have long petioles, whereas upper ones are sessile leaves. The flower heads are grouped into corymbs. Involucral bracts are arranged into several rows. Tubular and bisexual florets are positioned in the middle of the corymbs, while ligulate and unisexual (female) florets are positioned on the periphery of the corymbs. Each flower has a pappus. The fruit is an achene with five ribs and it is 3 mm long. The flowering period is from June to August.

Habitat. It belongs to the Pontic-sub-Mediterranean floral element. It grows in meadows, light oak forests, on limestone, and in serpentine soils.

Distribution. Corymbflower tansy is spread in central Europe, southern Europe, the Mediterranean region, and southeast Asia.

Main constituents with toxic and dermatological effects. Corymbflower tansy contains a variety of allergens including sesquiterpene lactones (e.g., alantolactone), alkaloids, acetylenes, and related compounds, such as alkamines, sulphuric compounds, and isocoumarins. A greater amount of alantolactones and sesquiterpene lactones were found in the leaves and flowers, respectively, whereas smaller amounts of sesquiterpene lactones were detected in the leaves and stems (Chadwick *et al.* 2013). These compounds are potent agents of dermatitis. Some plants from the *Chrysanthemum* genus (e.g., *Chrysanthemum leucanthemum*) contain at least 15 polyacetylene compounds. The main constituents of leaf and flower essential oils are α-cadinine (50.9 %) and β-cadinine (Thomos, 1988). The largest amounts of allergens are found in its leaves and flowers. Photosensitivity occurs when one of the chemicals in corymbflower tansy (possibly alantolactone) irritates the skin and causes symptoms of red inflamed patches of the skin when exposed to sunlight or any other source of ultraviolet light.

Contact allergic dermatitis caused by corymbflower tansy often starts on the fingers (from the removal of flower buds), but usually then spreads to the forearms and the face. It can sometimes be very persistent and can cause chronic allergic dermatitis.

Figure 2-124: *Chrysanthemum corimbosum* L. (photo, Gorica Djelic)

Figure 2-125: *Chrysanthemum corymbosum* L. (photo, Gorica Djelic)

Erigeron canadensis L.
HORSEWEED

Genus name. Derived from the Greek words “eri” meaning “early” and “geron” meaning “old age”, “old man”, or “elderly” because it flowers and fades early in spring and has pappi made of white hairs.

Species name. Derived from the word “canadensis” meaning “of Canada”.

Morphological description. Horseweed is an annual, herbaceous plant with a thin, spindle-shaped root and an upright stem that grows from 10 to 150 cm. Alternately arranged, simple, lanceolate to linear lanceolate leaves are 2–10 cm long and up to 1 cm wide. Flower heads of 3–5 mm in diameter are grouped into paniculate inflorescence. The ligulate florets are unisexual (female) and are positioned on the outer side of the inflorescence. The tubular florets are bisexual, yellow, and located towards the centre of the inflorescence. The pappus is made of a single row of hairs that easily fall off. It blossoms from June to October.

Habitat. It grows alongside roads, railroads, on dike slopes, at the edge of maize fields, and on arable lands.

Distribution. The plant is native to North America, and has been introduced to Asia, Europe, and Australia. Horseweed is an invasive species in Serbia.

Main constituents with toxic and dermatological effects. This plant can cause contact allergic dermatitis. The major constituents of its essential oil are limonene, spathulenol, β-pinene, cis-lachnophyllum ester, and (2Z, 8Z)-matricaria ester (Ayaz *et al.* 2017).

Figure 2-126: *Erigeron canadensis* L. (photo, Vaskrsija Janjic)

Figure 2-127: *Erigeron canadensis* L (photo, Vaskrsija Janjic)

Figure 2-128: *Erigeron canadensis* L. (photo, Vaskrsija Janjic)

Figure 2-129: *Erigeron canadensis* L. (pixabay.com; conyza-canadensis-848782)

Family *Boraginaceae*

Echium vulgare L.
VIPER'S BUGLOSS

Genus name. Derived from the Greek word "echis" meaning "viper" or "venomous snake", as its corolla resembles the head of a viper.

Species name. Derived from the Latin word "vulgaris" meaning "common", "everyday" "ordinary", or "vulgar".

Morphological description. Viper's bugloss is a biennial, semi-shrubby plant, with a branched, spindle-shaped root. The erect stem is about 1 m tall and it is covered with stout, short hairs, and also sporadically with long ones. The linear-lanceolate leaves are narrowed into petioles, whereas sessile, entire, pale green leaves are positioned at the top of the stem. The flowers are densely crowded along a curved or coiled stem and are clustered into boragoid inflorescences. The 13 mm long calyx is covered with bristly hairs. The funnel-shaped, almost bilabiate, corolla is 14–22 mm long. It is covered with short hairs. Initially, it will be pink or white, and then it may become blue. The style has pinnate hairs. The fruits are pyramidal nutlets. The plant blossoms in June.

Habitat. Viper's bugloss is distributed in dry, open habitats, along roadsides and watercourses, on walls and embankments, and in dry artificial meadows and tilled fields.

Distribution. Viper's bugloss is spread throughout most of Europe: northwards to England and south-eastern Norway, Estonia, and western Siberia, and southwards to central Spain, southern Italy, Sicily, the Balkans, Asia Minor, and Armenia. It has been introduced to North America where it is now naturalised. Viper's bugloss belongs to the Eurasian floral element.

Variability. There are two subspecies within the species *Echium vulgare*:

- *Echium vulgare* subsp. *pustulatum*
- *Echium vulgare* subsp. *vulgare*

Main constituents with toxic and dermatological effects. In certain countries (Germany and Russia), this plant's juvenile leaves and stems are boiled and used as a vegetable. Parts of the juvenile plants contain vitamin C, carotene, and vitamin E. The seeds contain about 30 % oil (Czaplicki *et al.* 2009). This plant also contains high amounts of pyrrolizidine alkaloids that can permanently damage the liver. No cases of human poisoning have been identified, but there have been numerous animal poisonings, particularly of sheep and horses. In the past, viper's bugloss was used in traditional medicine as an antivenom. During its flowering period, viper's bugloss contains the alkaloids, consolidin and cynoglossum, as well as low amounts of saponins, which make it poisonous (Janjić and Lazić, 2016).

Figure 2-130: *Echium vulgare* L. (photo, Vaskrsija Janjic)

Figure 2-131: *Echium vulgare* L. (photo, Vaskrsija Janjic)

Figure 2-132: *Echium vulgare* L. (photo, Vaskrsija Janjic)

Family *Buxaceae*

Buxus sempervirens L.

COMMON BOX

Genus name. Originates from the Latin word "buxus" meaning "box", which refers to the prior use of the wood to make boxes.

Species name. Originates from the Latin word "sempervirens" meaning "evergreen" or "always alive", because its leaves are green the whole year round.

Morphological description. Common box is a densely branched evergreen shrub or small tree that grows slowly and can reach a height of 4 m. It is a long-lived species. The root system is well developed. The bark is light brown and smooth in juvenile plants, but later becomes cracked. Alternate and decussate leaves with short petioles are ovate or elliptical and long (approximately 3 cm) with entire margins; they are also leathery and evergreen with dark green upper surfaces and pale green lower surfaces. There are no bracts. The plant is a hermaphrodite with unisexual flowers. One inflorescence contains both male and female flowers. The male flowers have four perigonium leaflets and four stamens. Bracteoles envelop the female flowers. The perigonium consists of 4–8 leaflets. There are three carpels and an ovary with three detached styles. The inflorescences are located in the leaf axil. The fruit is a black-brown capsule that matures in June. Common box is propagated vegetatively. It tolerates pruning well, and has been grown as an ornamental shrub since ancient times. It flowers during March and April.

Habitat. It grows in deep, well-drained, neutral to alkaline soils rich in calcium. It is a semi-skiophilous plant that tolerates drought and low temperatures.

Variability. The following varieties exist within this species:

- *Buxus sempervirens “Argentea marginata”*: the leaf margins are silverfish white in colour.
- *Buxus sempervirens “Aureo marginata”*: the leaf margins are golden yellow.
- *Buxus sempervirens “Suffruticosa”*: a low type (up to 1 m in height), with small leaves; tolerates low temperatures better than the other varieties.
- *Buxus sempervirens “Anquistifolia”*: 3.5 cm long bifarious leaves.

Distribution. It belongs to the sub-Mediterranean-mountainous element; it is a Tertiary relict. It is native to southern and central Europe, western Africa, southwest Asia, and the Caucasus all the way to the Himalayas. It is locally naturalised in certain parts of North America. It is grown widely in the world as a cultivated plant, including in our country.

Main constituents with toxic and dermatological effects. Common box is a plant with leaves and barks that contain steroidal alkaloids, such as cyclobuxine and buxine. Over 135 steroidal alkaloids have been found in leaves of plants belonging to the genus *Buxus* (Ata and Andersh, 2008*)*. In addition to buxine, this plant contains parabuxine, buxein, resins, tannins, and essential oils. This plant was used as a traditional remedy to treat jaundice, rheumatism, and certain skin diseases, as well as diseases of the gallbladder, kidney stones, and malaria. It also acts as a laxative and stimulates sweating. Today, it is considered that common box, due to its large amounts of alkaloid buxine and its derivatives, should not be used for treatments. Fatalities due to the improper use of common box in healing have been reported. The following constituents have been found in this plant: triterpene alkaloids ((+)-16α,31-diacetylbuxadin-Nb-demethylcyclo-micuranin, (-)-cyclomicuranin, (-)-cyclobuxophylline-K, (+)-buxacoumarin steroidal alkaloids (N_{20}-formylboxaminol E [(20S)-16α-hydroxy-20-(formylamino)-3-β-(dimethylamino)-9,10-seco-buxa-9(11), 10(19)-diene], O_{16}-syringylbuxaminol E [(20S)-16α-syringoyl-3β-(dimetilamino)-20-(amino)-9,10-seco-buxa-9(11),10(19)-diene], N_{20}-acetyl-buxamine G [(20S)-20-(acetylamino)-3β-(methylamino)-9,10-seco-buxa-9(11),10(19)-diene] and N_{20}-acetylbuxamine E [(20S)-20-(acetylamino)-3 β-(dimethylamino)-9,10-seco-buxa-9(11), 10(19)-diene 31 acetylcyclomicrophylline-A, benzylbuxadiene, buxamine-C, buxabenzamidine, buxadiene, and buxacuamarin. (Ata *et al.* 2002; Fisher, 1996). The species' toxicity is due to steroidal alkaloids. The plant's sap and leaves cause contact dermatitis.

Figure 2-133 (left): *Buxus sempervirens* L. (pixabay.com; book-blossoms-324094);
Figure 2-134 (right): *Buxus sempervirens* L. (photo, Vaskrsija Janjic)

Figure 2-135: *Buxus sempervirens* L. (photo, Vaskrsija Janjic)

Figure 2-136: *Buxus sempervirens* L. (photo, Gorica Djelic)

Family *Euphorbiaceae*

Euphorbia amygdaloides L.
WOOD SPURGE

Genus name. Derived from the name of the Ancient Greek physician, Euphorbos from the 1st century BC

Species name. Derived from the Latin word “amygdaloides” meaning “resembling an almond” (Greek word “oidos” meaning “in the shape of”).

Morphological description. Wood spurge is a perennial plant, which is 30–70 cm tall with a lignified horizontal root. The stem is upright or sometimes decumbent but will then ascend again. It has a great number of fertile and sterile stems. The elongated obovate leaves of its sterile stems have petioles of 5–10 cm long, which have narrow base and entire margins; they are dark green in colour. The sessile, oblanceolate, or obovate leaves of its fertile stems have obtuse tips, entire margins, and are yellow-green. The cyathium is 2.5–4 mm long and hairy inside. The fruit is a three-celled capsule of about 4 mm long. Its seeds are oval or spherical, 2–2.5 mm long, and a smooth, bluish grey. Wood spurge flowers from April to June.

Habitat. Wood spurge usually occurs in deciduous forests, particularly in light beech forests and in calcareous soils.

Distribution. Wood spurge is widely spread throughout Europe: from Ireland, France, and Portugal eastwards through to central and southern Europe all the way to southern Russia and the Caucasus. It has also been introduced to North America. It is quite widespread in the Balkan Peninsula, as well as in our country. It belongs to the sub-Atlantic-sub-Mediterranean floral element.

Main constituents with toxic and dermatological effects. Wood spurge is a poisonous plant. The toxicity of the above-ground parts of the plant is higher than of the root. It originates from the presence of the poisonous constituent euphorbin, which is, in fact, euphorbinic acid anhydride. It is present in the milky sap (latex) of juvenile above-ground wood spurge plant parts (Nelson *et al.* 2014). The species of this genus tend to accumulate large amounts of selenium. The selenium content is higher in plants that grow on soils rich in selenium compounds. Diseases in cattle and horses resulting from the absorption of selenium from their feed have been reported. The toxic components found in the milky sap of wood spurge cause contact skin irritation (Crosby, 2004). Dermal exposure causes moderate effects, which do not always appear immediately; therefore, it is very important to clean contaminated surfaces. Erythema first appears on the skin, which is then followed by oedema and blisters. The blisters vary from small pimples to large bullae. Furthermore, they last from one to three days, and then secondary complications occur, which, if treated, disappear in four to seven days. Numerous problems occur if the sap from these plants gets into eyes; the effects include tearing, keratitis, iritis, reduced visual activities, and conjunctivitis.

Its toxic compounds also affect the colour, taste, and odour of milk and milk products. Euphorbin is a volatile compound. It decomposes in plants after mowing; therefore, dried plants are less poisonous than fresh ones.

Figure 2-137: *Euphorbia amigdaloides* L. (photo, Gorica Djelic)

Figure 2-138: *Euphorbia amigdaloides* L. (photo, Gorica Djelic)

Euphorbia cyparissias L.
CYPRESS SPURGE

Genus name. The genus is probably named after Euphorbos, the Greek physician from the 1st century BC.

Species name. Derived from the Latin word “cyparissias” meaning “resembling cypress” or “like cypress”.

Morphological description. Cypress spurge is a perennial plant, 15–50 cm in height, glabrous or slightly hairy, and grey-green with a cylindrical creeping root. The stems are erect and branched. Its sessile leaves are densely spirally arranged. The leaves are narrow and linear, with same width over the entire length (2–3 mm). The tips are obtuse or shortly tapered with one rib. The spathes are ovoid-rhombic or triangular-cordate, blunt, and yellow but later they usually become purple. The inflorescence is a cyathium in which the growth of the central axis is terminated by a flower that opens first and then the growth is continued by several dichasial cymes. The fruit is a three-sectioned capsule about 3 mm long, and it is prominently dotted. The ovate-ovoid seeds are smooth and about 2 mm long. The flowering period is from April to July.

Habitat. Cypress spurge grows on sunny, warm, and usually dry sites. It occurs in light forests, shrubs, glades, ploughed fields, sandy sites, upland arid meadows, and moderately moist meadows and pastures from lowlands to alpine regions (above 2500 m above sea level).

Distribution. It is widespread in central and southern Europe, southern parts of Scandinavia, southern parts of European Russia, and in Siberia (as far as Lake Baykal). It has been introduced to North America. In Serbia, it grows like a weed species (Djelić and Vićentijević-Marković, 2002: Djelić and Vićentijević-Marković, 2005).

Variability. Two varieties of this species have been established:

- *Euphorbia cyparissias* var. *esuloides*
- *Euphorbia cyparissias* var. *major*

Main constituents with toxic and dermatological effects. Cypress spurge is a poisonous plant because all of its parts contain toxic latex, which is made up of diterpene, lactone euphorbon, up to 15% resin, some gum, rubber, and insufficiently chemically analysed euphorbin. Resins and euphorbin have a very irritant effect and they cause inflammation on the skin, blisters, ulcers, deep mucosal necrosis, and inflammation of the cornea (keratitis). When resorbed, it causes severe poisoning with a loss of consciousness, mydriasis, and damage to the blood flow. Furthermore, cypress spurge has the ability to accumulate large amounts of selenium, whose content in a plant is dependent on its content in the soil. Selenium content is higher in plants that grow on soils rich in selenium compounds.

The toxic components contained in the milky sap of cypress spurge cause skin inflammation (Crosby, 2004). Dermal exposure causes moderate effects that do not always appear immediately; this means that it is very important to wash clean contaminated areas. Erythema first appears on the skin, and then oedema and blisters follow (Frohne and Pfander, 2005). The blisters vary from small pimples to large bullae. They last from one to three days, and then secondary complications occur, which, if treated, disappear in four to seven days. Many problems occur if the sap of these plants is introduced to eyes; this can cause tearing, keratitis, iritis, reduced visual activities, and conjunctivitis.

Almost all grazing animals avoid fresh cypress spurge, except sheep but they consume the plant as hay, although dry cypress spurge is also poisonous. The symptoms of poisoning in cattle are severe inflammation in the bowels, accompanied with colic, possibly vomiting, haematuria, muscle tremors, staggering, and cramps. A diseased cow's milk will be reddish in colour and it will have a bitter taste. An infected animal can die within one to three days. Animal poisoning from cypress spurge is rare, but it does occur because the plant is widely spread and significant amounts of it can get into hay (Gilleron and Dissard, 1981).

Figure 2-139: *Euphorbia cyparissias* L. (pixabay.com; euphorbia-cyparissias-846508)

Figure 2-140 (left): *Euphorbia cyparisias* L. (photo, Gorica Djelic);
Figure 2-141 (right): *Euphorbia cyparissias* L (photo, Vaskrsija Janjic)

Figure 2-142 (left): *Euphorbia cyparissias* L. (photo, Gorica Djelic);
Figure 2-143 (right): *Euphorbia cyparissias* L (photo, Vaskrsija Janjic)

Figure 2-144 (left): *Euphorbia cyparissias* L (pixabay.com; cyparissias-87643);
Figure 2-145 (right): *Euphorbia cyparissias* L. (photo, Gorica Djelić)

Euphorbia helioscopia L.
SUN SPURGE

Genus name. The genus is probably named after Euphorbos, the Greek physician from the 1st century BC.

Species name. Derived from the word "helioscopius": "helio" meaning "sun-observing" or "sun-watching" (the Latin word "helio" means something related to light, the sun, or sunlight; it is derived from the Greek word helios, which refers to the Greek sun god) and "scopus" meaning "one that watches".

Morphological description. Sun spurge is an annual plant, which is covered with sparse hairs or hairless, with a thin spindle-shaped root. An erect, single stem is merely 5–40 cm tall. The obovate, almost spherical, leaves are arranged alternately. The leaves close to the flowers are larger than those on the stem. The bracts are similar to the leaves, as they are ovate or obovate, and spherical or elliptical. The inflorescence is a single cyathium up to 3 mm long. The fruit is a 3-celled capsule, which is 3 mm long. The seeds are spherical-ovate, densely netted, and pitted. The plant blossoms and produce fruits from April to November.

Habitat. Sun spurge is a weed species that grows in crops, especially in vegetable gardens. It is also found in vineyards, wastelands near settlements, and along paths and roads, particularly in sunny sites.

Distribution. It is widely spread throughout Europe, northern Africa, Asia Minor, and eastward through most of Asia (all the way to Japan). It has been introduced to North America, Australia, and New Zealand. Sun spurge was also broadly distributed in former Yugoslavia. It belongs to the European floral element.

Variability. No lower taxonomic units have been established within this species.

Main constituents with toxic and dermatological effects. Sun spurge, like some other species in the *Euphorbia* genus, is a poisonous plant. Its toxicity is particularly pronounced in the above-ground parts and it originates from the compound euphorbin, which is present in the plant's milky sap. Sun spurge contains jatrophone-type diterpenoids, euphoheliosnoids A, B, C, and D, and other diterpenes, such as euphoscopins, epieuphoscopins, euphornins, cuphohelioscopins, and euphohelionone (Zhang and Guo, 2006; Yamamura *et al.* 1989; Zang and Guo, 2005). The following four esters of 12-deoxyphorbol have been isolated from this plant: deoxyphorbol-13-phenylacetale-20-acetate, 12-deoxyphorbol-13-dodecdienoate-20-acetate, 12-deoxyphorbol-13-[2-methyl-*cis*-2-butenoate]-20-acetate, and 12-deoxyphorbol-13-[2-methyl-*cis*-2-butenoate. These substances are major skin irritants (Schmidt and Evans, 1980). Euphorbin, as a euphorbinic acid anhydride, is a volatile compound that is easily decomposed after mowing and drying plants. Therefore, it has no ill effects on animals when it is in the form of hay. Euphorbin and other constituents found in the milky sap of sun spurge cause skin inflammation by their physiological action.

The toxic components contained in the sun splurge's milky sap cause skin inflammation. Dermal exposure causes moderate effects that do not always appear immediately, which is why it is very important to clean contaminated areas. Erythema first appears on the skin, and then oedema and blisters occur. Blisters vary from small pimples to large bullae. They last from one to three days, and then secondary complications occur, which, if treated, disappear in four to seven days. Many problems occur if the sap of these plants gets into the eyes, such as tearing, keratitis, iritis, reduced visual activities, and conjunctivitis (Karimi *et al.* 2010).

Sun splurge's toxic compounds also affect the colour, taste, and the odour of milk and milk products. Sun spurge, as the remaining species of this genus, tends to accumulate large amounts of selenium if it grows on soils rich in selenium compounds. In such cases, the increased amounts of selenium can have a toxic effect on various animals, but primarily cattle and horses. Alkaloids helioscopinin-A, helioscopin-A, helioscopin B, and the following eight tannins can be found in sun spurge plants: corilagin, punicafolin, geraniin, elaeocaprusin, furosin, terchebin, mallotusinin, and caprinusin (Lee *et al.* 1990).

Figure 2-146 (left): *Euphorbia helioscopia* L. (photo, Gorica Djelic);
Figure 2-147 (right): *Euphorbia helioscopia* L. (photo, Gorica Djelic)

Figure 2-148: *Euphorbia helioscopia* L. (photo, Vaskrsija Janjic)

Figure 2-149: *Euphorbia helioscopia* L. (pixabay.com; euphorbia-helioscopia-855328)

Family *Ginkgoaceae*

Ginkgo biloba L.
GINKGO

Species name. Derived from the Greek words “bi” meaning “two” and “lobus” meaning “lobe”, because the leaf blade is divided into two lobes. In China, the seeds are used as food and it is called silver almond, silver apricot, or white walnut.

Morphological description. Ginkgo is a living fossil that from the Permian age. It is a deciduous gymnosperm that can reach a height of up 40 m, while its diameter can be up to 2.5 m. Its bark is grey and cracked in mature trees. Its canopy is pyramidal. It grows symmetrically and spherically for up to hundred years; after this, it will curve and have no regular shape. Its leaves are soft, pale green clustered at the tips of the short shoots, and alternately arranged on long shoots. In addition, its leaves are simple, and have petioles and leaf blades cleft at their tips, which are divided into two lobes. Ginkgo is a dioecious plant. It starts producing seeds when it is between 20 and 35 years old. Male plants produce catkin-like strobili displayed on short shoots, which reach up to 3 cm long, and consist of an axis and microsporophylls with pollen sacs (microsporangia). The female plants on its short shoots have a “female” flower called megasporophyll. Two ovules are formed at the end of a stalk and, after pollination, one or both develop into seeds. The mature seed has a flashy outer layer (sarcotesta) that has an unpleasant odour. The inner part is a stone hard sclerotesta. Germination is hypogeal, and seeds retain the ability to germinate for a year.

Habitat. It naturally grows in subtropical climates, with the annual precipitation sum ranging from 1.270 to 1.400 mm, and with an air humidity of 80% in the June–September period. It is resistant to low temperatures and can tolerate temperatures of -25°C and even -30°C. It is also tolerant to high temperatures. It does not tolerate shade and exclusively grows in full daylight.

Distribution. It is native to eastern China (the Dalou Mountain in the Guizhou Plateau region). There are several trees in China older than 2500 years. It was introduced to Europe in the 18th century. It is cultivated as an ornamental species all over the world.

Variability. No lower taxonomic units have been established within this species.

Main constituents with toxic and dermatological effects. Extracts of ginkgo leaves contain phenolic acids; proanthocynidins; flavonoid glycosides, such as myricetin, kaempferol, isorhamnetin, and quercetin; terpene trilactones, ginkgolides; and bilobalides (Van Beek, 2002). Moreover, its leaves contain unique ginkgo biflavones, as well as alkylphenols and polyprenols (Van Beek and Montoro, 2009). Ginkgo alkylphenols (anacardic or ginkgolic acids, cardols and cardanols) are the major constituents that cause allergic contact dermatitis. Ginkgolic acid 1, which is its most important allergen, is commonly found in a flashy seed coat. Contact dermatitis primarily occurs on contact with mature seeds, rather than the leaves. The first extract from a ginkgo leaf was obtained as late as 1965 (Dr. Corey won the Nobel Prize for this achievement).

Figure 2-150: *Gingo biloba* L. (photo, Gorica Djelic)

Figure 2-151: *Ginkgo biloba* L. (pixabay.com; vlad-kutepov-9ikbG_8k8KY-unsplash)

Figure 2-152: *Ginkgo biloba* L. (pixabay.com; gingko-1523580)

Family *Hypericaceae*

Hypericum perforatum L.

PERFORATE ST. JOHN'S WORT

Genus name. Derived from the Greek words "hyper" meaning "above" or "over" and "eikon" meaning "figure", "image", or "reflection", which refers to this genus' exceptional medicinal properties.

Species name. Derived from the Latin word "perforatus" meaning "bored through" or "perforated".

Morphological description. Perforate St. John's wort is a perennial plant with a spindle-shaped, extensively branched root. The stem is erect and branched at the top. It can grow up to 2–0100 cm. It is glabrous with two pronounced stripes. Its leaves are ovoid, oblong or linear, with obtuse or short acuminate apices, almost stalkless, and with numerous scattered translucent dots on their surfaces. Its flowers are clustered into wide umbel inflorescences. Its sepals are ovoid-lanceolate or lanceolate-linear with acuminate tips, with a smaller or greater number of transparent or black dots and streaks on their surfaces. Its petals are 2–4 times longer than its sepals. They are elliptical, pointed, and golden yellow with black dots, particularly along their margins. Its fruit is a capsule with warty oil pits. Verruculose seeds are black or dark brown. The flowering period is from June to August.

Habitat. St. John's wort has a broad ecological base and so it is found in different environments. It grows in various types of oak forests, boscages, forest glades, burnt areas, meadows, and pastures.

Distribution. It is widespread in Europe, central and western Asia, and northern Africa; it has also been introduced to eastern Asia, North and South America, Australia, and New Zealand. St. John's wort grows extensively on the territory of former Yugoslavia. It belongs to the Eurasian floral element.

Variability. There are four subspecies within the *Hypericum perforatum* species:

- *Hypericum perforatum* subsp. *perforatum*
- *Hypericum perforatum* subsp. *latifolium*
- *Hypericum perforatum* subsp. *veronense*
- *Hypericum perforatum* subsp. *angustifolium*

Main constituents with toxic and dermatological effects. This plant has been extensively used in medicine. Little is known about its berries' composition and toxicity. Gastrointestinal discomfort (nausea, abdominal pain, loss of appetite, and diarrhoea), dizziness, confusion, fatigue, dry mouth, restlessness, and headache occur as side effects. The immature, red berries are assumed to be more toxic than the mature black berries. St. John's wort contains volatile oil and hypericin that have poisonous effects (Greeson *et al*. 2001). Hypericin has been found in animal blood and is considered to be a major sensitising substance. Dermatitis or skin inflammation occurs as a result of sensitivity to light. Other *Hypericum* species also contain poisonous constituents; therefore, they should not be used as food or feed.

Figure 2-153: *Hypericum perforatum* L. (photo, Gorica Djelic)

Figure 2-154: *Hypericum perforatum* L. (photo, Vaskrsija Janjic)

Figure 2-155: *Hypericum perforatum* L. (photo, Vaskrsija Janjic)

Figure 2-156: *Hypericum perforatum* L. (photo, Vaskrsija Janjic)

Family *Liliaceae*

Colchicum autumnale L.

AUTUMN CROCUS

Genus name. Originates from the ancient name “Colhis” meaning the Caucasian area.

Species name. Originates from the Latin word “autumnalis” meaning “of autumn”.

Morphological description. Autumn crocus is a perennial plant with a bulb-like corm, which is 2.5–4.5 cm long and enveloped in a dark brown layer. Erect, narrow-lanceolate leaves (3–5) are 20-40 cm long and 2–5 cm wide; these grow out of the corm in spring. At the end of summer and at the beginning of autumn, a large, fennel-shaped purple flower occurs. The flower resembles saffron. The fruit is a three-sided capsule of an elongated oblong shape, which is 3-4 cm long with splits up to its middle. The seeds are spherical, brown, and up to 2 mm long. The flowering period is from August to November.

Habitat. Autumn crocus grows in meadows and pastures, from lowlands to the subalpine zone.

Distribution. Autumn crocus is widely spread in southern, central, and western Europe. In Serbia, it is a common meadow plant.

Variability. There are two recognised varieties in our country:

- *Colchicum autumnale* var. *autumnale* and
- *Colchicum autumnale* var. *pannonicum.*

In the world, there are two subspecies, eight varieties, and six forms within this species:

- *Colchicum autumnale* subsp. *Pannonicum*
- *Colchicum autumnale* subsp. *Vernum*
- *Colchicum autumnale* var. *bulgaricum*
- *Colchicum autumnale* var. *elatius*
- *Colchicum autumnale* var. *pannonicum*
- *Colchicum autumnale* var. *speciosissimum*
- *Colchicum autumnale* var. *transsilvanicum*
- *Colchicum autumnale* var. *vernale*
- *Colchicum autumnale* var. *vernum*
- *Colchicum autumnale* var. *viridiflorum*
- *Colchicum autumnale* f. *bulgaricum*
- *Colchicum autumnale* f. *macropetala*
- *Colchicum autumnale* f. *milosi*
- *Colchicum autumnale* f. *pannonicum*
- *Colchicum autumnale* f. *radei*
- *Colchicum autumnale f. transsilvanicum*

Main constituents with toxic and dermatological effects. Colchicine is a toxic alkaloid, which is found in its seeds (1%), corms (0.15–0.25%), and flowers (0.2–0.3%). Alkaloids are partially bound to tannins and are largely localised in the inner cell layers of testae. Therefore, smaller seeds have a greater number of alkaloids than larger ones, because they have a relatively larger testae surface. Colchicine is a highly toxic alkaloid whose action occurs gradually (Kurek, 2018). It is toxic for all animal species. Colchicine poisonings are most common during May and June at the time of seed maturation. Colchicine is a cell poison that stops cell division; this causes karyopycnosis, which ends with the death of the cells: first the epithelial cells of the digestive tract, then the renal tubules, and finally the urinary tract. In addition to colchicine, the plant also contains colchiceine, colchicoside, demecolcine, and lumicolchicine.

Fresh autumn crocus plants are much more toxic than dried ones (hay), although the dried plants will also be poisonous over the course of many years. Animals frequently avoid this plant in lawns. However, poisoning can occur when, due to food shortages, animals are fed with green fodder or hay containing autumn crocus. The most sensitive are horses, pigs, and cows, then sheep and goats, although goats can consume greater amounts of this plants with no ill effects. The most common symptoms of horse poisoning are a loss of appetite, lethargy, dizziness, and inability to stand with an erect head. When walking, the animal will be insecure, have respiratory difficulties, and its muscles and hind limbs will tremble. Sometimes, the animal will restless, have colic pain, sweats, a rapid heart rate is rapid, a higher temperature, and a weaker and more rapid pulse. Moreover, the animal will salivate profusely, its peristalsis will be noisy, and its thirst will be intensified due to dehydration (Adamesteanu *et al.* 1966).

Autumn crocus is one of the most dangerous weeds and harmful plants found in meadows and pastures. Its toxicity for domestic animals and humans has been known for a long time, and there is evidence of a large number of people who have been poisoned by consuming milk from goats that have eaten autumn crocus. Even when the meadows are mown, autumn crocus plants do not disappear. These plants flower in autumn after regrowth, whereas the fruiting stage occurs the year after the meadow has been mown. During the first mowing in May, the seeds are partially mature and they are spread during hay-time. The seeds germinate in autumn of the same year, but the plant only blooms in its fourth year. When meadows with autumn crocus are ploughed, pigs should not be in these fields, as they can easily be poisoned.

Figure 2-157: *Colchicum autumnale* L. (photo, Vaskrsija Janjic)

Figure 2-158: *Colchicum autumnale* L. (photo, Gorica Djelic)

Tulipa spp.
TULIPS

Genus name. Derived from a Persian word, “dulbend”, and a Turkish word, “tulipant” because the plant is thought to resemble a “turban”, which is a cloth that is wrapped around the top of the head.

Morphological description. Plants of the *Tulipa* genus are perennial herbaceous flowering plants, which, because of their long history of cultivation, have a high degree of variability, which makes classification complex and controversial (Everett, 2013). The *Tulipa* genus belongs to the family *Liliaceae*, which consists of over 600 species; the genus has over 200 plant species. These plants are perennial geophytes with tunicate bulbs from which the aboveground stem emerges with leaves. The bulbs are tolerant to low temperatures. The sessile leaves are broadly lanceolate with a parallel venation and they are alternately arranged. The flower is terminal, bisexual, and radially symmetric. The perigonium is formed from six tepals and six stamens, and the gynoecium from three carpels. The fruit is a three-sided, locular capsule with numerous seeds.

Habitat. Tulips are adapted to the climate conditions of steep and mountainous regions in temperate climates.

Distribution. Tulips are spread from southern Europe to central Asia. The word “tulip” was first mentioned in 1554 in western Europe. In the Netherlands, the world’s main producer of tulips, over three billion of tulip bulbs are produced annually for export. They are produced from the seed through micropropagation and tissue culture. In horticulture, tulips are classified into 16 groups based on their flower morphology and the plant’s height:

1. Single early
2. Double early
3. Triumph
4. Darwin hybrid
5. Single late
6. Lily-flowered
7. Fringed (Crispa)
8. Viridiflora
9. Rembrandt
10. Parrot
11. Double late
12. Kaufmanniana
13. Fosteriana (Emperor)
14. Greigii
15. Species of Botanical
16. Multi-flowering

Variability. Tulip cultivation started in Persia in the 10th century. The plant was brought to Europe by Ogier Ghiselin de Busbecq, ambassador of Emperor Ferdinand II, to the court of Suleiman the Magnificent (Christenhusz et al. 2013). This genus includes 75 species and is divided into four subgenera:

- *Clusianae*
- *Orithyia*
- *Tulipa*
- *Eriostemones*

Main constituents with toxic and dermatological effects. Tulips contain anthocyanin tulipanin. It has the 3-rutinoside of delphinidin. Tuliposides and tulipanins are responsible for allergies (Lim, 2014). Tulipalin is α-methylene-γ-butyrolactone that is generated from tuliposide A. (Bruyzeel, 1997). It induces dermatitis, which occurs when the stems are cut (Christensen and Kristiansen, 1999). Tulipanin A causes numerous hyperkeratotic and erythematous changes in the skin. Reactions do not occur immediately but usually appear within 12 hours. Conjunctivitis and eye oedema appear in susceptible persons. In the majority of cases in the Netherlands, dermatitis occurs on hands and spreads to the forearms, legs, face, and genital areas (Ducombs and Schmidt, 2001).

Figure 2-159 (left): *Tulipa* spp (photo, Gorica Djelic);
Figure 2-160 (right): *Tulipa* spp (photo, Vaskrsija Janjic)

Figure 2-161 (left): *Tulipa* spp (photo, Vaskrsija Janjic);
Figure 2-162 (right): *Tulipa* spp (photo, Vaskrsija Janjic)

Figure 2-163 (left): *Tulipa* spp (photo, Gorica Djelic);
Figure 2-164 (right): *Tulipa* spp (photo, Vaskrsija Janjic)

Veratrum viride Aiton
INDIAN POKE

Genus name. Derived from the Latin word "verare" meaning "to speak the truth", because the ground root makes people sneeze, and when someone sneezes it is common to say "the truth" (to what you are saying).

Species name. "Viride" meaning "green" because the perigonium's leaflets are green in colour.

Morphological description. Indian poke is an herbaceous, perennial plant with a short and robust rhizome. The stem is green, round, hollow, and reaches up to 2 m in height. The leaves are alternately arranged, elliptic to a broad lanceolate shape, reach up to 35 cm long and up to 20 cm broad, and are heavily ribbed. The leaves are narrow at the base into the leaf sheaths that envelop the stem. The flowers are grouped into an apical complex (panicle) inflorescence up to 70 cm long. The flowers are bisexual and radially symmetric. There are six stamens. The gynoecium is formed from three carpels. The fruit is a 3-mm capsule with many seeds that grow up to 10 mm in diameter. It blossoms from July to August.

Habitat. It grows in wet soils in meadows and open forests; it can be found from sea level (in the north) to 1,600 m (in the southeast) and up to 2,500 m (in the southwest).

Distribution. It is native to eastern and western parts of North America.

Variability. There are two varieties of *Veratrum viride*:

- *Veratrum viride* var. *viride*
- *Veratrum viride* var. *eschscholzianum*

Main constituents with toxic and dermatological effects. The whole plant is highly toxic because it contains steroidal alkaloids. Poisoning symptoms include cold sweats, vertigo, slower respiration, and a drop in blood pressure. More than 50 steroidal alkaloids have been isolated in Indian poke: veratrine ($C_{32}H_{49}NO_9$), protoveratrine ($C_{32}H_{51}NO_{11}$), O-acetyljervin, cevadine, cryptenamine, cyclopamine (11-deoksojervine), veratramine, veratridine, veriloid.

cycloposine, germitrine, germidine, jervine, muldamine, vertroidine, and pseudo-valine, etc. (Roesch, 1954; Freis 1950; Marchetti, 1954). The highest concentration of these alkaloids is in the rhizomes and roots (Janjić *et al*. 2008).

Figure 2-165: *Veratrum viride* Aiton (photo, Gorica Djeli)

Figure 2-166: *Veratrum viride* Aiton (photo, Gorica Djelic)

Family *Moraceae*

Ficus carica L.

FIG

Genus name. Derived from the Greek word "sycon" meaning "fig".

Species name. "Carica", after its original location in the Caria district in Asia Minor.

Morphological description. Fig is a deciduous shrub and occasionally a tree that grows up to 10 m tall with a broad sparse canopy. The bark is smooth and light grey. Bracts are large and fall off. Alternate, simple, leaves have 3–6 cm long petioles. Polymorphic leaf blades are deeply lobed with 3–7 lobes. The upper surface is covered with dense trichomes. The inflorescence is complex. Flowers are unisexual, small, and closed in the hollow fleshy structure; the syconium that has a narrow orifice at the tip. Female flowers are positioned at the base, whereas male flowers are at the tip of the inflorescence axis. Male flowers have a perianth consisting of four sepals and have three stamens. The perianth of female flowers is five-lobed and the gynoecium is formed from two carpels. Fig wasp (*Blastophaga psenes* (L.)

Grav.) pollinates the flowers. The edible fruit consists of a mature syconium that contains one-seeded fruits called druplets. The fruit can be formed even without pollination. The fleshy fruit skin can be yellow-brown to dark purple. All parts of the plant contain a dense milky sap. It blossoms in April and May, and produces fruits from June to September. The fig is described in legends as a symbol of fertility and reproduction.

Habitat. It grows in warm, sunny habitats, on well-drained soils, and does not tolerate temperatures below 0°C.

Distribution. It is native to the Middle East and western Asia and has been introduced to Europe and North America. It thrives in the Mediterranean, but it is also cultivated in the continental regions.

Variability. No lower taxonomic units have been established within this species.

Main constituents with toxic and dermatological effects. Fig contains polyphenols, such as gallic acid, chlorogenic acid, syringic acid, (+)-catechin, (-)-epicatechin, and rutin (Veberić *et al.* 2008). The fig fruit colour varies over cultivars due to various concentrations of anthocyanins, with cyanidin-3-O-rutinoside having an exceptionally high content (Solomon *et al.* 2006). Photo-contact dermatitis is induced by the furocoumarins (5-methoxypsoralen and 8-methoxypsoralen) that are present in the milky sap (Bonamonte, 2010). The milky sap also contains ficin, which is a proteolytic enzyme with irritants and puritogens (Angelini *et al* 1989). Contact urticaria occurs in 13 out of 18 cases exposed to figs. Symptoms of dermatological activity appear in the form of conjunctivitis, rhinitis, and asthma (Alvarez-Cuesta *et al*. 2004).

Figure 2-167: *Ficus carica* L. (photo, Gorica Djelic)

Figure 2-168: *Ficus carica* L. (photo, Gorica Djelic)

Figure 2-169: *Ficus carica* L. (pixabay.com; figs-2691547)

Figure 2-170: *Ficus carica* L. (pixabay.com; fig-56402)

Family *Papaveraceae*

Chelidonium majus L.
GREATER CELANDINE

Genus name. The Ancient name of this plant is derived from the Greek words “chelidon” or “chelidonioides” meaning “swallow”, because the plant was thought to flower at the same time as their migratory arrival.

Species name. Derived from the Latin word “majus” meaning “larger”.

Morphological description. Greater celandine is a perennial herbaceous plant. Its stem is erect, branched, round, hairy, and 30–100 cm tall. The plant contains yellow-orange milky sap. The impair-pinnate lower leaves have petioles, while the upper ones are sessile. The leaf blades have lobed and wavy margins with hairy surfaces. Yellow, actinomorphous flowers are bisexual, and 3–6 flowers are clustered into umbelliform cymes. It blooms all summer long. The fruit is a pod-like capsule filled up with small, oval, black seeds.

Habitat. Greater celandine is found everywhere, from lowlands to mountainous regions. It grows as a weed alongside roads, on embankments, and in wastelands. In ancient times, it was used to heal eye diseases.

Distribution. It grows almost all over Europe including the Mediterranean region. It reaches as far as sub-Arctic Scandinavia.

Main constituents with toxic and dermatological effects. There are a large number of different alkaloids in the yellow sap of greater celandine, some of which are related to poppy opium. The highest content of alkaloids is found in the root (up to 3%), while it is three-fold lower (up to 1%) in the stem. About 25% of the plant is made of yellow sap, which encompasses approximately ten different alkaloids, of which chelidonine is mostly significant at 0.66% (Cahlikova *et al.* 2010). Other alkaloids in this plant include chemochelinidine, chelerytrine, sanguinarine, chelidocystatin, chelidoxanthin, protopine, allocryptopine, coptisine, and sparteine (Li *et al.* 2011; Rogelj, 1998). Its alkaloids exhibit harmful effects on domestic animals only if the plants are fresh, , while the drier plants have less toxic compounds (Park *et al.* 2011; Hahn and Nahrstedt, 1993). Pigs, goats, cows, and horses are the most sensitive animals to greater celandine. A cow and a horse can eat up to 500 g of this plant daily without ill effects. Poisonings are rare due to its acrid and unpleasant taste (Janjić, 1987). If poisoning does occur, then the symptoms include dizziness, inflammation in the stomach and intestines, vomiting, colic, and diarrhoea. Sensitive animals can also suffer from inflammation in their mouths and throats, as well as from haematuria. An intoxicated pig will stagger, sometimes vomit, and its pulse and breathing will be accelerated. Diarrhoea is the most common symptom of poisoning in goats (Forenbacher, 1998).

Greater celandine is used in traditional medicine to treat abdominal pains and liver disease. There is also data on its cytostatic effect; therefore, its yellow sap is used to remove warts, calluses, lichens, eczema, and other skin issues (Etxenagusia *et al.* 2000), as well as to treat tumours and changes in the female genital organs (tumours, fibroids, and inflammation).

Figure 2-171: *Chelidonium majus* L. (photo, Vaskrsija Janjic)

Figure 2-172 (left): *Chelidonium majus* L. (photo Vaskrsija Janjic);
Figure 2-173 (right): *Chelidonium majus* L. (photo, Vaskrsija Janjic)

Figure 2-174 (left): *Chelidonium majus* L. (photo, Vaskrsija Janjic);
Figure 2-175 (right): *Chelidonium majus* L. (photo, Gorica Djelic)

Family *Polygonaceae*

Polygonum multiflorum (L.) All.
TUBER FLEECEFLOWER

Genus name. Derived from the Greek words, "polys" meaning "many" and "gony" meaning "knees", in reference to the plant's numerous, jointed stems.

Species name. Derived from the Latin word "multiflorus" meaning "many-flowered".

Morphological description. Tuber fleeceflower is a perennial plant with a thick and articulate rhizome. Its glabrous stem is 30–80 cm high. Alternately arranged leaves are broadly ovate or elliptical, substantially narrowed at the base, without or with short petioles, and dark green on the upper surface and grey-green on the reverse. Two to five white-green flowers are clustered into racemes. Perianth leaflets are fused into a narrow, terete tube, which is 15–20 mm long. Stamens are fused to the perianth tubes. Filaments are covered with soft hairs. The fruit is an 8–9 mm bluish-black berry with a waxy coating. The plant flowers in May and June.

Habitat. It grows in shady deciduous forests, especially beech and oak.

Distribution. It occurs in almost all of Europe, the temperate regions of Asia, and in North America. It belongs to the circumpolar floral element.

Variability. There are two subspecies and four varieties within this species:

- *Polygonatum multiflorum* subsp. *bracteatum*
- *Polygonatum multiflorum* subsp. *broteroi*
- *Convallaria multiflora* var. *ambigua*
- *Convallaria multiflora* var. *bracteata*
- *Polygonatum multiflorum* var. *bracteatum*
- *Polygonatum multiflorum* var. *latifolium*

Main constituents with toxic and dermatological effects. There are conflicting opinions about the toxicity of tuber fleeceflower. American authors believe that all types of tuber fleeceflower are edible, whereas Japanese authors think that they are all poisonous. This is the most poisonous plant from the *Polygonum* genus. Over 100 chemical compounds have been isolated from this plant. Stilobenes, quinines, flavonoids, and stilobene glycosides are its main constituents. Stilbenes are 1,2-diphenylethylene and can exist as two possible stereoisomers (trans and cis isomer). The berries are particularly poisonous because they contain cardiac glycosides. They are repellent and of insipid sweet taste. Symptoms of poisoning include nausea, vomiting, diarrhoea, visual disturbances, hallucinations, heart failure, and acute hepatitis (Cárdenas *et al.* 2006; Jung *et al*. 2011; Wang *et al*. 2009; Wang *et al*. 2012). In cases of poisoning, gastric lavage should be performed and cleansing preparations should be undertaken. It is important to pay attention to children when they are outdoors so that they do not eat this plant's berries.

Figure 2-176: *Polygonum multiflorum* (L.) All. (pixabay.com; solomons-seal-1678175)

Figure 2-177: *Polygonum multiflorum* (L.) All. (pixabay.com; yoksel-zok-eYlU2o_97-M-unsplash)

Polygonum verticillatum (L.) All.
WHORLED SOLOMON’S SEAL

Genus name. Derived from the Greek words, “polys” meaning “many” and “gonu” meaning “knee”, “joint” in reference to the plant’s numerous, jointed stems.

Species name. Derived from the Latin word “verticillatus” meaning “whorled” and “verticillate”.

Morphological description. Whorled Solomon’s seal is a perennial plant with a long and branched rhizome. The glabrous, erect, and angular stem is 30–60 cm high. Verticillate, lanceolate laves with or without short petioles are numerous on the stem. Their upper surfaces are pale green and smooth, while their lower surfaces are grey-green and have short hairs along the leaf veins. The flowers are clustered into short racemes in leaf axils in the middle part of the stem. The filaments are very short and, together with anthers, are covered with hairs. The fruit is a semi-globular berry, which is initially green with many red spots, and later blackish blue with 6–7 yellow seeds. The plant flowers in May and June.

Habitat. Whorled Solomon’s seal grows in shady forests, brushwood, rocks, riverbanks, and mountainous meadows.

Distribution. It grows in almost all of Europe, on the Ural, Caucasus, and in Afghanistan. It belongs to the sub-Central European floral elements.

Variability. There are one subspecies and one variety within this species:

- *Polygonatum verticillatum* subsp. *stellifolium*
- **Polygonatum verticillatum** var. *gracile*

Main constituents with toxic and dermatological effects. The aboveground parts of the plant, especially its berries, are poisonous. The toxicity results from the presence of glycosides, which are mostly present in the berries (Nelson *et al*. 2014). Compounds 2-hydroxybenzoic acid and β-sitosterol were isolated from this plant. β-sitosterol is one of several phytosterols that are chemically similar to cholesterol. Sitosterol is a white powder with a characteristic odour that is widely distributed in the plant kingdom. It is a precursor of the anabolic steroid, boldenone. Boldenone is used in veterinary medicine as an anabolic agent, but it is also one of the most commonly abused steroids in sports (Oda and El-Ashmawy, 2012).

Whorled Solomon’s seal grows in mountainous regions. Its berries are red in colour and ripen in late summer and early autumn. It is also a time when children go hiking; therefore, attention should be paid to the dangers that may arise from consuming these attractive berries. In cases of poisoning, the following symptoms occur: nausea, vomiting, diarrhoea, visual disturbances, hallucinations, and heart failure. Gastric lavage and cleansing preparations are recommended as first aid. In some countries (the USA and the former USSR), its young shoots and rhizomes are used for their nutritional content.

Figure 2-178: *Polygonum verticillatum* (L.) All

Figure 2-179: *Polygonum verticillatum* (L.) All (https://commons.wikimedia.orgwikiFilePolygonatum_verticillatum01)

Figure 2-180: *Polygonum verticillatum* (l.) All (https://commons.wikimedia.orgwikiFilePolygonatum_verticillatum_Giant_One02)

Rumex acetosa L.
COMMON SORREL

Genus name. Derived from the Latin word "rumex" meaning "a shot", as the leaf is shaped like an arrow.

Species name. Derived from the Latin word "acetosus" meaning "acid".

Morphological description. Common sorrel is a perennial plant, with the erect, glabrous or sericeous, deeply ridged stems that grow up to 1 m in height. It has branched rhizomes. Lanceolate lower leaves have petioles and an arrow-shaped base. Middle leaves gradually narrow into the petiole, while upper leaves are sessile. Flowers with septate pedicels are unisexual and the plant is dioecious. The fruit is a cuspate, dark brown achene. It blooms from May to August.

Habitat. It generally grows in natural mesophilic meadows, from lowlands to highlands. It is found in disturbed areas.

Distribution. It is distributed in Europe, Asia, and North America, except arctic regions. It belongs to the Eurasian floral element.

Variability. There are six subspecies within this species:

- *Rumex acetosa* subsp. *acetosa*
- *Rumex acetosa* subsp. *ambiguus*
- *Rumex acetosa* subsp. *arifolius*
- *Rumex acetosa* subsp. *hibernicus*
- *Rumex acetosa* subsp. *hirtulus*
- *Rumex acetosa* subsp. *vinealis*

Main constituents with toxic and dermatological effects. Common sorrel is a plant that is used for nutrition and in medicine. Although its taste is pleasant, common sorrel lags behind the rest of its genus in terms of its nutritional value. The leaves contain 40–80 mg % of vitamin C and about 5 mg % carotene. However, the highest amounts of oxalic acids are found in common sorrel. In addition, the plant contains iron, corotenoids, tannins, and anthraquinones (Lampe *et al*. 1968). The leaves have a pleasant, lemon-like, and refreshing taste. The plant is used as a leafy vegetable all over the world. Various mixed stews, salads, soups, sauces, porridges, puddings, and creams are prepared from the leaves. Some people make sorrel pies with cheese. This plant is used as a remedy for severe diarrhoea, intestinal worms, irregular menstrual periods, haemorrhoids, and fevers in folk medicine. Due to the increased amount of oxalic acid, which is usually in the form of salts (oxalates), commonly potassium oxalate, the excessive and frequent use of common sorrel can cause insoluble oxalates and thus contribute to the formation of kidney stones. If an animal is not able to degrade all of the oxalic acid or if the amount of calcium in their feed is low, then the acid is resorbed and it forms insoluble calcium oxalate with the free calcium in the blood; this is highly toxic and causes acute hypocalcaemia. The concentration of oxalic acid in the leaves amounts to 6.6–13 % in the dried plant matter (Djelić and Vićentijević-Marković, 2003). When the concentration of calcium oxalate in the blood exceeds 20 mg/100 ml then it crystallises in the urine and damages the kidneys. Oxalates are mainly responsible for the occurrence of dermatoses in people. Hematuria and albuminuria (blood and proteins in the urine) and urinary retention are the symptoms of its toxic effects. Cases of fatal poisoning have also occurred, especially in children who ate large quantities of common sorrel. Depending on many factors, poisoning with common sorrel can be acute, subacute, and chronic. Acute poisoning is a result of the abrupt development of hypocalcaemia, which leads to the death one to two days after ingestion. Clinical signs of acute poisoning are apathy, loss of appetite, teeth grinding, profuse salivation, aggravated breathing, tremor, tetanic cramps, pulmonary oedema, difficulty walking, and inability to get up. In cases of subacute poisoning, hypocalcaemia gradually weakens and damages the kidneys but the animal will gradually recover following treatment. In cases of chronic poisoning, calcium oxalate is gradually deposited in the renal tubules, leading to damage to the nephrons, fibrosis, renal insufficiency, and eventually urolithiasis.

Figure 2-181: *Rumex acetosa* L. (pixabay.com; sorrel-5073344)

Figure 2-182: *Rumex acetosa* L. (photo, Gorica Djelic)

Figure 2-183: *Rumex acetosa* L. (pixabay.com; rumex-acetosa-855429)

Figure 2-184: *Rumex acetosa* L. (pixabay.com; meadows-sauerampfer-54054)

Rumex acetosella L.
RED SORREL

Genus name. Derived from the Latin word “rumex” meaning “a shot”, as a leaf is shaped like an arrow.

Species name. Derived from the Latin word “acetosellus” meaning “slightly acid”.

Morphological description. Red sorrel is a perennial plant, which grows up to 50 cm tall, with single or caespitose furrowed stems that are sometimes reddish in colour. The leaves are smooth or finely hairy, and often reddish in colour. The lower leaves are narrow and hastate with long petioles, while the upper leaves are sessile and linear-lanceolate. The plant is dioecious with unisexual flowers encased in separate individua. The perianth consists of six sepals: the three inner ones (valves) envelop and close the fruit. There are six stamens in the male flower and three carpels in the female flower. The fruit is a brown three-sided achene.

Habitat. It grows in arid habitats and often in meadows, but also in disturbed areas. It is found in mountainous regions.

Distribution. Red sorrel is a cosmopolitan plant. It is broadly distributed in former Yugoslavia.

Variability. There four subspecies within the species *Rumex acetosella*:

- *Rumex acetosella* subsp. *pyrenaicus*
- *Rumex acetosella* subsp. *acetosella*
- *Rumex acetosella* subsp. *angiocarpus*
- *Rumex acetosella* subsp. *multifidus*

Main constituents with toxic and dermatological effects. Red sorrel and similar species from the *Rumex* genus are used in the diet. Various meals and salads are prepared from this plant’s juvenile leaves. Starches, sugars, and other substances with insufficiently known compositions are contained in the rhizomes of this plant and others belonging to this genus. These unknown substances found have purgative effects. The leaves of the juvenile plant contain vitamin C, carotene, tannins, chlorophyll, carotenoids, anthraquinones, and oxalic acid (Lewis *et al.* 2017). This acid is in the form of oxalates. Calcium oxalates cause dermatoses in sensitive people. If leaves from juvenile red sorrel plants are consumed too often and in large quantities, they can cause poisoning but this is rarely fatal.

Figure 2-185: *Rumex acetosella* L. (photo, Gorica Djelic)

Figure 2-186: *Rumex acetosella* L. (pixabay.com; rumex-acetosella-846563)

Rumex crispus L.
CURLY DOCK

Genus name. Derived from the Latin word “rumex” meaning “a shot”, as a leaf is shaped like an arrow.

Species name. Derived from the Latin word “crispus” meaning “curly”.

Morphological description. Curly dock is a perennial large plant, which grows up to 1 m tall, with thick, well-developed root. The leaves are large, and somewhat fleshy, with petioles as long as the blades (about 30 cm). The lower leaves are lanceolate, while the upper ones are linear. The flowers are clustered in whorls, which are clustered into panicled racemes. The flowers are bisexual, and two-fold shorter than pedicels. The fruit is a brown 3 mm long nutlet narrowing to a sharp point. The flowering period is from June to August.

Habitat. It grows in wastelands, disturbed (ruderal) areas, and mainly wet or **mesophilic meadows**.

Distribution. It is distributed in Europe, Asia, and North and South America. It also occurs in all parts of former Yugoslavia.

Variability. There two subspecies within the species *Rumex crispus*:

- *Rumex crispus* subsp. *Littoreus* (Hardy) Akeroyd
- *Rumex crispus* subsp. *Uliginosus* (Le Gall) Akeroyd

Main constituents with toxic and dermatological effects. In certain regions (such as Bosnia and Herzegovina, and Dalmatia), its young leaves, while in the rosette stage and prior to the stem emergence, are used in the diet to make stews, especially with potatoes and pork. The leaves are rich in vitamins, particularly vitamin C (100–150 mg %). The amount of carotene is significantly lower (approximately 10 mg %). Curly dock also contains anthraquinone glycosides (nepodin, emodin, and chrysophanol), flavonoid tannins, and prumycin (Janjić and Lazić, 2016). The leaves of this plant, similar to the leaves of many other plants, contain O-glycoside avicularin, which has been isolated from *Juglans regia* and *Foeniculum vulgare* for the first time. Curly dock roots contain compounds that have purgative effects, while the fruit’s constituents stop diarrhoea. The leaves, as well as other parts of curly dock contain significant amounts of oxalic acid, which most commonly found in the form of potassium salts. Due to the high levels of oxalic acid, this plant should only be consumed in moderate amounts in order to avoid kidney stones. The level of an animal’s intoxication due to curly dock depends on the amount consumed, their adaptation to the amount of oxalic acid, the calcium concentration in the feed, and the condition of their (Abdullah et al. 2013). There are some reports about children who have consumed large amounts of curly dock with fatal effects. The plant is used in folk medicine to treat skin diseases, and as a laxative, anti-anaemic agent, and diuretic.

Figure 2-187: *Rumex crispus* L. (photo, Gorica Djelic)

Figure 2-188: *Rumex crispus* L. (photo, Vaskrsija Janjic)

Figure 2-189: *Rumex crispus* L. (photo, Vaskrsija Janjic)

Figure 2-190: *Rumex crispus* L. (photo, Gorica Djelic)

Family *Primulaceae*

Anagallis arvensis L.
SCARLET PIMPERNEL

Genus name. Its name was found in Hippocrates's notes and is derived from the Greek words "ana" meaning "again" and "agallo" meaning "to delight in", which refer to the fact that the flowers open every time the sun strikes them; this allows them to be enjoyed each day.

Species name. Derived from the Latin word "arvensis" meaning "field", "in the field", and "of the field".

Morphological description. Scarlet pimpernel is an annual plant with a decumbent or gradually ascending stem that is square in a cross-section. The young leaves and the stem have short lollipop hairs, while the older leaves do not have hair. The leaves are ovate, sessile, bright green, and in opposite pairs. The flowers are bisexual, radially symmetrical, with pedicels twice as long as the leaves. The five sepals are narrow lanceolate and acuminate. The corolla is composed of five petals that are fused in a wheel shape; they are 10–12 mm long, which is somewhat longer than the calyx, with glandular hairs at margins. The fruit is a capsule, which is only 4–5 mm in diameter. It blooms from May to October.

Habitat. Scarlet pimpernel grows in the fields as a weed, on fallow lands, in ruins, disturbed areas, and alongside roads.

Distribution. It is widespread in Europe, western and central Asia, Arabia, northern Africa, certain regions of North America, in Mexico, southern Brazil, and western Australia. Scarlet pimpernel is almost a cosmopolitan species.

Varijability. There are many subspecies of *Anagallis arvensis*:

- *Anagallis arvensis* subsp. *Carnea*
- *Anagallis arvensis* subsp. *Latifolia*
- *Anagallis arvensis* subsp. *Micrantha*
- *Anagallis arvensis* subsp. *Moneli*
- *Anagallis arvensis* subsp. *Parviflora*
- *Anagallis arvensis* subsp. *Phoenica*
- *Anagallis arvensis* subsp. *Platyphyla*

Main constituents with toxic and dermatological effects. The whole plant is poisonous, especially the seeds (Alsultan et al. 2003). It is toxic to mammals (horses, sheep), and also to fish and birds. The poisonous constituents are also found in the above-ground parts of the plant. The plant contains glycoside cyclamen and triterpenoid saponin, which has recently been found to synergistically enhance the cytotoxicity of chemotherapeutic drugs in human liver cancer cells (Li *et al*. 2014). Moreover, lactate significantly increases the permeability of the cell membranes, which may contribute to the mechanism of chemosensitising activity and to the occurrence of dermatoses in sensitive people. Anagaligenone, as a hexacyclic triterpenoid, has been isolated from this plant. The chemical composition of these constituents is unknown, but it is clear that the plant contains saponins, tannins, proteolytic enzymes, iron, and calcium.

Scarlet pimpernel used to be widely used in folk medicine. It helps excretion of kidneys and bladder stones, and it is used as remedy to treat joint pain, wounds, ulcers, and certain eye diseases, etc. The plant tastes bitter and is odourless. Poisoning symptoms involve vomiting, diarrhoea, and stomach cramps, but respiratory paralysis may also occur.

Figure 2-191: *Anagalis arvensis* L. (photo, Vaskrsija Janjic)

Figure 2-192: *Anagalis arvensis* L. (photo, Vaskrsija Janjic)

Figure 2-193: *Anagalis arvensis* L. (photo, Vaskrsija Janjic)

Figure 2-194: *Anagalis arvensis* L. (photo, Vaskrsija Janjic)

Primula obconica Hance
POISON PRIMROSE

Genus name. Derived from the Latin word “prima rosa” meaning “first rose”, because it blooms in early spring.

Species name. “*Obconica*” refers to the flower, which is in the shape of an inverted cone. In the United Kingdom, it is also called “plant poison”, because it causes contact dermatitis and it was the leading causative agent of contact dermatitis until 1960.

Morphological description. Poison primrose is a perennial plant that can grow up to 40 cm. the leaves form a rosette; they are simple with a petiole and a heart-shaped leaf blade. The leaves have long hairs that can cause mechanical damage and tiny glandular hairs that contain a skin irritant benzoquinone derivative, primin, which causes contact dermatitis. The flowers are at the apex of the flower axis that is longer than leaves. Flowers are radially symmetrical, bisexual, 2.5 cm in diameter. Petals are fused into the tube in their lower part, while the upper part consists of five lobes. There are five stamens. The syncarpous gynaecium is composed of five carpels. It blooms in late winter and early spring. The fruit is a capsule.

Habitat. It grows on siliceous soils at an altitude of 800–2000 m. It is grown as an indoor plant.

Distribution. Poison primrose is native to central and southwestern China.

Variability. There are six subspecies of *Primula obconica*:

- *Primula obconica* subsp. *begoniiformis*
- *Primula obconica* subsp. *werringtonensis*
- *Primula obconica* subsp. *obconica*
- *Primula obconica* subsp. *fujianensis*
- *Primula obconica* subsp. *nigroglandulosa*
- *Primula obconica* subsp. *petitmengin*

Numerous types have been developed and the *Libre Magenta* variety was awarded the Award of Garden Merit by the British Royal Horticultural Society. There are over 200 plant species in the *Primula* genus.

Main constituents with toxic and dermatological effects. *Primula obconica* plants contain benziquionone derivatives, primetin, miconidin (2-methoxy-6-pentyl-1,4-dihydroxybenzene), and possibly quinines which, on contact, cause dermatitis in humans. Primin (2-methoxy-6-pentyl-1,4-benzoquionone) is a main allergen (Connolly *et al.* 2004). It was isolated for the first time from the plant, *Primula mistassinica*, and it is found in the leaves, stems, and flowers, but mainly in the trichomes on the leaves and stems. Primin is found in terminal cells of the microscopic glandular hairs on leaves, stems, and flowers. Its concentration depends on the season, number of sunshine hours, temperature, air, light, humidity, and soil pH. The highest concentrations occur in the summer period, and the lowest ones during the winter. Dermatitis occurs primarily on the face and the hands (Nelson *et al.* 2014). Three major types of dermatitis described in the literature depend on the person’s sensitivity. Highly sensitive individuals develop intensive inflammation, including erythematous vesicular eruption that sometimes involves bullae and swellings (Rozas-Munoz, *et al*. 2012). Chronic cases resulting from exposure over shorter intervals lead to acute exacerbation at the infiltration sites. The skin of the face, particularly around the eyes, will become thick and yellowish-red in colour. A patch test is commonly used to detect susceptibility to the toxic effects of the primin found in *Primula obconica*.

Figure 2-195: *Primula obconica* Hance. (pixabay.com; primrose-3308293)

Figure 2-196: *Primula obconica* Hance
(https://commons.wikimedia.orgwikiFilePrimula_obconica1)

Figure 2-197: *Primula obconica* Hance. (pixabay.com; primroses-4783107)

Family *Ranunculaceae*

Actaea spicata L.

BANEBERRY

Genus name. In ancient times, the word “agnymi”, which means “to break”, was derived from the Greek “akte” or “aktea”.

Species name. Originates from the Latin word “spicatus” meaning “spiky”, “spike-like”, and “spiked”.

Morphological description. Baneberry is a perennial plant with well-developed nodular rhizome. The stem is erect, glabrous, branched, and 30–65 cm tall. The leaves are two to three tripinnate. A great number of flowers are formed and they are clustered into racemes. The perianth leaflets are white, sometimes with purple tips. There are many stamens in the flower that have white or light purple filaments. There is one stamen with a sessile stigma. The fruit is initially a green berry, and then it becomes glossy black. It blooms from May to June.

Habitat. Baneberry is a typical woodland plant, most commonly found in mesophilic upland forest communities.

Distribution. It is widespread throughout Europe, central and northern Asia, and China. It belongs to the sub-Boreal floral element.

Variability. There are two varieties within this species:

- *Actaea spicata* var. *spicata*
- *Actaea spicata* var. *acuminata*

Main constituents with toxic and dermatological effects. Baneberry berries are extremely poisonous, but because of their unpleasant odour and bitter taste, instances poisonings from them is very rare. Their main toxic constituents are made up of group of poisons called magnoflorine, which is contained in many plants, especially the family to which baneberry belongs (Wink, 2010). If only 5–6 berries are eaten the following can occur:

digestive disorders, a drop in blood pressure, dizziness, delirium, and hallucinations. If more berries are consumed, then death can result from cardiac arrest. The berries can cause redness and blisters on the skin. However, the berries are absolutely harmless to birds and are, in fact, their favourite food.

Figure 2-198: *Actaea spicata* L. (http://commons.wikimedia.orgwikiFile)

Figure 2-199: *Actaea spicata* L. (https://commons.wikimedia.orgwikiFile)

Figure 2-200: *Actaea spicata* L. (http://commons.wikimedia.org)

Caltha palustris L.
MARSH MERIGOLD

Genus name. Originates from the Greek word “kalathos” meaning “scale” and “goblet”, due to the shape of the flower.

Species name. Derived from the Latin word “palustris” meaning “of the marsh”, “marsh-loving”, and “of the bog”.

Morphological description. Marsh marigold is a perennial plant with well-developed rhizomes. The stems are usually decumbent, rarely erect, 15–30 cm high, green, but reddish at the base, hallow, glabrous, strongly branched, and with many flowers. The basal leaves have long petioles and they are ovoid-cordate to reniform, dark green, and glossy. Flowers are single, bisexual, and radially symmetrical. There are usually five, ovate petals, which are 12–18 mm long. The petals are yellow and lustrous on the inside, and greenish on the outside. There are many stamens and 5–8 ovaries. The fruits are follicles radially arranged with touching sides. The seeds are up to 2.5 mm long. The plant blooms from March to June.

Habitat. Marsh marigold grows in wet, waterlogged sites, and marshy meadows.

Distribution. Marsh marigold is spread in Europe, Asia, and North America. In Serbia, it grows in appropriate habitats.

Variability. The following subspecies and varieties of the species *Caltha palustris* are also known:

- *Caltha palustris* subsp. *polyptala*
- *Caltha palustris* var.*alba*
- *Caltha palustris* var. *bartei*
- *Caltha palustris* var. *himalensis*
- *Caltha palustris* var. *palustris*

The subspecies *Caltha palustris* subsp. *polyptala* has one variety:

- *Caltha palustris* var. *radicans*

There are also some cultivated forms of *Caltha palustris* (Flore Pleno) including the following:

- *Caltha palustris* Semiplena
- *Caltha palustris* Trotters
- *Caltha palustris* Yellow Giant
- *Caltha palustris* Marilyn
- *Caltha palustris* Multiplex

Main constituents with toxic and dermatological effects. Marsh marigold belongs to the group of poisonous plants (Fuller and McClintock, 1986). It has a bitter and acrid taste; due to this, grazing cattle will avoid it. The leaves and flowers contain significant amounts of vitamin C (150–180 mg %) and larger quantities of carotenes. The plant's sap, especially from its leaves, can cause blisters on the skin. The fresh plant parts contain protoanemonin and some other poisonous compounds whose composition is still unknown. Protoanemonin is a volatile substance that primarily causes conjunctivitis and nasal irritation. It is developed through the maceration of plant tissues, alkaline hydrolysis, or distillation. Protoanemonin is a γ-hydroxyvinyl-acrylic acid lactone. Protoanemonin is converted into anemonin through polymerisation or cooking. Anemonin is 1,2-dihydroxy-1,2-cyclobutandiacrylic acid di-γ-lactone. The marsh marigold plant contains 0.000026% protoanemonin in its leaves, unlike *Ranunculus bulbosus* and *Helleborus niger*, which have significantly higher amounts of this compound (0.78% and 0.58%, respectively). In cases of poisoning, the principal symptoms are diarrhoea, vertigo/dizziness, fainting, and cramps. These poisonous substances decompose by cooking; therefore, the cooked leaves do not exhibit toxic effects. In some countries (the USA and Germany), the leaves and flower buds are used to prepare meals, but they should first be cooked for 20–30 minutes, and the water should be at least twice changed. Due to the significant percentage of carotene, which gives the plant its yellow colour, marsh marigold petals are used to colour butter in some countries. This plant must not be eaten fresh.

Figure 2-201: *Caltha palustris* L. (photo, Vaskrsija Janjic)

Figure 2-202: *Caltha palustris* L. (photo, Vaskrsija Janjic)

Figure 2-203: *Caltha palustis* L. (photo, Gorica Djelic)

Clematis vitalba L.
OLD MAN'S BEARD

Genus name. Derived from the Greek word "klema" meaning "tender and flexible branch", "shoot or branch of vine", "vine sprout", and "tendril".

Species name. Derived from the Latin word "vitalba" meaning "white vine".

Morphological description. Old man's beard is a perennial climbing plant with very knotty rhizomes. The stem is 3 cm in diameter; it climbs and entwines around other plants. In older plants, the stem lignifies and longitudinally brakes down into threads. Alternate leaves are odd-pinnate with petioles. Single leaves (3–5) are oblong-ovate to nearly cordate, with their margins entire or irregularly incised. The flowers have long pedicels, with four (less often five) perianth leaflets, which are oblong, whitish, or green on the outside, and covered with white, silky hairs on both sides. It has many stamens and pistils (covered with hairs). The fruit is a one-seeded achene, which oblong, reddish, up to 4 mm in length, and covered with hairs. The flowering period is from July to August.

Habitat. It grows alongside roads, hedgerows, in shrubberies, and in various forest communities.

Distribution. It grows in southern and central Europe, Asia Minor, and northern Africa. It belongs to the Central European floral element.

Variability. There are the following three forms of *Clematis vitalba* L. in our country:

- *Clematis vitalba* f. *vitalba*
- *Clematis vitalba* f. *vestita*
- *Clematis vitalba* f. *integrata*

Main constituents with toxic and dermatological effects. Although this plant is poisonous, in some countries (France, Italy, and Dalmatia in Croatia) it is used as a form of food. The young shoots are often used, but they have to be well cooked and prepared in a specific way, usually with acetic acid as a salad. The plant contains a poisonous substance called protoanemonin in the amount of 0.015 % (Jin, 2012). It causes blisters and wounds on the skin. In the past, this plant and some others belonging to the *Cleatis* genus (*Clematis flamula* L. and *Clematis recta* L.) were used as remedies to treat various diseases, but they also caused severe poisonings. Old man's beard plants contain substances that exhibit strong bactericidal and fungicidal effects.

Figure 2-204: *Clematis vitalba* L. (photo, Vaskrsija Janjic)

Figure 2-205: *Clematis vitalba* L. (pixabay.com; clematis-vitalba-848713)

Figure 2-206: *Clematis vitalba* L. (photo, Vaskrsija Janjic)

Figure 2-207: *Clematis vitalva* L. (pixabay.com; clematis-vitalba-99886)

Consolida ajacis (L.) Schur.
DOUBTFUL KNIGHT'S SPUR

Genus name. Derived from the Latin words "com-" and "solidare" meaning "together" and "to make solid" (i.e. "to consolidate").

Species name. Named after Ajax, a Greek hero in the Trojan war.

Morphological description. Doubtful knight's spur is an annual plant; it is 30–100 cm tall. The stem is erect; it is rarely simple, as it is more often intensively branched and covered with short hairs. The bracts are similar to remaining leaves, but divided in a simpler way. The bracteoles are very small. The flowers with short pedicels are dark blue, and occasionally pink or white; they are clustered into dense racemes. The flower has five petal-like sepals and the upper sepal forms an upward-curving spur about 13–18 mm long. The stamens are extended filaments. The fruit is a follicle; it is 1.5–2.5 cm long, and gradually narrows into a short beak. The seeds have transverse, sinuous, and almost parallel narrow furrows. The flowering period is from June to August.

Habitat. It commonly grows in crops, especially small grain cereals, in gardens, and alongside roads.

Distribution. It is widespread in southern Europe and has been introduced to central Europe. It belongs to the sub-Mediterranean floral element.

Variability. There are two varieties of the species *Consolida ajacis* in our country:

- *Consolida ajacis* var. *ajacts*
- *Consolida ajacis* var. *subconsolida*

Main constituents with toxic and dermatological effects. As far back as 1914, the first alkaloid, ajaconine, was isolated from the seeds of *Consolida ajacis*. Doubtful knight's spur is a poisonous plant due to the fact it contains ajaconine and other diterpenoid alkaloids, such as methyl aconitine (Wada, 2002). The minimum lethal dose of doubtful knight's spur depends on the type of animal and part that has been consumed. Sheep are less sensitive to its toxic effects than cattle and horses. This plant's toxic and dermatological effects are caused by the presence of diterpene alkaloids (Shen *et al*. 2020). Delphinine is one of these alkaloids. It is a compound of a known structure. These alkaloids exert their effects on the central nervous system. The symptoms of their toxic effects are as follows: weakness, nausea, vomiting, rapid or slow pulse, and respiration. Fatal effects occur because of respiratory paralysis. Physostigmine, pilocarpine, and strychnine are used as antidotes to poisoning from this substance.

Figure 2-208: *Consolida aiacis* (L.) Schur (https://commons.wikimedia.orgwikiFileConsolida_ajacis_hatem_moushir)

Figure 2-209: *Consolida ajacis* (L.) Schur. (pixabay.com; fence-167346)

Figure 2-210: *Consolida ajacis* (L.) Schur. (pixabay.com; flower-167243)

Ranunculus arvensis L.
CORN BUTTERCUP

Genus name. Derived from the Latin word “rana” meaning “little frog”. This probably refers to the species of this genus that are very often found near water and moist places, like frogs.

Species name. Originates from the Latin word “arvensis” meaning “of cultivated ground”, “field”, “cornfield”, “in the fields”, and “of the field”.

Morphological description. Corn buttercup is an annual plant; it is up to 60 cm tall, with a “thread” root. The stem is erect, branched, and glabrous or covered with sparse hairs. The basal leaves have petioles, while the terminal ones are sessile leaves. The pedicels are round and hairy. The flowers are 4–10 mm in diameter, with five pale yellow-green sepals that are adjacent to and are more protruded than the corollas. There are five obovate lemon-yellow petals, with a broad gland (nectary) at the base. There are many stamens (up to 13) and pistils (up to 8). The fruit is a flat achene, which is 6–8 mm long, with spines and a beak that is approximately 3 mm long. It flowers from May to July.

Habitat. It grows in fields, especially with cereals, alongside roads, railroads, and sometimes in meadows.

Distribution. Corn buttercup is widespread throughout Europe (except the northernmost regions), in the temperate parts of Asia, and in northern Africa. It belongs to the Eurasian floral element.

Variability. In our country, there are two varieties of *Ranunculus arvensis*:

- *Ranunculus arvensis* var. *arvensis* (widespread)
- *Ranunculus arvensis* var. *tuberculatus*

Main constituents with toxic and dermatological effects. All species of the *Ranunculus* genus, including corn buttercup, are more or less poisonous plants. They contain anemonin, which is a volatile and poisoning substance. Furthermore, all the species from the *Ranunculus* genus contain the same or similar substances, but the amount varies. Like the majority of these species, corn buttercup is toxic to animals when consumed fresh. Young corn buttercup plants are slightly poisonous in spring, but their toxicity gradually increases and it is the strongest during the flowering period. Different amounts of protoanemonin (0.27–2.5%) were found in the following species: *Ranunculus sceratus*, *Ranunculus flammula*, *Ranunculus parviflorus*, *Ranunculus acris*, *Ranunculus bulbosus*, and *Ranunculus repens*. Therefore, the dermatological effects depend on the species (Rudzki and Dajek 1975).

The symptoms of corn buttercup poisoning are disorders of the digestive organs, vomiting, bloody diarrhoea, and cramps. Anemonin has an irritating effect on the skin; it causes a burning sensation, pain, local growth of blood vessels, and redness. It causes a burning sensation in the mouth and the mucous membranes become irritated, inflamed, and swollen. Irritation of a stomach and bowels is manifested by severe gastrointestinal symptoms. As it is resorbed, anemonin, first causes irritation to the brain, particularly the motor centres, and then a decline in brain functions, which is followed by respiratory arrest and death. Susceptibility to its poisonous constituents varies; young animals are the most susceptible, and especially cattle, horses, sheep, and pigs (Hidiroglou and Knutti, 1963). In cases of poisoning, it is essential to remove the consumed amount as soon as possible and to drain the stomach. So far, no antidotes have been found to eliminate the effects of the poisonous substances contained in corn buttercup.

Figure 2-211: *Ranunculus arvensis* L. (photo, Vaskrsija Janjic)

Figure 2-212: *Ranunculus arvensis* L. (photo, Gorica Djelic)

Figure 2-213: *Ranunculus arvensis* L. (pixabay.com; buttercup-3327279)

Ranunculus acer L.
MEADOW BUTTERCUP

Genus name. Derived from the Latin word “rana” meaning “little frog”. This probably refers to species of this genus often found near water and moist places, like frogs.

Species name. Derived from the Greek word “acer” meaning “acuminate”, “pointed”, and “sharp”.

Morphological description. Meadow buttercup is a perennial plant with short and thickened rhizomes; it grows to a height of 30–100 cm. The stem is erect, usually very branched, and covered with appressed hairs. The basal leaves with long petioles are palmately divided into 5–7 lobes each with three irregularly dentate leaflets. The upper leaves look like the lower ones, but their petioles are short and they become sessile towards the stem top. The flowers have five ovoid, glossy, golden-yellow to pale yellow petals that are covered with appressed hairs. The fruit is an ovoid-oval achene with a very short beak, which is straight or slightly bent. The plants bloom from May to September.

Habitat. Meadow buttercup usually grows alongside roads, in ditches, and wet meadows and pastures.

Distribution. Meadow buttercup is widespread in Europe, northern Africa, and has been introduced to North America. It is very common in Serbia.

Main constituents with toxic and dermatological effects. Like most other species of the *Ranunculus* genus, meadow buttercup is toxic to animals when consumed fresh. Juvenile corn buttercup plants are slightly poisonous in spring, but their toxicity gradually increases and it is at its highest during the flowering period. The flowers are the most poisonous parts of the plant, followed by leaves and stems. Immature plants are toxic due to the presence of anemonin. When dried in hay, meadow buttercup is not a treat for domestic animals, because the anemonin breaks down into non-toxic constituents in the process of drying.

Symptoms of meadow buttercup poisoning leads to disorders of the digestive organs, such as vomiting, bloody diarrhoea, and cramps. Anemonin has an irritating effect on the skin, as it causes a burning sensation and pain, as well as the local growth of blood vessels and redness. It causes a burning sensation in the mouth and the mucous membranes become irritated, inflamed, and swollen. Irritation of a stomach and bowels is manifested by severe gastrointestinal symptoms. As it is re-absorbed, anemonin firstly causes brain irritation, particularly in the motor centres, then a decline in brain functions, respiratory arrest, and death. Susceptibility to the poisonous constituents of corn buttercup varies; young animals are the most susceptible, especially cattle, horses, sheep, and pigs (Hidiroglou and Knutti, 1963). The anemonin found in meadow buttercup affects the quantity and quality of milk in dairy cows and sheep. If animals consume greater amounts of meadow buttercup, their milk and milk products will be red in colour and have a bitter taste.

Figure 2-214 (left): *Ranunculus acer* L. (photo, Gorica Djelic);
Figure 2-215 (right): *Ranunculus acer* L. (photo, Gorica Djelic)

Figure 2-216 (left): *Ranunculus acer* L. (photo, Gorica Djelic);
Figure 2-217 (right): *Ranunculus acer* L. (photo, Gorica Djelic)

Figure 2-218: *Ranunculus acer* L. (photo, Gorica Djelic)

Figure 2-219: *Ranunculus acer* L. (pixabay.com; ranunculus-acris-855300)

Ranunculus repens L.
CREEPING BUTTERCUP

Genus name. Derived from the Latin word “rana” meaning “little frog”. This probably refers to species of this genus often found near water and moist places, like frogs.

Species name. Derived from the Latin word “repens” meaning “repent”, “creeping”, “prostrate”, and “rooting”.

Morphological description. Creeping buttercup is a perennial plant with short rhizomes, but also with aboveground stolons. The stolons bear leaves, while the aerial roots are developed form nodes. The stems are erect, but sometimes prostrate at the base; they are glabrous or hairy, and usually branched. The basal leaves are trifoliate. Certain leaflets with petioles are irregularly, coarsely dentate. The leaves that are higher on the stem are similar to the basal ones. They are divided into three lanceolate lobes. The flowers are golden yellow, glossy, 2–3 cm in diameter, and often have hairy and grooved pedicels. There are five ovate and hairy sepals. Moreover, its five petals are longer than sepals. The fruit is achene, 3 mm long, round, hairless, and with a broad triangular, straight, or slightly bent beak. Achenes are placed in a spherical, hairy receptacle. The plant blooms from May to September.

Habitat. Creeping buttercup grows in wet habitats, canals, alongside roads, in meadows, on creek banks, and in wet forests, especially willow, oak, and ash forests.

Distribution. Creeping buttercup is widespread in Europe, Asia, northern Africa, and has been introduced into North America.

Variability. There are three known forms of creeping buttercup in Serbia:

- *Ranunculus repens* f. *myrrhiphyllus*
- *Ranunculus repens* f. *repens*
- *Ranunculus repens* f. *glabratus*

The following varieties of *Ranunculus repens* exist in the world:

- *Ranunculus repens* var. *elatior*
- *Ranunculus repens* var. *villosus*
- *Ranunculus repens* var. *lucidus*
- *Ranunculus repens* var. *glabratus*
- *Ranunculus repens* var. *erectus*
- *Ranunculus repens* var. *albomaculatus*

Main constituents with toxic and dermatological effects. Creeping buttercup is a poisonous plant because it contains anemonin, which is a poisonous and volatile substance that can be found in other species belonging to this genus. Anemonin is toxic to all domestic animals, but cattle are the most commonly poisoned. Since creeping buttercup grows in meadows and pastures where cattle most often graze, it is possible for them to consume this plant together with other pasture plants. The poison is lost when it is dried with hay. As in the cases of poisoning with other plants from the *Ranunculus* genus, animals experience symptoms of indigestion, diarrhoea, neuroses, respiration arrest, partial paralysis, and convulsions. Digestive tract inflammation is the first sign of poisoning with creeping buttercup. In the later stages, hyperaemia occurs in the small intestines of diseased animals. The milk from diseased cows and sheep is bitter and reddish. In cases of poisoning, it is necessary to provoke vomiting as soon as possible and to drain the stomach. No antidote agents have been found so far.

Figure 2-220: *Ranunculus repens* L. (https://commons.wikimedia.orgwikiFileRanunculus_repens_%27Flore_Pleno%27_Jaskier_roz%C5%82ogowy_2017-05-21_0)

Figure 2-221: *Ranunculus repens* L. (pixabay.com; the-buds-5158049)

Family *Rosaceae*

Agrimonia eupatoria L.

COMMON AGRIMONY

Genus name. Derived from the Greek words “agros” meaning “field” and “monos” meaning “solitary”, “alone”, and “lonely”, which refer to the species’ solitary habitats.

Species name. Derived from the Greek word “eupatorium” after Mithridates Eupator, King of Pontus (1st century BC), who observed medicinal plants.

Morphological description. It is a perennial plant with a short rhizome and an erect stem up to 30–100 cm tall. The basal leaves form a rosette. The alternate upper leaves are shorter than stem internodes. The pinnate laves have coarsely serrate margins. The upper leaf surface is covered with sparse hairs, while the inverse surface is covered with dense, silky hairs. Bracts are present. Bisexual flowers, with short pedicels, appear in dense, spike-like racemose inflorescences. There are five sepals, five petals, a large number of stamens, two carpels, and two calyx tubes. The fruit is an achene with hooked prickles. The flowering period is from June to September.

Habitat. It grows in sunny and dry habitats, on rocks, xerophytic meadows, thermophilic forests, and from lowlands to highlands.

Distribution. It belongs to a cosmopolitan floral element (Europe, Asia, Africa, North and South America; it is widespread in Serbia).

Variability. There are two subspecies, two varieties, and four forms within this species:

- *Agrimonia eupatoria* subsp. *asiatica* (Juz.) Skalický
- *Agrimonia eupatoria* subsp. *grandis* (Andrz. ex C.A.Mey.) Bornm.
- *Agrimonia eupatoria* var.*hirsuta* Muhl.
- *Agrimonia eupatoria* var. *mollis* Torr. & A. Gray
- *Agrimonia eupatoria* f. *minor*
- *Agrimonia eupatoria* f. *eupatoria*
- *Agrimonia eupatoria* f. *rotundifolia*
- *Agrimonia eupatoria* f. *longifolia*

Main constituents with toxic and dermatological effects. The common agrimony plant mainly contains tannins (up to 21%), and therefore it is considered to be a typical tannin containing plant (Murozović *et al.* 2016). In addition, the plant is also rich in organic acids (nicotinic acid, palmitic acid, and stearic acid), vitamins (C, B_1, and K), flavonoids (apigenin, luteolin, and quercetin) and tripertene glycosides (including euscaphic acid and tormentic acid), bitter compounds, and essential oils (cedrol, α-pinene, linalool, α-terpineol, bornyl acetate, and eucalyptol). Dermatitis is accompanied by the appearance of vesicles and blisters, which will occur in a sensitive person after contact with common agrimony. Moreover, dark spots can also appear in the presence of sunlight.

Figure 2-222: *Agrimonia eupatoria* L. (photo, Gorica Djelic)

Figure 2-223: *Agrimonia eupatoria* L. (pixabay.com; agrimonia-eupatoria-848711_1280)

Figure 2-224: *Agrimonia eupatoria* L.
(https://commons.wikimedia.orgwikiFileAgrimonia_eupatoria_002.JPG)

Family *Rutaceae*

Citrus maxima (J. Burm.) Merr

POMELO

The taxonomy and systematics of the *Citrus* genus are complex because of the high number of hybrids; there is even evidence that some wild species are actually hybrid in origin. *Citrus maxima* is one of four natural, i.e. non-hybrid, species of the *Citrus* genus.

Genus name. It originates either from the Italian word “citriola” meaning “pumpkin” or the Latin word “citrus” meaning “lemon”, because of its appearance or the uses for the fleshy part of the fruit.

Species name. Originates from the Latin word “maximus” meaning “the greatest”.

Morphological description. The pomelo tree is of a medium size (5–15 m) but it is the largest in comparison to the other *Citrus* genus’ species and hybrids. Its canopy is oval. Its leaves are evergreen, simple, elliptic and 15-20 cm long. The leaf petioles are noticeably winged and green. Single, large, bisexual, radially symmetrical flowers have five sepals, five petals, 16–24 stamens, and 4–5 carpels. The fruit can be up to 30 cm in diameter, and weigh up to almost 5 kg. It tastes sweet and its structure is firmer than that of grapefruit. The rind of this species is much thicker than other citruses. The fruit's flesh can be white, red, or pinkish. The latter two are sweeter than a pomelo with white flesh. Pomelo starts bearing fruit eight years after sowing. The plant blooms from May to October.

Habitat. It grows in tropical regions, at low altitudes (at the sea level), and in saline soils.

Distribution. Pomelo originates from southeast Asia. It is cultivated in many tropical and subtropical regions. This plant is a symbol of prosperity and happiness in Chinese culture.

Variability. The following species within the *Citrus* genus are important:

- *Ctrus maxima*: pomelo
- *Citrus medica*: citron
- *Citrus micrantha*: papeda
- *Citrus reticulata*: mandarin orange/mandarin

Important hybrids. *Citrus × aurantiifolia* (Christm.) Swingle: hybrid between *C. micrantha* x *C. medica*;

Citrus × aurantium L.-bitter orange: hybrid between *C. maxima* and *C. reticulate*;

Citrus × latifolia (Yu. Tanaka) Tanaka: Persian lime is a hybrid between *C. s aurantiifolia* and *Citrus × limon*;

Citrus × limon (L.) Osbeck: lemon, according to some studies it is a hybrid between *C. latifolia*, *C. maxima*, and *C. medica*, while other studies show that it is a hybrid between *C. aurantium* and *C. medica*;

Citrus × limonia Osbeck: mandarin *C. reticulata* and limun *Citrus× limon*;

Citrus × paradise Macfad.: grapefruit-hybrid between *C. maxima* and *C. sinensis*;

Citrus × sinensis (L.) Osbeck: sweet orange

Citrus × tangerine Tanaka: tangerine

Main constituents with toxic and dermatological effects. Seven compounds were isolated from young fruits of pomelo: naringenin, marmin, naringin, β-sitosterol, 5,7-dihydroxylcoumarin, 1,3,5-trihydroxyhenzene, and xanthotoxol (Xu *et al*. 2015). *Citrus maxima* contains the following alkaloids: 5-hydroxycronicyne, acriginine A, atalafoline, buntanine, buntanmine, grandisine I and II, pumiline, honyumine, natsucrin, prenyl citpressine, citropone, and glycocitrine. These are only present in the plant's roots and bark, whereas caffeine is present in the flowers. It also contains amino acids (alanine, 289sparagine, aspartic acid, coline, and glutamic acid, while glycine and proline are just present in the leaves); carbohydrates (phytol, synephrine, methyl antralinate, fructose, glucose, and pectin); carotenoids (carotene and roseoside); coumarins (5-geranoxy-7-methoxy-coumarin, aurapte, auraptene, 5-methoxy seselin, 5-methyltodannol, and 6-hydroxy methylherniarin); flavonoids (acacetin, rutin, tangeretin, cosmosiin, diosmetin, diosmin, eriocitrin, hespeidin, and naringin); monoterpenes (α-pinene, α-terpineol, anethole, β-pinene, camphene, camphor, citral, citronellal, citronellol, farnesol, geraniol, myrcene, neral, and terpinene); sesquiterpenes (α-bisabolol, α-cadinene, α-copaene, and elemol); steroids (β-sitosterol, campesterol, daucosterol, and stigmasterol); α-tocopherol; ascorbic acid; chlorophylls; decyl acetate; malonic acid; fumaric acid; succinic acid; and citric acid (Vijaylakshmi *et al*. 2015). Geraniol, citral, and hydro-peroxide d-limonene derivative are sensitisers that cause allergic contact dermatitis. Cardullo *et al*. (1989) pointed out that contact dermatitis was caused by sensitivity to citrus peel (geraniol and citral). The symptoms of contact dermatitis are skin redness; a burning sensation; intense itching; dry, cracked, and flaky skin; swelling; and blisters.

Figure 2-225: *Citrus maxima* (J. Burm) Merr. (https://species.wikimedia.orgwikiCitrus_maximauselang=sr#mediaFileStarr_070313-5664_Citrus_maxi)

Figure 2-226: *Citrus maxima* (J. Burm.) Merr. (pixabay.com; pomelo-1900795)

Figure 2-227: *Citrus maxima* (J. Burm.) Merr. (pixabay.com; thai-pomelo-1900794)

Dictamnus albus L.
BURNING BUSH

Genus name. Derived from the Greek word “Dikti”, which is a mountain range called Dicte on the island of Crete, and “thamnos” meaning “bush” and “shrub”, which refers to the plant’s origin.

Species name. Originates from the Latin word “albus” meaning “white”, because its flowers are white to pale purple.

Morphological description. Burning bush is a perennial, herbaceous plant with a branched, nodular-cylindrical, thickened rhizome. Several erect stems develop from one rhizome. Its unbranched stems, covered with many black glands, grow up to 120 cm in height. Lower, simple, sessile leaves are alternately arranged, whereas the upper, impair-pinnate leaves have narrowly winged petioles. Large, bisexual, zygomorphic flowers with pedicels of 2.5 cm in length are clustered into racemes. Five lanceolate sepals remain long on the flower. There are five broadly lanceolate petals: four of which are upper and upright, while one is lower and turned downward. There are 10 stamens and the syncarpous gynoecium has five carpels. The fruit is a 1.5 cm long capsule. The pyriform seeds are about 4 mm long. The plant blooms from May to July.

It is one of the few plants that that excretes a volatile essential oil whose components can be ignited due to the high air temperature (as the plant grows in sunny habitats); therefore, the air around the plant burns but not the plant. This is why the plant is called burning bush in the UK, and “Brennender Busch” (“flaming bush”) in Germany.

Habitat. It grows in warm, arid, and open habitats, in slightly alkaline to acid soils, and from lowlands to the lower regions of the highlands.

Distribution. Burning bush is a Eurasian species native to central and southern Europe, Siberia, and the Himalayas.

Variability. There are three varieties within this species:

- *Dictamnus albus* L. var. *albus*
- *Dictamnus albus* L. var. *macedonica*
- *Dictamnus albus* L. var. *purpureus*

Main constituents with toxic and dermatological effects. Burning bush contains furocoumarin xanthoxin, furoquinoline alkaloid skimmianine, benzofuran, glycoside flavonol glycoside rutin, isorhamnetin-3-O-β-rutinoside, and kaempferol-3-O-β rutinoside (Ivanova *et al*. 2004). According to Dr. Duke’s Phytochemical and Ethnobotanical Databases (Duke, 2017), this species contains (E)-anethol, (E)-beta-ocimene, (Z)-3-hexenyl-acetate, α-pinene, α-terpineol, aurapten, bergapten, β-caryophylline, β-sitosterol, camphene, carvacrol, cineole, cyanidin-rhamnoglucoside, delphinidin-rhamnoglucoside, dictagymnin, dictamnolactone, diosmin, estragole, feniculin, isodictamnine, isomaculosidine, isoquercitrin, limonene, limonin, linalol, methyl-chavicol, myrcene, myricetin, nonanal, p-cymol, phenolcarbonic acid, psoralen, rutin, terpinen-4-ol, terpinolene, trigonelline, and xanthotoxin, etc.

All parts of the plant can cause mild disturbances in the intestinal tract if consumed, while photodermatitis can appear on contact with its leaves. Henderson and Des Groseilliers, (1984), Knüchel and Luderschmidt (1986), and Schempp *et al*. (1996) have described phototoxic dermatitis in patients that have had contact with *Dictamnus albus* and pointed out its increasing importance as an ornamental plant. The following components of *Dictamnus albus* are phototoxic: furocoumarin 5-methoxypsoralen (bergapten), 8-methoxypsoralen, and alkaloid dictamnine (Schempp *et al*. 1996).

Figure 2-228: *Dictamnus albus* L. (pixabay.com; blossom-4247190)

Figure 2-229: *Dictamnus albus* L. (pixabay.com; burning-bush-853096)

Ruta graveolens L.
RUE

Genus name. Derived from the Greek word “rhuesthai” meaning “to rescue” and an “all around cure” from diseases.

Species name. Originates from the Latin word “graveolens” meaning “very scented”, “strong smelling”, and “having an unpleasant smell”.

Morphological description. Rue is a perennial aromatic semi-shrubby plant with a stem covered with warty glands, which can reach a height of 100 cm. The lower part of the stem is lignified, while the upper part has branches. Alternate, impair-pinnate, fleshy leaves are pale green or bluish green in colour without bracts. They have a characteristic sharp and pungent odour, and a slightly bitter taste. The lower and middle leaves have petioles, while the upper leaves are sessile. The inflorescence is a terminally positioned corymb. A terminal flower consists of five sepals and five petals, whereas lateral flowers are four-sepaled. There are twice as many stamens as there are petals, and there are 4–5 carpels. The fruit is a knotty capsule with many seeds that have a warty coat. Rue blossoms from June to September.

Habitat. It grows in xerothermic rocky habitats. It grows in the thermophilic *Carpinetum orientalis serbicum* community in south-eastern Serbia.

Distribution. It is native to south-eastern Europe, but it is cultivated all over the world.

Variability. No lower taxonomic units have been established within this species.

Main constituents with toxic and dermatological effects. The plant contains citronellal, geraniol, lialol, α-turpentine, carotene, and furanocoumarins. The phototoxicity of furanocoumarins, 5-methoxypsoralen (bergapten), and 8-methoxypsoralen (xanthotoxin) are well known and the phototoxic properties of furanoquinoline dictamnine have been detected (Schempp *et al.* 1999; Arias-Santiago *et al*. 2009).

Furanocoumarins react in the presence of ultraviolet light and exhibit phototoxic effects manifested by the appearance of burns, erythema, and blisters on the skin, as well as hyperpigmentation. Even low concentrations can result in phytophotodermatitis (Wessner *et al*. 1999; Tisserand and Long, 2013). The plant contains flavonoid rutin, alkaloids rutacridone epoxide, hydroxyrutacridone epoxide, graveolin, graveolinin, kokusaginine, rutacridone, and skimmianine. Most of these can be found in the roots (Verzár-Petri *et al.* 1976).

Figure 2-230: *Ruta graveolens* L. (https://commons.wikimedia.orgwikiFileDie_ Weinraute,_lat._Ruta_graveolens,_Pflanze_mit_den_gelben_Bl%C3%Bcten.jpg)

Figure 2-231: *Ruta graveolens* L. (pixabay.com; common-rue-1015785)

Family *Solanaceae*

Datura stramonium L.
JIMSONWEED

Genus name. Derived from the Hindi name “dhatūra” meaning “white thorn-apple”.

Morphological description. Jimsonweed is an annual plant with a spindle-shaped and branched root. The stems are erect, up to 30–120 cm tall, usually glabrous, and rarely hairy. The leaves are ovate, and the upper surfaces are dark green with firm hairs, while the bottom surfaces are light green and usually hairless. The basal leaves are very large. Single flowers have an unpleasant odour. The tubular, slightly swollen calyx has five prominent longitudinal ribs and five sharp lobes with sparse hairs along margins. The funnel-shaped corolla, which has a long tube and broad, wrinkled five-segmented margin, is 6–10 cm long. The ovary is ovoid with short soft prickles, a long style, and a bipartite stigma. The fruit is a large capsule, and is up to 5 cm long with firm spines. The seeds are flat, reniform, reticulate, dimpled, and 3.5 mm long (Gutman and Djelić, 2018). The plants flower from June to September.

Habitat. Jimsonweed is a ruderal plant that grows in wastelands, degraded areas, alongside roads, fences, near settlements, in gardens, fields, vineyards, and from lowlands to highlands.

Distribution. Jimsonweed is widespread in Europe, Asia, Africa, and North America. It is a cosmopolitan species of the moderate and warm regions.

Main constituents with toxic and dermatological effects. All parts of the jimsonweed plant are poisonous, because it contains toxic tropane, alkaloids atropine, hyoscyamine, scopolamine, meteloidine, and cuscohygrine. The plant has unpleasant smell, and the leaf has a weak one; it is also acrid and salty. The content of alkaloids amounts to 0.2–0.6%, 0.4%, 0.3–0.5%, 0.1%, and 0.1% in its leaves, flowers, seeds, roots, and stems, respectively. L-hyoscyamine, L-scopolamine, and some atropine are present in the leaves, whereas only L-scopolamine is found in the roots (Soni *et al,* 2012). The seeds contain more L-hyoscyamine and atropine than the leaves and a certain percentage of L-scopolamine. Tropane alkaloids are competitive inhibitors of acetylcholine at the postganglionic synapses in the parasympathetic nervous system.

The amounts of toxic substances vary widely in jimsonweed plants depending on the plant’s age and the local weather conditions. This variation can be as much as 5:1. The scopolamine to atropine ratio amounts to 3: 1 in young plants, while this reverses after flowering. Spontaneous poisoning with jimsonweed is rare. The jimsonweed seed contains about 0.1 mg of atropine, and the estimated fatal dose for adult humans is 10 mg or above 10 mg of atropine and 2–4 mg of scopolamine (Arnett, 1995). Jimsonweed poisoning causes delirium, hyperthermia, tachycardia, bizarre behaviour, and severe mydriasis, which results in painful photophobia that can last several days. Symptoms occur 30 to 60 minutes after ingesting the plant material or seeds and they last 24 to 48 hours, but there have also been cases with symptoms that have lasted for almost two weeks.

The symptoms of jimsonweed poisoning are the same as those of belladonna poisoning. The most severe forms of poisoning are manifested in horses, which is accompanied by agitation, frightfulness, restlessness, loss of appetite, moderate bloat, and even dizziness. The animal will move with difficulty, stumble, its head and neck will sometimes be stiff, the nostrils will flare, and the head muscles will contract. Sweating, palpitations, and shallow or rapid breathing may also occur. The disease usually appears abruptly and often progresses to frenzy. Some animals push the wall with their heads, climb racks, try to go through obstacles, cycle in one direction, become malicious, kick with their legs, try to bite, grind the teeth, salivate/drool, often do not urinate, and do not produce manure. The animal can die after 24 hours, or just several hours; it will collapse with cramps and die (Forenbacher, 1998). Tropane alkaloids are used in medicine as galenic preparations, which are made from jimsonweed leaves and stem tops.

Figure 2-232: *Datura stramonium* L. (photo, Vaskrsija Janjic)

Figure 2-233: *Datura stramonium* L. (photo, Gorica Djelic)

Figure 2-234: *Datura stramonium* L. (photo, Vaskrsija Janjic)

Figure 2-235: *Datura stramonium* L. (photo, Gorica Djelic)

Figure 2-236: *Datura stramonium* L. (photo, Vaskrsija Janjic)

Lycium halimifolium Mill.
MATRIMONY VINE

Genus name. Derived from the Greek word “lykos” meaning “wolf” or “lykion” meaning “thorny shrub”.

Species name. Derived from the Latin word “halimifolius”; it has leaves like the *Atriplex halimus* (Mediterranean saltbush).

Morfološki opis. Matrimony vine is a shrub that grows 1–3 m high and has numerous slender, light grey branches. The lanceolate or lanceolate-elliptic leaves are up to 2–3 cm long and have short petioles. The flowers are single or grow in groups of 2–6 in the leaf axils. Its bilabiate calyx is bell-shaped. The infundibular corolla is reddish-purple in colour. There are five stamens with filaments that are pubescent at the base. The ovary is two-celled, and has a filamentous style with a rounded stigma. The fruit is an elliptic or ellipsoid berry and red, but rarely yellowish in colour. The reniform seeds are brown. The plant blossoms from July to September.

Habitat. It is often cultivated as a hedge, but it also grows as a wild species alongside roads, in wastelands, and on dry slopes.

Distribution. Matrimony vine is of Mediterranean origin, and it is widespread in southern and central Europe, northern Africa, and western Asia. This plant is an adventive species.

Main constituents with toxic and dermatological effects. Many authors consider the matrimony vine to be a poisonous plant. Its poisonous effects are only manifested if a large amount of the plant material is consumed. The toxic constituents, although not sufficiently studied, are found in all parts of the plant (Qian *et al*. 2017). These constituents cause nerve damage and cerebral aberration, including mania and blindness. In addition to the various compounds of unknown compositions and physiological activities, it is believed that matrimony vine contains steroidal saponins. It is well known that these compounds increase secretion in the stomach and intestines, while in larger quantities they can cause intestinal inflammation. Parenterally administered saponins are toxic because they cause haemolysis. This is considered to be saponins' most significant property and therefore they should not be directly introduced to the bloodstream. The fruits (berries) of the matrimony vine are very similar to those of the common barberry (*Beberis vulgaris* L.) and bittersweet (*Solanum dulcamara* L.).

Figure 2-237: *Lycium halimifolium* (photo, Gorica Djelic)

Figure 2-238: *Lycium halimifolium* (photo, Gorica Djelic)

Figure 2-239: *Lycium halimifolium* (photo, Gorica Djelic)

Family *Thymelaeaceae*

Daphne mezereum L.
MEZEREUM

Genus name. Derived from the Greek word “phainomai” meaning “to appear” or “to come into being”. The genus name was originally used for laurel (*Laurus nobilis*) but it was later was transferred to this genus.

Species name. Dderived from the Persian word “mezereum/mezariyun” meaning “silky bark”.

Morphological description. Mezereum is a deciduous shrub that grows from 30 to 150 cm in height. The leaves are spirally arranged, oblong obovate, with short petioles. Their upper surface is green, whereas the reverse is grey-green. The flowers (2–3) are clustered into loose panicles at the apex of the leafless axis. The fruit is a red, oblong-ovate berry. The flowering period is from February to April, which is extended to July in the alpine region.

Habitat. It grows in mountain shady forests, moist deep soils, and open sites. It is also sometimes found in coniferous forests.

Distribution. Mezereum is widespread throughout Europe, the Caucasus, Asia Minor, and Siberia.

Main constituents with toxic and dermatological effects. All parts of the plant, and its fruits in particular, are very poisonous. The plant contains toxic glycosides and resins whose nature has not yet been fully established. Moreover, it contains the toxic compounds, mezerein and daphnin, which are particularly present in the berries of this plant (Nelson *et al.* 2014; Ronlan and Wickberg, 1970). Its twigs can cause rashes and eczema on the hands of people who are sensitive to the plant. The poisonous constituents of mezereum are considered to be highly carcinogenic substances. Contact with the skin causes redness and blisters. If consumed, the berries cause a burning and itching sensation in the mouth, swelling of the lips, and saliva secretion. Later, stomach pain, diarrhoea, and thirst will also occur. Severe headache, fever, impaired kidney function, collapse, and death occur after absorption. Fatal poisoning for children occurs after consuming 8–10 berries. However, poisoning is rare because of the fruit’s acrid and pungent taste. In the case of poisoning, vomiting, gastric lavage, and immediate medical attention should be sought as soon as possible.

Figure 2-240: *Daphne mezereum* L. (photo, Gorica Djelic)

Figure 2-241: *Daphne mezereum* L. (photo, Gorica Djelic)

Figure 2-242: *Daphne mezereum* L. (pixabay.com; daphne-mezereum-694888)

Figure 2-243: *Daphne mezereum* L. (pixabay.com; mezereon-334556)

Family *Urticaceae*

Urtica dioica L.

COMMON NETTLE

Genus name. Derived from the Latin word “urere” meaning “to burn away or, “to scorch”.

Species name. Derived from the Greek word “dioica” meaning “of two houses”: “dioecious” (“dis” = “two times”, “twice”, “two” and “oiko” = “home”, “house”).

Morphological description. Nettle is a perennial plant with wide spreading stolons. The stem is erect and rectangular, as well as covered with short bristles or long stinging hairs. The leaves are borne oppositely on the stem, and there may be, although very rarely, three leaves in a whorl. The leaves are ovate or lanceolate with strongly serrated margins; both surfaces are covered with short non-stinging, appressed hairs, and stinging hairs (trichomes). The bracts are linear-lanceolate and acuminate. The flowers are unisexual and clustered into auxiliary inflorescence. The male inflorescences are erect, whereas the female ones are usually longer and higher. All of the flowers are longer than pedicels. The perianth of the male flower is simple and four-segmented. There are four stamens. The female flower has a perianth of four unequal segments: the two outer ones are smaller than the two inner ones. The fruit is a small achene and grey-brown in colour. The plant produces flowers from June to November.

Habitat. It grows in various sites around houses, in fields, alongside roads, in logging areas, abandoned yards, and the like. It prefers disturbed areas.

Distribution. Nettle is a cosmopolitan plant; it grows all over the world, particularly in our country.

Variability. There are six subspecies, two varieties, and two forms within this species:

- *Urtica dioica* subsp. *dioica*
- *Urtica dioica* subsp. *galeopsifolia*
- *Urtica dioica* subsp. *afghanica*
- *Urtica dioica* subsp. *gansuensis*
- *Urtica dioica* subsp. *gracilis*
- *Urtica dioica* subsp. *holosericea*
- *Urtica dioica* var. *dioica*
- *Urtica dioica* var. *glabrata*
- *Urtica dioica* f. *latifolia*
- *Urtica dioica* f. *angustifolia*

Main constituents with toxic and dermatological effects. The nettle is a sort of natural multivitamin concentrate. Its leaves contain some of the most important vitamins (such as K_1, B_2, and C), carotenoids (β-carotene, xanthophyll, and violaxanthin), organic acids (gallic acid, formic acid, silicic acid, pantothenic acid, acetic acid, and butyric acid), minerals (iron, manganese, calcium, and phosphorus), chlorophylls, acetylcholine, and histamines (Hughes *et al*. 1980). It contains glycoquinine and similar substances, which are especially important because they regulate blood sugar content. Urticin glycoside is also found in nettle leaves. The poisonous content of nettle leaves and hairs (predominantly formic acid) evaporates and neutralises when cooked. Furthermore, trichomes contain acetylcholine, histamine, serotonin, moroidin, and leukotrienes. This mixture of compounds, which is found in the nettle's trichomes, is released upon contact with human skin; it is then spread over the skin and causes a specific rash and inflammation called hives or urticaria. This name was derived from the name of this plant (Tekin, *et al.* 2009). The nettle causes intense itching that lasts for several minutes to several days. If angioedema occurs, then hives develop under the skin and often cause uncomfortable swelling in the internal organs; this can create a life-threatening airway obstruction or severe involuntary intestine movements. If swelling occurs in the throat then it can cause suffocation. It is often accompanied by fever, nausea, stomach cramps, and heavy breathing. Cooked leaves and stem tops from young nettle plants have been used since ancient times to prepare very tasty and healthy meals (sauces, salads, soups, and pies, etc.). The nettle has been used as a preventive agent from Ancient Rome onwards. It is considered to have beneficial effects in the treatment of anaemia, gastrointestinal tract disorders, haemorrhages, diabetes, dermatoses, rickets, rheumatism, sciatica, nephritis, gastric and duodenal ulcers, lung tuberculosis, kidney disorders, and migraines, etc. (Vogl *et al.* 2013; Westfall, 2003).

Figure 2-244 (left): *Urtica dioica* L. (photo, Gorica Djelic);
Figure 2-245 (right): *Urtica dioica* L. (photo, Gorica Djelic)

Figure 2-246: *Urtica dioica* L. (photo, Vaskrsija Janjic)

Figure 2-247: *Urtica dioica* L. (photo, Vaskrsija Janjic)

Urtica urens L.
BURNING NETTLE

Genus name. Derived from the Latin word “urere” meaning “to burn away” or “to scorch”.

Species name. Derived from the Latin word “urens” meaning “burning” (from the Latin word “uro” meaning “to incinerate”, “to burn”, or “to bake”).

Morphological description. The stinging nettle is an annual plant, which is only 10–60 cm tall with a spindle-shape root. The stem is erect, simple, or branched. The leaves are borne opposite to each other. They are oval or elliptic, obtuse, and sharply serrated with long hairs and bracts. The flowers are unisexual; the male and female flowers are mixed. The perianths of the female flowers have one or two stinging hairs. The flowering period is from June to November.

Habitat. It grows in wastelands, uncultivated sites, in yards, on walls, around fences, alongside roads, in dumps, and beside stables. It can be found from lowlands up to mountainous regions.

Distribution. A cosmopolitan plant, which is also widespread in our country.

Main constituents with toxic and dermatological effects. The nutritional value of the stinging nettle has been known since ancient times. Due to its distribution, as well as its nutritional and vitamin values, the stinging nettle is one of the most beneficial and healthiest leafy vegetable. This plant is frequently used in cooked meals. It is made up of about 5% proteins, 7% carbohydrates, and 0.7% fats, as well as calcium, phosphorus, and iron. It is a richer source of vitamins C and A than the majority of vegetables (Rajput *et al.* 2018). Its composition is very similar to that of the common nettle. In addition to vitamin K_1 (0.2%), vitamin C (up to 0.6%), carotenoids (up to 30 mg%), vitamin B_2, and pantothenic acid, the following constituents were found in the leaves of the plant: formic acid, silicic acid, and urticin glycoside, which all contribute to the fresh plant’s toxicity (Dar et al. 2012). This mixture of compounds, which are all found in stinging nettle trichomes, is released upon contact with human skin; it is then spread over the skin, which causes a specific skin rash, as well as inflammation called hives or urticarial (Singh *et al.* 2012). This latter term was derived from the name of this plant. Stinging nettles cause intense itching that lasts for several minutes to several days. If angioedema occurs, then hives will develop under the skin; this often causes uncomfortable swelling in the internal organs, life-threatening obstruction of the airways, or severe involuntary intestine movements. If the swelling occurs in the throat, the person can suffocate. It is often accompanied by fever, nausea, stomach cramps, and heavy breathing. The toxic constituents from the leaves and trichomes (predominantly formic acid) are removed by cooking and then discarding the cooking water; this means that this green cooked mass can be used to feed domestic animals, as well as pigs, cattle, and poultry. Stinging nettles can be used in many ways to prepare meals for people.

Figure 2-248: *Urtica urens* L. (Urtica_urens_flower_kleine_brandnetel_bloemen)

Figure 2-249: *Urtica urens* L. (pixabay.com, small-nettle-766130)

Figure 2-250: *Urtica urens* L. (pixabay.com; stinging-nettles-228246)

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