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Innovative Approaches for Nanobiotechnology in Healthcare Systems

Touseef Amna and M. Shamshi Hassan

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Detailed Table of Contents

Phytochemicals have been attributed beneficial health properties, mainly their anticancer potential. Cancer treatment seeks to shrink the tumor and kill cancer cells; however, the conventional treatment available frequently fails due to the emergence of drug-resistant cell lines. Plant-derived compounds have been studied for their potential anticancer effects or as adjuvant drug to conventional treatment. However, some of the physicochemical properties and stability characteristics of the phytocompounds generate biopharmaceuticals difficulties that limit their efficacy and clinical applications in oncology. In this sense, nanomedicine offers an alternative for the development of biocompatible, biodegradable, safe, and efficacy phytoformulations. Nanostructured delivery systems show immense potential in the bioavailability of phytodrugs by providing better alternatives to conventional dosage forms, through improving physicochemical and biopharmaceutical properties of the phytocompounds and along with it to enhance the therapeutic efficacy.

Extensive studies in the field of oncology are able to identify potential cancer biomarkers with tumor-specific molecular characteristics that exceed or complement those of existing biomarkers. However, there are challenges in the development and clinical validation of the cancer biomarkers due to the complexity of the biological process involved. Standalone or integrative approach of broad range of biomolecules, their expression pattern, epigenetic alterations, and metabolic effects are well studied in the cancer research. The potential cancer biomarkers need to be studied extensively with advanced technologies to bring about a great change in cancer screening and therapy. This chapter provide an overview on recent studies about potential cancer biomarkers. Also, specific characteristics of potential biomarkers in three common types of cancer are discussed.

action of insulin. Globally, diabetes is an increasing health concern which is now emerging as an epidemic. About 700-800 plants are exhibiting anti-diabetic activity that has been studied. As far as nanotechnology in diabetes research is concerned, it has made possible the buildout of novel glucose measurement as well as insulin delivery modalities that possess the potential to excellently enhance the quality of life of the diabetic patient.

This chapter deals with the formation of biofilms, their resistance to antibacterial agents, the importance and risk of biofilms, and nanotechnology methods for biofilm control in the food industry. Biofilm is a multi-layer cell cluster embedded in an organic polymer matrix, which protects microbial cells from environmental stress, antibiotics, and disinfectants. Microorganisms that live in contact points and the environment in food processing are mostly harmful because the microbial community in the wrong location can lead to contamination of the surfaces and products produced during the processing. When new nanomaterials (for example, silver or copper are incorporated) are used, the growth of surface biofilms can also be reduced. In recent years, new nanotechnology-based antimicrobials have been designed to kill planktonic, antibiotic-resistant bacteria, but additional requirements rather than the mere killing of suspended bacteria must be met to combat biofilm-infections.

Over 100 types of arthritis have been recognized in which the dominating forms are osteoarthritis and rheumatoid arthritis. Joint stiffness, pain, swelling, lowered range of motion of joints affected, redness around joints are the main complications of almost all types of arthritis. Medications like non-steroidal anti-inflammatory drugs (NSAIDs), opioids, corticosteroids, and immunosuppressants are only used to control the symptoms of the disease but are not able to alleviate them properly. However, with the incorporation of disease-modifying antirheumatic drugs (DMARDs) as well as tumor necrosis factor inhibitors (TNFi) in treatment, there are now promising therapeutic options to select from for the management of rheumatoid diseases. Nanotherapeutic approach has enabled us to deliver the disease-modifying agents directly to the inflammation site, thus eschewing off-target and unwanted systemic effects. Therefore, it provides an opportunity to reconsider the therapeutic compounds that were considered too toxic to be administrated via oral or parenteral route.

Chapter 10

The term "flavonoid" is a broad term given to the collection of natural polyphenolic compounds which occur in plants (fruits, vegetables, roots, flowers, stems, bark, leaves) as their secondary metabolites. Subsequent research reveals that flavonoids possess anti-inflammatory, anti-mutagenic, anti-oxidative, anti-ageing, and anti-carcinogenic effects along with their capacity to modulate enzymatic activities, inhibit cell proliferation, and inhibit bacterial growth, among others. The main shortcomings of oral administration of flavonoids as therapeutic that various studies have revealed are related to their stability, bioefficacy, and bioavailability. Novel nanotechnological strategies involving nanocarrier systems are proving promising to overcome the delivery challenge of flavonoids as therapeutics. Nanocapsules, nanospheres, solid lipid nanoparticles, nanoemulsions, micelles are examples of novel nanocarrier systems that are currently being explored for targeted and efficient bio functioning of flavonoids after their oral administration.

Chapter 11

Water pollution is one of the key global problems which require immediate attention. Worldwide, it is predicted that more than 50% of countries will encounter water scarcities by 2025 which will increase to 75% by 2075. Each year more than 5 million people die due to water-borne diseases. The threat due to pollution by industries, exponential population growth, urbanization, by pathogenic microorganisms from human and animal waste, etc. The rise in water pollution and its subsequent effects on human health and environment is a matter of great concern. The water pollutants ought to be removed to improve water quality for human use. Nanoparticles or zero dimensional materials have been extensively studied since long, whereas one dimensional material (nanorods, nanotubes, nanowires, or nanofibers) have recently grabbed a lot of interest from global researchers. Nanofibers having large aspect ratio are grabbing incredible attention owing to dependency of physical property on directionality having high porosity and surface area as compared to normal fibers.

With nanoscience, new environmental benefits have emerged to aid pollution control. Nanotechnology is becoming beneficial for air and water pollution control and eradication in the future. Air pollution can be controlled with nano-adsorptive materials, nanocatalysis, and nano filters. For water pollution, nanofiltration and nano sorbents techniques are used. Nanotechnology establishes a framework to manipulate the molecular structure of objects depending on the characteristic to generate new materials. Environmental pollution is being controlled more efficiently and strategically through the application of nanotechnology. The technology deals with numerous contaminants like nitrogen oxides, volatile organic compounds, carbon dioxide, among other harmful gases. The research narrows down to the argument that nanotechnology has a positive impact on environmental protection and provides an effective way to eliminate pollution by developing reliable treatment plans. In this chapter, the authors have briefly discussed the different nontechniques applied to control the pollution.

Preface

Innovative and fusion technologies have shown incredible influence to improve various aspects of society for the betterment of mankind and healthcare systems. Nanobiotechnology as well as nanomedicine refers to the application of nanotechnology in various aspects of life. Nanobiotechnology aspires to endow with economically sound yet excellent performing health and medical pieces of equipment, amenities as well as treatment approaches through continuous research investigations and studies. Many pharmaceutical and medical companies all over the world now count on medical nanotechnology due to its abundant applications and practical uses.

This book is a pivotal reference source that provides insights into a comprehensive collection of different new and novel techniques used for the development of safe drugs that use available resources for diverse deadly diseases. It also discusses the various platforms of nanobiotechnology to be utilized in various fields. Nevertheless, the safety of nanotechnology is not yet entirely clear. However, it is expected that in the near future, the bionanosytems will play a crucial role in the treatment of human diseases and also in the improvement of existing healthcare systems.

This book, *Innovative Approaches for Nanobiotechnology in Healthcare Systems*, is a collection of 12 chapters contributed by leading experts in nanotechnology field. This book is ideally designed for Scientists, Medical professionals, Entrepreneurs, Researchers, Academicians and Students. Nevertheless, this book is premeditated to act as a reference source on conceptual, methodological and technical aspects, as well as to provide insight into emerging trends and future opportunities within the healthcare systems. In this book, each chapter covers a special subject that falls within these areas: General introduction, properties, specific applications as well as escort to future directions.

Chapter 1 gives an outlook on recent techniques of developing nanoscale medicines. In this chapter, emphasis has been made on understanding the concept of nanomaterials based therapeutic system with recent advances and exploration of characteristics of nanomaterials as well as their interactions with the biological environment. Chapter 2 deals with the research being carried out to further enhance the drug loading/and release kinetics of nanofibers. This chapter briefly summarizes the history, effects of

various parameters, and drug delivery applications of electrospun nanofibers. Also, the drug incorporation techniques are highlighted. In addition the challenges and future perspectives have been covered. Accordingly, Chapter 3 describes therapeutic potentials of different formulations of nanoparticles or nanovectors in combating cancer, with a special focus on their suppressive effects on angiogenesis process using the *in vitro* and *in vivo* models.

Furthermore, Chapter 4 particularly focuses on phytomedicine for cancer therapy based on nanocarrier systems to address them to tumor site, because nanosystems allow modifying physicochemical properties of the drugs and offers targeting ability in addition to their specificity. Similarly, Chapter 5 provides an overview on recent studies about potential cancer biomarkers. Also, specific characteristics of potential biomarkers in three common types of cancer are discussed herein.

On the other hand, Chapter 6 pays attention on the synthesis and applications of CNTs in therapeutics, mainly about the research in all areas of pharmacy and medicine. Chapter 7 addressed the significance of some medicinal plants and novel herb-based formulations from Himalayan region of India that offers numerous possible advantages for synergistic activity in the medication of diabetes with or without structural modifications.

Moreover, Chapter 8 draws attention on to the development of preventive strategies and methods for biofilm control using new nanotechnology. Interestingly, Chapter 9 is targeted on potential of phytochemicals, in particular flavonoids in the management of Rheumatic diseases. Likewise, Chapter 10 attempts to obtain understanding on the biological effects of flavonoids with special references to their targeted and efficient delivery via novel nanosystems to treat various diseases and disorders.

Subsequently, Chapter 11 spotlights the application of electrospinning method and electrospun nanofibers for water purification, in order to control the spread of waterborne diseases. The last chapter (Chapter 12) endows awareness about the role of nanoscience to control pollution and its contribution in environment mitigation.

Conclusively, it has now been accepted that the innovative technologies have clout to supplement numerous sections of civilization. Unquestionably, the current times have observed an unmatched development in research in the field of nanotechnology. There is always an escalating confidence that nanotechnology subjected to medicine will fetch noteworthy progress in the area of cure, diagnosis, as well as deterrence of infectious diseases. Ever rising awareness about the prospective therapeutic potential of nanoscience is escorting to the appearance of a novel area eminently known as nanomedicine.

Nevertheless, the field of nanomedicine requires conquering the challenges for its uses, to advance the thoughtfulness of basis of illness, fetch advance and classy analytical methods and to deliver outstanding remedies and shielding applications. Nanomaterials are probing almost into each and every facet of our life, such as

nanoscale materials are progressively being applied in pharmaceutical and medical purposes, makeup and private stuffs, to store energy, for purification of water, air filtration as well as cleaning of environment, chemical and biological sensors, military defense etc. Furthermore, nanotechnology is also swiftly developing in industrial uses, medical imaging, targeted drug delivery applications, cancer cure, gene management therapeutics, and assist in visual imaging.

In summary, nanotechnology irrefutably, is at the climax of revolutionary stage of swift development of healthcare stuff/or nanomedicine, as it possesses numerous imminent human health significances. Admittedly, on the other hand nanotechnology still needs more in-depth research to investigate its possible potential health hazards. We hope that this book, *Innovative Approaches for Nanobiotechnology in Healthcare Systems*, will build a positive influence on students and scientists and aid in the development of novel healthcare materials/or nanomedicine for amelioration of society, simultaneously keeping in consideration the safety and environment. The Editors are highly grateful to all who facilitated in compiling the book project successfully in the given time frame.

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Chapter 1
Nanomedicine and Healthcare Systems

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ABSTRACT

The chapter presents an outlook on the recent techniques of developing nanoscale medicines. With advancement in technology, nanoscale therapeutics is slowly becoming the future of medicine and smart diagnostics. The combined activity of therapeutic agents with assistance of nanomaterials have proved effective in troubleshooting the issues concerned with the conventional therapeutic techniques. Despite of these benefits, improvement in certain issues like side effects and toxicity needs to be studied extensively before real-time application in biological systems. Thus, in this chapter, emphasis has been made on understanding the concept of a nanomaterial-based therapeutic system with recent advances and exploration of the characteristics of nanomaterials which would allow us to further develop strategies that are supportive towards effective treatment and disease diagnosis.

INTRODUCTION

In the today's modern world, the field of nanotechnology is emerging as an interdisciplinary branch of science and technology which is slowly capturing a vital position in the development of latest technologies and techniques (Nair et al., 2010).

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Its interdisciplinary property has allowed one to find its extensive employment in the field of research essentially in the areas of physics, chemistry, pharmaceutical science, material science, and agriculture. Apart from these scientific areas, use of nanotechnology can also be projected for therapeutics and diagnostics. In 21st century nanotechnology can be projected as an advanced tool in the field of medical science either as therapeutics or for diagnostics. At present, the conventional methods of drug administration can be considered as the only source but with certain limitations like occurrence of unwanted side effects, marginal efficiency, weak biodistribution (Kadam, Bourne, & Kompella, 2012). Whereas, new attempts along with the assistance of nanotechnology has proved fruitful in overcoming such kind of issues through reduction in the concentration of raw materials with optimum synthesis parameters (Cerrillo, Barandika, Igartua, Areitioaurtena, & Mendoza, 2017). However, a deep level standardization is highly desired as optimization process may involve use of harmful solvents that may prove fatal for the environment.

As a therapeutic source, nanomedicine can provide platform for promoting the therapeutic potency in drugs with marginalized side effect, therefore, an innovating strategy in conventional therapeutic approach could be anticipated (Pautler & Brenner, 2010). With implementation of nanomedicine, a strong prospect for sustained administration of target specific drug can be projected. Moreover, use of nanomedicines also provide additional benefit of protecting the drug from harsh environment thereby improving its overall performance (Bobo, Robinson, Islam, Thurecht, & Corrie, 2016; Brand et al., 2017; Havel et al., 2016). In a close aspect, the key reason behind formulating nanomedicines is to achieve effective therapy with high throughput and drug bioavailability with least toxicity that overall ensures patient's safety through better efficacy (Agrawal et al., 2018; Brand et al., 2017). When it comes to select a nanomaterial for therapeutic applications, a critical evaluation based on fulfilment of specific objectives is strongly desired (Ciappellano, Tedesco, Venturini, & Benetti, 2016). These prime objectives chiefly account on:

1. Enhanced solubilization of hydrophobic drugs
2. Improved drug residence span in patient's body
3. Reduced or no additional unwanted effect of the administered drug
4. Observation of drug release scheme

In addition to the fulfilment of key objectives, emphasis are also made on analysing the toxic profile in accordance to the dose administered *in vivo* (Oberdörster, 2010). Based on the aforementioned facts, the current chapter aims to present a descriptive overview to understand the utilization of the nanomaterials as a critical vehicle for targeted drug administration against various disorders like cancer, tumours, chronic as well as neurodegenerative diseases.

DEVELOPMENT OF NANOMATERIALS

Nanomaterials offer unique property of demonstrating high surface to volume ratio. This enables them to potentially elevate the bioavailability of the drug via improvising its pharmacokinetic and dynamic profile via surface modification techniques like ligand binding, PEGylation (H. Kumar et al., 2017). Typically for active drug targeting, the ligand (like antibodies or peptides) bound nanomaterial-drug complex is preferentially selected. The selection is made on the account that upon systemic movement, when the ligand bound nanomaterial-drug complex reaches the target site, the ligand gets itself bound to the receptor followed by engulfment of the nanomaterial-drug complex via endocytosis (Etheridge et al., 2013). Besides, a critical selection of binding entity has to be performed for effectiveness. This can be ascertained on the fact that once entering the bloodstream the most significant challenge is to mitigate the aggregation of nanomaterial (if bounded to protein as there is a chance of protein opsonization) that may lead to break down of nanomaterial-drug complex before reaching the target site. Hence, the nanomaterial might get itself cleared from bloodstream before its activity either via phagocytosis or through natural filtration (liver, spleen, and kidney). Thus, the overall drug retention time gets reduced leading to a limited bioavailability. Alternatively, decorating the surface of the nanomaterial with polymers like polyethylene glycol (PEG), acetyl groups, proteins (like albumin) or carbohydrates can troubleshoot the issue of low retention span (Shreffler, Pullan, Dailey, Mallik, & Brooks, 2019). However, these strategies might vary the recognition potential for targeted drug delivery. Another factor that plays a critical role in effective targeted drug delivery is the size of the nanomaterial. Nanomaterials with size less than 10 nm might get themselves cleared through physiological system, whereas structures with size higher than 200 nm might be cleared via phagocytic cells in the RES (reticuloendothelial system). Besides, for therapeutic applications nanomaterials with size up to 100 nm show longer retention time in bloodstream (Wu et al., 2018). According to the report of Wu *et al.* therapeutic nanomaterials ranging between 20–200 nm demonstrate strong accumulation rate in tumours due to low recognition potential for RES (Wu et al., 2018) . The blood vessels in and across the tumour region are found to be larger in number as well as in volume compared to normal tissues. Therefore, nanomaterials offering appropriate dimensions can approach the tumour area in a facile manner with long accumulation time [referred as enhanced permeability and retention (EPR) effect] (Nakamura, Mochida, Choyke, & Kobayashi, 2016). For such kind of approach, active and passive targeting can be opted. Passive targeting allows accumulation of nanomaterials across the tumour site without surface functionalization. Whereas for active targeting, surface of nanomaterials is functionalized either with protein, peptide, nucleic acid etc (Yu, Park, & Jon, 2012). Shape is another factor that controls the effectiveness of

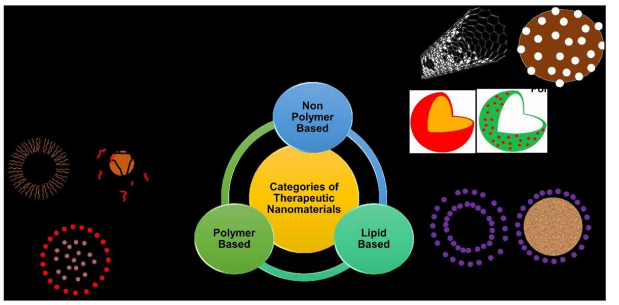
the nanomaterial for therapeutic applications. If nanomaterial exhibit a rod-shaped configuration then they will act an easier target for endosomal uptake compared to other structural configurations indicating that rod shaped nanomaterials might get grasped by immune system cells marking as rod-shaped bacteria (Yetisgin, Cetinel, Zuvin, Kosar, & Kutlu, 2020). Surface charge of therapeutic nanomaterials is also considered as a critical factor that ensures its clearance for targeted drug delivery applications as nanomaterials with positive charge develops a strong immune response in contrast to neutral and negatively charged nanomaterials. For instance, nanomaterials offering surface potential ranging between −10 to +10 mV are found to be less vulnerable to phagocytosis as well as non-specific interactions (Bhatia, 2016; Wu et al., 2018). Besides, surface charge also shows close proximity to pH sensibility of nanomaterials e.g. nanomaterials with pH below 6 (acidic) offers high targeting susceptibility towards endosomes or lysosomes for their cargo release (Casey, Grinstein, & Orlowski, 2010; C. Wang et al., 2017).

It is observed that among all these factors the development of nanomaterial for targeted drug delivery application relies chiefly on surface modification that overall controls the phagocytic uptake and accumulation at non-target organs (Walkey, Olsen, Guo, Emili, & Chan, 2012; Yetisgin et al., 2020). In spite of availability of various surface encapsulants for drug delivery application, long chain polymer PEG has shown preferential selectivity on the basis of low phagocytic uptake and accumulation at non-target organs. The preference to PEG is generally made in context to the factors like density, length and shape that control the surface hydrophilicity and phagocytosis.

CATEGORIES OF THERAPEUTIC NANOMATERIALS

In general, nanomaterials are classified in two prime types i.e., nanostructured and nanocrystalline. A suitable representation to understand the categories of nanomaterials can be done through **Fig. 1.**

Figure 1. Schematic illustration of various categories of therapeutic nanomaterials



Lipid-Based Nanomaterials

Lipid-based nanomaterials (LBNM) have been explored for many years to offer advantages similar to that of polymers. A common feature that both lipid-based nanoparticle and polymer share, is their potential to collect across the regions having enhanced vascular permeability such as sites of inflammation, infection or tumours, known as the EPR (Maeda, Wu, Sawa, Matsumura, & Hori, 2000). The EPR effect associated with LBNM was first introduced by Morgan *et al.* labelled with indium-111 for image-based detection of deep sealed infections and solid tumours (Morgan, Williams, & Howard, 1985). The preferential selection of lipids for therapeutic applications relies on the fact that they offer ability to encapsulate both hydrophobic and hydrophilic drugs in bilayer and aqueous core (Böttger et al., 2020; Wisse, de Zanger, Charels, van der Smissen, & McCuskey, 1985). At present development of lipid-based nanoparticles chiefly involves exploration and association of nanoparticles with liposomes, exosomes and solid lipid nanoparticles (SLN).

Liposomes are vesicles which are realized via hydration of dry phospholipids. The realized liposomes offer discrete structure, configuration, flexibility and size. Interestingly, liposomes offer ability to fuse with the cell membrane followed by releasing of carried content thereby making them an intelligent carrier for targeted delivery system. Ideally, a simple liposome is composed of a lipid bilayer surrounding a hollow core having diameter of 50–1000 nm. The hollow core acts as a loading site for therapeutic molecules. Besides; the number of bilayers variates, liposomes is selected in configurations i.e., multilamellar, small unilamellar and large unilamellar. Multilamellar vesicles comprise of several lipid bilayers parted from one another via aqueous spaces whereas, unilamellar vesicles comprise of a single bilayer surrounding the entrapped aqueous space. These structural properties collectively allow liposomes to host both hydrophobic and hydrophilic molecules (Patil & Jadhav, 2014). In addition to this, the liposomes offer advantage of loading more than one drug either in two compartments or in different layers of multilamellar liposomes overall allowing the drug molecule to get released in a sequential manner (Patil & Jadhav, 2014). Currently, liposomes are wide explored in different configurations as Long-Circulating Liposomes (S. Kumar, Dutta, Dutta, & Koh, 2020; Smith, Selby, Johnston, & Such, 2019), Active-Targeting Liposomes (Moghimipour et al., 2018a; Naeem et al., 2020), Stimuli-Sensitive Liposomes (Bi et al., 2019; Juang, Chang, Wang, Wang, & Lo, 2019; Mansoori et al., 2020; Moghimipour et al., 2018b), Cationic Liposomes (Garcia, Mertins, Silva, Mathews, & Han, 2020; Hashemi et al., 2018; Lu et al., 2019). A better understanding of these liposomal variants can be acquired from the recent review by Yang *et al.* (C. Yang & Merlin, 2020).

Besides liposomes, exosomes are another lipid based entity that are generally endosome-derived extracellular vesicles offering size variation between 30–150 nm

and usually found in body fluids like saliva, blood and urine (C. Yang & Merlin, 2020). Ideally these are cell membrane like lipid bilayer vesicles, comprising of substances like RNA, DNA, glycolipids, and proteins. Their key feature is to perform intracellular communication via transferring different compounds in the physiological mechanisms like neural communication, antigen presentation, immune response etc in case of diseases like cancer, diabetes and inflammation (Shimasaki, Yamamoto, & Arisawa, 2018; Yamashita, Takahashi, & Takakura, 2018). With the advantage of eased isolation from patients' body allogenic exosomes offer advantage of protecting the loaded drug from rapid clearance thereby improving the drug delivery at targeted site (Batrakova & Kim, 2015). These facts strongly account the motif behind the exploration of exosomes as drug delivery carrier for treating diseases like cancer, or during tissue regeneration (Familtseva, Jeremic, & Tyagi, 2019). For instance, Liang *et al.* has recently developed 5-fluorouracil- and miR-21 inhibitor oligonucleotide (miR-21i)- surface capping exosomes using engineered 293T cells (Liang et al., 2020). The realized exosomes significantly altered the miR-21 expression in the 5-fluorouracil-resistant HCT-116^{5FR} cell line. The co-addition of miR-21i and 5-fluorouracil through exosomes enhanced the cytotoxicity of 5-fluorouracil as well as reversed the drug resistance in 5-fluorouracil-resistant CRC cells. Further, trial administration in tumour-bearing mice yielded that realized exosome showed potent anti-tumour effect (Liang et al., 2020).

SLNs are considered as colloidal lipid particles made of lipids and surfactants and possess a solid lipid core matrix at the physiological temperature (Mishra et al., 2018). The realization of SLNs involves practicing of methods like ultra-sonication, homogenization, solvent emulsification/evaporation and micro-emulsion (Doktorovová, Kovačević, Garcia, & Souto, 2016). Their non-payload lipids are composed of nontoxic compounds allowing them to prove a safer than polymeric nanoparticles (Doktorovová et al., 2016). They offer significantly good drug-loading capacity, better drug-retention span as well as particle stability compared to other polymers. This results that an enhanced overall bioavailability of the loaded drug is received at the targeted site. Besides, sustained drug release can also be obtained via adjusting the degradation rate of the lipid matrix in SLNs. According to the recent report by Kim *et al.*, sustained release of docetaxel drug has been demonstrated through activity of docetaxel-loaded cationic SLNs, further coated with an anionic polymer conjugated with glycocholic acid (DOX@SLN@GA) (Kim, Youn, & Bae, 2019). The working activity involved targeting of distal ileum which was found to be mediated through the apical sodium bile acid transporter. Post single oral dose (in treated mice), sustainable release of drug was experienced in the blood stream for 24 h. Moreover, daily dosage resulted in subdued growth of existing tumours that eventually reduced further tumour formation (Kim et al., 2019). Besides, these advantages, SLNs has a limiting factor of being poor encapsulator for hydrophilic

drugs, thereby exhibiting low drug loading capacity (Wong, Bendayan, Rauth, & Wu, 2004). To cater this situation, Wong *et al.* introduced addition of organic counterions during SLN synthesis (Wong et al., 2004). The process involved formation of ion pairs consisting of the charged hydrophilic drug molecule along with added organic counter ion. As a result, an increased distribution of the drug in the melting lipids was obtained. Alternatively, polymer-lipid hybrid nanoparticles having electrostatically attached hydrophilic drug (with polymer and drug polymer complex) can be distributed into lipid droplets for SLN preparation. Both these strategies have improved the performance of SLN containing hydrophilic drug and has expanded the future scope of SLN (Y. Li, Taulier, Rauth, & Wu, 2006).

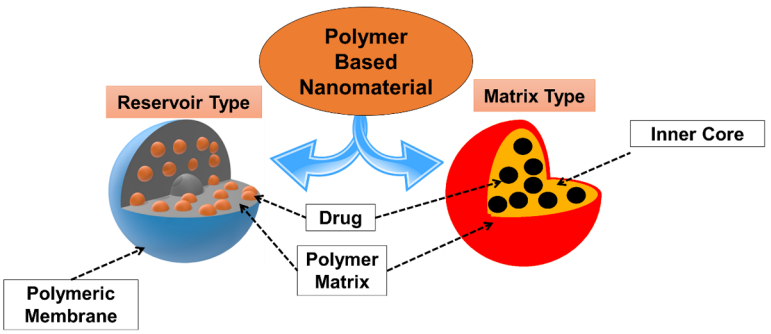
Plant-Isolated Lipid Nanoparticles (PILPs) have been recently explored and gained attention on the account of their isolation from plants like fresh vegetables or fruit, ginger, garlic, lemon and grapefruit (Mu et al., 2014; Teng et al., 2016; C. Yang, Zhang, & Merlin, 2018). Oral administration of these PILPs effectively perform across the target specific tissues like colon and liver (Teng et al., 2018; M. Zhang, Xiao, et al., 2016). In contrast to bilayered liposomes, PILPs offer presence of glycolipids, phospholipids and digalactosyl-diacylglycerol. However, they lack in cholesterol, here presence of cholesterol is essential as it stabilizes the PILPs performance potential. To cater this issue, Wang *et al.* performed synthesis of PILPs isolated from grapefruit which was found to be more stable when incubated with bovine serum (10%) for 30 days (Q. Wang et al., 2013). Similarly, Zhang *et al.* also reported the formation of ginger based PLNPs that was found to be stable and efficient in preventing colitis-associated colon cancer (M. Zhang, Viennois, et al., 2016). The anticancer activity can be attributed to the inherent presence of secondary metabolites, peptides, proteins and mRNA in the encapsulating ginger. However, further studies suggests that PILPs can be also acquired via self-assembly (Jung, Yang, Viennois, Zhang, & Merlin, 2019; C. Yang et al., 2018).

Polymer-Based Nanomaterial

Polymer based nanomaterials (PBNs) have gained significant interest in due time as a result of their inherent morphological properties (Cano et al., 2019, 2020). Typically for therapeutic application, PBNs offer advantage of protecting the drug as well as controlled release thereby enabling the enhanced overall therapeutic index and bioavailability (Cano et al., 2019, 2020). Adapting polymer nanomaterials for targeted drug delivery, employs use of two configurations i.e., either in form of a reservoir (similar to a capsule) or in form of a matrix (sphere) (As shown in **Fig. 2**) (Christoforidis, Chang, Jiang, Wang, & Cebulla, 2012). Considering the profile of drug to be loaded as well as administration route, the synthesis technique for PBNs is selected (Jawahar & Meyyanathan, 2012). Generally, two strategies are employed

i.e. polymer dispersion or polymerization (Pinto Reis, Neufeld, Ribeiro, & Veiga, 2006). The initial selectivity of polymer is a critical stage, typically for drug delivery applications wide variety of polymers are being explored which chiefly involve dendrimers, micelles, polymer-drug conjugates. Dendrimers are widely explored polymers for clinical applications as they exhibit compartmentalized structure, hyperbranching and high monodispersity. A precise control in the branches of these polymers allows realization of PBN's with size range of 1-5 nm. Their realization can be performed effectively using polymerization allowing them to gain spherical shape with in build cavities thereby offering space of entrapment of therapeutic agents. Interestingly significant entrapment is obtained with higher generation of dendrimers in contrast to lower generation ones. Besides, dendrimers comprise of free end groups, which can be modified for providing further scope for conjugating biocompatible compounds to improve low cytotoxicity and better bio-permeability of the molecule. Such kind of surface modifications can also be practised to further enhance the target-specific delivery of therapeutic agents. The dendrimer assembling process is generally done either using encapsulation or complexation, therefore enabling them attractive vehicles for the delivery of biologically active molecules to the target locations (Hsu, Bugno, Lee, & Hong, 2017; Mendes, Pan, & Torchilin, 2017).

Figure 2. Schematic illustration of various types of polymer-based nanomaterials



Micelles are another type of polymers that are explored for systemic delivery of water-insoluble therapeutic agents. Micelles generally offers dimensions less than 100 nm allowing component molecules to get arranged in spheroidal structure enabling the overall structure to appear as a mantle of hydrophilic groups surrounding the hydrophobic cores. The presence of hydrophilic surface acts as a defence against nonspecific uptake by the reticuloendothelial system, thus, ensures their high stability within physiological systems. On the other hand, the hydrophobic core offers strong

attraction towards the water-insoluble, hydrophobic therapeutic agents. However, the component molecules can get themselves linked to the hydrophobic core via covalent forces.

Table 1. Recent advances of PBNs as potential candidate in drug delivery applications

Type of PBN's	Drug Formulation Loaded	Active Polymer	Therapeutic Application	Reference
Nanocapsule	Amphotericin B	poly(ε-caprolactone)	anti-leishmanial	(Saqib et al., 2020)
	Fenofibrate	Copolymers based on methacrylic acid and methyl methacrylate	Oral delivery	(Torres-Flores, Nazende, & Emre, 2019)
	Ciprofloxacin	poly(lactide-co-glycolide); poly(ε-caprolactone)	Tissue regeneration and accelerated healing, anti-inflammatory	(Günday et al., 2020)
	Curcumin	poly(lactide-co- glycolide); poly(ethylene glycol)	antibacterial activity, anticancer	(Bechnak, Khalil, El Kurdi, Khnayzer, & Patra, 2020; Gao et al., 2020)
	Pegademase bovine	poly(ethylene glycol)	immunodeficiency disease	(Moncalvo, Martinez Espinoza, & Cellesi, 2020)
	Paclitaxel (PTX)	poly(ethylene glycol); poly(lactide-co-glycolide); poly(ε-caprolactone)	Anticancer (active against breast, pancreatic and ovarian and brain cancers)	(Avramović, Mandić, Savić-Radojević, & Simić, 2020)
	Palmarosa oil; Geraniol	poly(ε-caprolactone)	antioxidant, antimicrobial	(Jummes et al., 2020)
Nanosphere	Coumarin-6	poly(ε-caprolactone); poly(lactide-co- glycolide); poly(lactic acid)	Bioimaging	(Szczęch & Szczepanowicz, 2020)
	Rapamycin	poly(lactide-co-glycolide)	anti-glioma activity	(Escalona-Rayo et al., 2019)
	Hyperforin	Acetalated dextran	anti-inflammatory	(Traeger et al., 2020)
	Fenofibrate	poly(lactide-co-glycolide)	diabetic retinopathy	(Qiu et al., 2019)

For effectively loading low molecular weight agents, particularly for cancer treatment, the active drug is conjugated with polymer. The conjugation of drug with polymer overall increases the molecular weight of the drug enabling them to promote an EPR effect in cancer cells (Markovsky, Baabur-Cohen, & Satchi-Fainaro, 2014). In contrast to other polymer type discussed above, covalently conjugated drugs are more reliable for sustained drug release and enhanced drug capacity (R. Yang, Mondal, Wen, & Mahato, 2017). The polymer drug conjugation can be made pH sensitive enabling them to actively perform drug release at the tumour site due to acidic environment (Pang et al., 2016). Besides, polymer drug conjugates also provide the advantage of offering increased drug bioavailability (R. Yang et al., 2017). Towards updated approach recent advances in PBNs for drug delivery applications is shown in **Table 1.**

Non-Polymer Based Nanomaterials

In addition to polymer, lipid-based nanomaterials for therapeutic applications, non-polymer based nanomaterials like Carbon nanotubes (CNT), carbon dots (CD), metallic nanoparticles, quantum dots (QDs) etc are also explored. CNT are allotropes of carbon which possess a tube-shaped hollow cylindrical structure (Hasnain et al., 2018). On the basis of layer arrangement CNTs are classified either as single walled nanotube (SWNTs) or multiwalled nanotube (MWNTs), SWNT offer structural diameter maximum up to 1nm whereas MWNT offer inner diameter ~ 2 -6 nm and outer diameter ~ 5-20 nm (Hasnain et al., 2018). CNT in its raw form is hydrophobic therefore, to bring it applicable for drug delivery application they first need to be functionalized to be hydrophilic and biocompatible (Z. Liu, Tabakman, Chen, & Dai, 2009). In order to make CNT biocompatible aromatic drugs like Doxorubicin can be attached to the CNT via supramolecular π–π stacking (Z. Liu et al., 2009). Once functionalized CNT can act as a carrier in various drug delivery applications enabling delivery of the active agents to various organs depending on the functionalization (Hasnain et al., 2018; Z. Liu et al., 2009). In addition to active contribution towards cancer treatment, CNT has also proved helpful against curing of other diseases as well. In a recent report of Leeper *et al.* combined use of PEG@SWNTs loaded with a fluorescent probe and a small-molecule inhibitor of the anti-phagocytic CD47-SIRPα signalling axis is supportive in curing atherosclerosis (Flores et al., 2020). With a potential to penetrate the cells in an eased way, CNTs hold certain potential of crossing the blood-brain barrier (BBB) to treat neurological diseases (Gonzalez-Carter et al., 2019). Based on these analysis Porter *et al.* has reported that MWNT has highest transportation rate across the human BBB (Gonzalez-Carter et al., 2019). In concern to the safety profile, studies suggested that endocytosis of the CNTs induces oxidative stress to the cells, indicating a close connection between

CNTs and inflammation, fibrosis, and cancer, impeding the translational value of this nanocarrier (Dong & Ma, 2019; Mohanta, Patnaik, Sood, & Das, 2019b). CDs were accidentally discovered by Xu *et al.* during the purification of SWNTs (Xu et al., 2004). Later on, Sun *et al.* reported the formation of carbon nanoparticles offering luminescence emission across the visible range and near-infrared region that enabled fluorescent carbon nanoparticles to be identified as CDs (Sun et al., 2006). Further surface functionalization of CDs allows them to be used for different biomedical purposes which chiefly covers bio-imaging and drug delivery (Boakye-Yiadom et al., 2019). Bioconjugation of CDs involves attachment of active drug with CD via non-covalent bonding with surface carboxyl group or via electrostatic interactions using functional groups (Yuan et al., 2017; Zeng et al., 2016). The CD based drug delivery mechanism involves entering of CDs through endocytosis followed by passive diffusion further enabling passive release of conjugated drug inside the cells (Kong, Hao, Wei, Cai, & Zhu, 2018). CD offer small size (~10 nm), this allows them to provide hopes for overcoming the challenge of delivering drugs across the BBB for the treatment of neurological diseases. In this context, Leblanc *et al.* reported the development of CDs conjugated with targeting ligand and therapeutic drugs in order to treat glioblastoma brain tumours (Hettiarachchi et al., 2019). In addition to this the same group also developed carbon nitride dots that are reported to be effective in treating pediatric glioblastoma (Liyanage et al., 2020). Further testing on zebrafish model indicated the suitability of carbon nitride to penetrate BBB (Liyanage et al., 2020). Besides, these advantages, a further exploration of CD in therapeutic applications is still desired (Pardo, Peng, & Leblanc, 2018).

Metallic nanoparticles offering size dimensions (1 -100 nm) are also considered for potential use in medical applications. They are mostly made up of cobalt, nickel, iron, gold, and their respective oxides like magnetite, maghemite, cobalt ferrite and chromium dioxide. They can be synthesized easily and modified with versatile functional chemical groups, which allows them to be decorated with various molecules including therapeutic agents, biological molecules like peptides, proteins, and DNA. As a carrier, they provide unique characteristics such as magnetic properties besides stability and biocompatibility. Thus, magnetic nanoparticles can be targeted to a specific location in the body by using an external magnetic field. At present iron oxide is being widely explored as drug carrier due to its appreciable biocompatibility, relatively low toxicity, and their ability to randomly flip direction of magnetization under the influence of temperature (supramagnetism) (Cuenca et al., 2006). They can be induced into magnetic resonance by self-heating or external magnetic field (Ali et al., 2016). Pristine iron oxide nanoparticles tend to agglomerate and result in the uptake followed by clearance via RES (Ali et al., 2016). Therefore, to limit this challenge surface medication using PEG, chitosan or gelatine can be preferred (Ali et al., 2016). According to the recent report of Zanganeh *et al.* ferumoxytol

(FDA-approved iron oxide nanoparticle) can be used to treat anaemia as well as inhibit growth of tumour by inducing pro-inflammatory macrophage polarization in tumor tissues (Zanganeh et al., 2016). Besides, the authors also stated that prophylactic administration of iron oxide nanoparticles *in vivo* was also found to limit the development of hepatic metastasis (Zanganeh et al., 2016). These facts suggests the positive prospect of employing ferumoxytol in treating cancer patients (Ali et al., 2016). Gold nanoparticles are another type of metallic nanoparticle that are widely explore for drug delivery as well as diagnostic applications (Tian et al., 2016; Yetisgin et al., 2020). The key reason for their high selectivity is based on their unique optical and localized surface plasmon resonance as well as relatively low cytotoxicity. When the light with suitable wavelength (as external stimuli) is made to fall on the gold nanoparticles, they exhibit photothermal conversion and heat up the targeted tumour tissue to kill the cancer cells. Besides, potential selective use of gold nanoparticles for drug delivery is also considered on the account of the fact that light irradiation can trigger the drug release (Tian et al., 2016).

Silica-Based Nanoparticles are also another type of non-polymer based nanomaterials that have gained significant attention as a potential tool in targeted drug delivery (F. Chen, Hableel, Zhao, & Jokerst, 2018). They offer a large surface area covered with polar silanol groups, which are suitable for water adsorption and enhance the stability of therapeutic agents. In addition, silica-based nanoparticles offer ability to interact with nucleic acids, which allows their use as targeted delivery vehicles (Bharali et al., 2005). As per the concentration and release of the drug, their pore size and density can be tailored to achieve a constant delivery rate. Besides, passivation of therapeutic agents within silica-based nanoparticles provides solid media for the delivery of agents. The pores of silica nanoparticles can be capped with various stimuli-responsive molecules to increase the rate of drug release in the targeted tissue (Mura, Nicolas, & Couvreur, 2013). Porous silica offers extremely hydrophobic as well as rigid matrix composition which enables them to make it simpler to stay homogeneously distributed in water as well as prevent deterioration shifts due to heat, pH, hydrolysis mechanical, and stress (Bagheri et al., 2018). It is clear that each carrier offers unique features however, they also face certain challenges that overall effects their performance in drug delivery applications. In this aspect, a summarized comparative matrix is shown as **Table 2** for better understanding.

Table 2. Comparative matrix summarizing advances of non-polymer based nanomaterials in drug delivery applications

Therapeutic Nanomaterials	Merits	Challenges	Safety Profile	Ref.
Lipid based Nanomaterials	• Biocompatible • Eased modification • Self assembly • Better drug loading potential	• Rapid clearance • Off Target build up	Good	(Naumenko et al., 2019)
Polymer Nanomaterials	• Biocompatible • Self assembly • Prolonged therapeutic efficacy • High surface to volume ratio • Capacity to entrap large molecular weight hydrophilic/ hydrophobic entities	• Low drug loading potential • Less effective in case of polymer drug conjugates • Off target buildup	• Good • Toxicity issues with cationic dendrimers	(Wiwanitkit, 2019)
Non-Polymer based Nanomaterials	• Easily internalized by cells • High drug loading • High fluorescent quality • Better performance in when directly conjugated with drug • Potent magnetic and catalytic properties • Biocompatibility	• Slow drug release • Insoluble unless functionalized • Performance directly related to size, shape, and surface charge	• Conflicting toxicity evidence • Toxicity depends on surface charge • Morphology induced toxicity	(Boakye-Yiadom et al., 2019; Dong & Ma, 2019; Gonzalez-Carter et al., 2019; Mohanta, Patnaik, Sood, & Das, 2019a)

PROGRESS IN DEVELOPMENT OF THERAPEUTIC NANOMATERIALS FOR EFFECTIVE DRUG DELIVERY

An ideal targeted delivery refers to the successful track of therapeutic agent and its dominant accumulation at a desirable site. Towards efficient targeted delivery, the agent-loaded system should be retained in the physiological system for the desirable time, evade the immunological system, target specific cell/tissue, and release the loaded therapeutic agent (Davis, Chen, & Shin, 2008). Currently, targeted delivery of nanoparticles is widely studied in treating cancer, infectious diseases, Autoimmune Diseases, Cardiovascular Diseases, Neurodegenerative Diseases, Ocular Diseases, Pulmonary Diseases, Regenerative Therapy. **Table 3** summarizes the current trends in the activity and performance estimation of therapeutic nanomaterials in pathway of treating significant health diseases.

Table 3. Current trends in activity and performance estimation of therapeutic nanomaterials

Disease	Nanomaterial	Type	Drug Conjugate	Evaluation	Ref.
Cancer	PEG-Platinum	Dendrimer	α-cyclodextrin	Pre-clinical	(X. Wang, Wang, Zhang, & Cheng, 2016)
	Polypropylene sulfide PEG- serine-folic acid zinc phtalocyanine	Micelle	doxorubicin	Clinical phase I	(Dai et al., 2016)
	PEG-polyaspartate polymeric micelle		paclitaxel	Clinical phase III	(Fujiwara et al., 2019)
	PEGylated single walled CNT	CNT	cisplatin	Pre-clinical	(Bhirde et al., 2010)
	Hollow mesoporous copper sulfide nanoparticle with iron oxides/ hyaluronic acid	Metallic nanonanomaterials	doxorubicin	Pre-clinical	(Feng et al., 2017)
	Azo-functionalized magnetite nanoparticles				(L. Chen et al., 2016)
	PEGylated gold nanorods				(J. Chen et al., 2018)
	Peptide-functionalized mesoporous silica	Silica based Nano materials	Lactobionic acid, doxorubicin	Pre-clinical	(Y. Liu et al., 2015)
	PEGylated mesoporous silica		amino-β-cyclodextrin, doxorubicin		(Q. Zhang et al., 2014)
	Mesoporous silica		cytochrome C conjugated lactobionic acid doxorubicin		(Pei et al., 2018)
Infectious Disease	Silver nanoparticle	Metallic nanomaterials	Fluconazole	*In vitro*	(Longhi et al., 2016)
	Silver and Gold nanoparticle		Ampicillin		(Brown et al., 2012)
	Polyethyleneimine capped ZnO nanoparticles		Tetracycline		(Chakraborti et al., 2014)
	Gold Nanoparticles		Vancomycin, Ampicillin		(Shimizu, Otsuka, Sawada, Maejima, & Shirotake, 2014)

continued on following page

Table 3. Continued

Disease	Nanomaterial	Type	Drug Conjugate	Evaluation	Ref.
Autoimmune Diseases	Poly(hexylcyanoacrylate) nanoparticles; Poly(isohexyl cyanate) nanoparticles	Polymeric	Zidovudine	Pre-clinical	(Dembri, Montisci, Gantier, Chacun, & Ponchel, 2001; Löbenberg, Maas, & Kreuter, 1998)
	PLGA nanoparticles		Ritonavir, Lopinavir, Efavirenz		(Liptrott, Giardiello, McDonald, Rannard, & Owen, 2018; Pham, Li, Guo, Penzak, & Dong, 2016)
	Poly(epsilon-caprolactone)		Saquinavir	*In vitro*	(Shah & Amiji, 2006)
Cardiovascular Diseases	Liposome	Lipid Based Nanomaterial	Phosphatidylcholine and cholesterol loaded with sirolimus	-	(Haeri et al., 2017)
	Niosome nanoparticle		Carvedilol		(Arzani, Haeri, Daeihamed, Bakhtiari-Kaboutaraki, & Dadashzadeh, 2015)

CHALLENGES IN FRONT OF THERAPEUTIC NANOMATERIALS

Utilization of nanoparticles can anticipate promising results for the treatment of a large variety of diseases. However, approaches based on nanoparticle technologies, unfortunately, come with some limitations and disadvantages. The most significant challenge that should be taken into consideration carefully while using administering the nanomaterial based drug in living organisms is nanoparticle toxicity, which eludes from the phagocytic system and refrains the physiological barrier, and initiate

immune response are only some of the issues (Ferrari, 2005). As the nanoparticle sizes get reduces, it become more prone to aggregation as well as its dispersion into the nucleus steadily elevates, which in return results to intrinsic toxicity both at cellular and systemic level (Su & Sun, 2013). Although surface functionalization is an effective approach but their eluding potential from the phagocytic system may trigger cellular toxicity (S. D. Li & Huang, 2010).Another factor that controls the applicability of therapeutic nanomaterials is protein corona. When nanoparticles are administered in human bodies, their interaction with the physiological environment forms protein corona around the nanoparticle (Z. Zhang et al., 2019). The protein corona is a major obstacle for the bench-to-bedside translation of targeted drug delivery systems as it induces unfavourable biodistribution (Z. Zhang et al., 2019). However, recent technological advances have improved the stability of nanocarriers using various surface modifications (Guerrini, Alvarez-Puebla, & Pazos-Perez, 2018). Besides, new discoveries have also helped us to challenge the old paradigm through new breakthroughs. For instance, Chan *et al.* re-examined the entry of nanoparticles into the solid tumours via four different models (Sindhwani et al., 2020). Here the authors reported that tumour vasculature is mostly continuous and offer a very low gap frequency. Up to 97% of nanoparticles enter solid tumours via an active process through endothelial cells, and passive extravasation contributed only a small fraction of the nanoparticle tumour accumulation (Sindhwani et al., 2020). Therefore, these findings encourage the refined design of the nanoparticle to improve its targeting potential. Despite of getting approved from Food and Drug Administration (FDA), large scale manufacture of nanomedicine is still challenging. This mostly occur on the account of factors like reduced active material loading, difficulty in homogeneous production, and purification (D'Mello et al., 2017). Most importantly, the size of the nanoparticle is the critical factor that ensures the overall absorption, biodistribution, and excretion of the nanoparticles (D'Mello et al., 2017). Thus, it is clear that with improving the methods of better drug delivery, the complexity of nanoparticles is also found to be increasing exponentially and is expected to further increase in the coming years.

FUTURE PROSPECTS

Over the years, an extensive study and development of nanoparticle-based therapeutic agents has been performed towards progressive treatment of many diseases. At present, the majority of nanoparticles employed for the targeting delivery approach are composed of either polymers or lipids. Although polymeric nanoparticles demonstrate great prospects in disease therapy, but certain demerits like usage of organic solvents in their fabrication process, biocompatibility, cytotoxicity etc needs

to be scaled up. In contrast to polymer-based nanomaterials, lipid-based nanomaterials possess similarity to cell membrane thereby enabling them to exhibit the potential of crossing hard-to-reach sites with ease (without any surface functionalization). Thus, lipid-based nanomaterials can emerge as the next generation of therapeutics. Nanoparticle-based delivery systems contribute significantly towards targeted therapy with improved performance and reduced side effect (with better bioavailability), however, more exploration is required for improving their clearance and toxicity of nanoparticles. In addition to this, the cost of nanomedicine manufacturing at larger scale is another important issue needing to be addressed. The marginalized financial support prevents the progress of therapeutics towards better market inception. Consequently, through better understanding of characteristics and behaviour of nanomaterials with biological environment or improving the mechanisms of action in disease curing, the factors associated with weak response of nanomaterial in drug delivery systems can be rectified.

CONCLUSION

This chapter outlines a discussion on the recent advances, limitations as well as future prospects of nanomaterial induced drug delivery system. A critical observation indicates that effectivity of nanomaterial based therapeutics is confined to act against mitigation of one single disease. However, with further improvement and optimizations, formulations of advanced nanomaterial based therapeutics that are active against multiple diseases can be projected. Moreover, it is clear that introduction of nanomaterial in drug delivery has revolutionized the entire medical field through new improved methods applicable in medical imaging and diagnostics or formulation of therapeutics (either as vaccine or biomaterials in regenerative medicine). Hence, through this chapter, the scholars who are actively working in the field domain of biomedical engineering, nanotechnology, microbiology and biotechnology can explore suitable insights and ideas to develop nanomaterial based therapeutics effective against multiple diseases including newly introduced Covid-19 infection.

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Chapter 2
Electrospun Nanofibers for Drug Delivery Applications

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ABSTRACT

Nanofiber systems with various composition and biological properties have been extensively studied for various biomedical applications. The electrospinning process has been regarded as one of the versatile techniques to prepare nano to microfibers. The electrospun nanofibers are being used especially in textile industries, sensors, filters, protective clothing, energy storage materials, and biomedical applications. In the last decade, electrospun nanofibers have been highly investigated for drug delivery systems to achieve a therapeutic effect in specifically targeted sites. Various drugs or biomolecules can be easily loaded into the electrospun nanofibers by direct or indirect methods. The proper selection of polymers (or blends of various polymers), drugs, solvents to prepare the composite nanofibers with desired morphology are the tools in enhancing the bioavailability, stability, and bioactivity of drugs.

INTRODUCTION

Nanofibers were initially defined as fibers with a dimeter of less than 100 nm in a narrow sense. However, in a broad sense, the nanofibers refer to the fibers with a diameter below 1000 nm (or 1μm) (Kajdič, Planinšek, Gašperlin, & Kocbek, 2019;

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Roodbar Shojaei, Hajalilou, Tabatabaei, Mobli, & Aghbashlo, 2019; Rošic, Kocbek, Pelipenko, Kristl, & Baumgartner, 2013). By reducing the diameter of fiber from micrometer to nanometers, several amazing features, for example, high surface to volume ratio, superior mechanical performance, flexibility, etc appeared. These properties make the nanofibers a promising candidate for various applications such as biomedical, filtration, sensor, personal care, energy storage, wastewater treatment, etc (Bhattarai, Bachu, Boddu, & Bhaduri, 2019; Pant, Ojha, Kim, Park, & Park, 2019; Pant et al., 2013; Pant et al., 2012; Pant, Park, Ojha, Park, et al., 2018; Pant, Park, & Park, 2019a; T. Xu et al., 2020). There are several techniques to fabricate the nanofibers from various polymer solutions. The examples include phase separation, drawing, template synthesis, and electrospinning (Gugulothu, Barhoum, Nerella, Ajmer, & Bechelany, 2019). Among the various methods, electrospinning is the most popular approach for generating fibers from polymeric solutions due to its outstanding feathers such as simplicity, versatility, and cost-effectiveness (Pant, Park, et al., 2019a). So far a large number of natural and synthetic polymers as well as their blends have been electrospun into the nanofiber form for various applications, including biomedical (Agarwal, Wendorff, & Greiner, 2008; Lagaron, Solouk, Castro, & Echegoyen, 2017; Pant, Park, et al., 2019a).

History of Electrospinning

In 1745, Bose described that a high electric potential is required to generate aerosols from fluid drops (Bose, 1745). Later, in 1882, Lord Rayleigh calculated the quantity of charge required for overcoming the surface tension of a drop (Rayleigh, 1882). In 1902, Cooley patented (Patent No: 692631) electrospinning and described it as an apparatus for electrically dispersing fluids (Anton, 1934). Anton Formhals developed preparation methods and designed the apparatus (Formhals, 1934). He published a series of patents between 1934 and 1944. From 1964 to 1969, Sir Geoffrey Ingram Taylor brought a significant advancement in the theoretical understanding of electrospinning technique. Taylor defined the characteristic droplet shape, which is now known as the "Taylor cone" (Taylor, 1969). Later on (the late 1990s), several research groups, notably Ranker, popularized electrospinning to study the structural morphology of a wide variety of polymeric nanofibers (Bognitzki et al., 2001; Doshi & Reneker, 1995; Fong, Chun, & Reneker, 1999). Since then, the electrospinning technique has become popular for preparing nanofibers.

Electrospinning Setup

Figure 1. A typical electrospinning setup (A) and morphology of electrospun nanofibers (B)

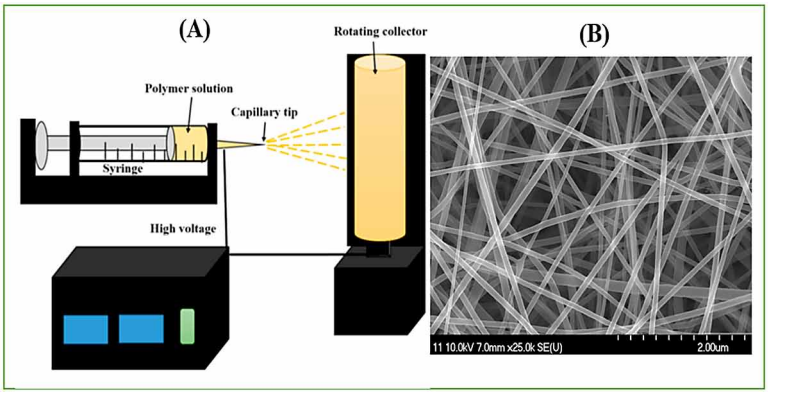


Fig. 1A illustrates a basic configuration of the electrospinning setup. The basic electrospinning setup consists of four parts: a high voltage power supply, a capillary tube containing a polymer solution, a spinneret or nozzle, and a collector (Pant, Park, et al., 2019a; S. Ramakrishna et al., 2006). The nanofibers can be achieved either from the polymer solution prepared by dissolving in the proper solvent or a polymer melt. In the typical electrospinning process, a polymer solution/melt is taken in a syringe and a high voltage is applied into it to induce a charge on the surface of droplet (Wang, Ding, Sun, Wang, & Yu, 2013). At high intensity of the electric field, the droplet deforms into the conical object, which is known as the Taylor cone. Then, the charged jet is ejected from the Taylor cone and blows towards the collector. During the flow of jets, the solvent evaporates leaving behind dry polymer on the collector surface (S. A. F. Ramakrishna, Kazutoshi%A Teo, Wee-Eong%A Lim, Teik-Cheng%A Ma, Zuwei; Wang et al., 2013). The morphology of nanofibers obtained by the electrospinning process is given in figure. 1B. As in the figure, continuous nanofibers can be obtained by this technique.

Affecting Parameters on Electrospinning

There are several parameters that can affect the electrospinning process and properties of nanofibers (Doshi & Reneker, 1995; Pant, Park, et al., 2019a; Thenmozhi, Dharmaraj, Kadirvelu, & Kim, 2017). The affecting parameters can be categorized

as solution parameters, process parameters, and ambient parameters. Table 1 presents a list of key factors affecting the electrospinning process.

Table 1. List of various parameters affecting the properties of nanofibers

Solution Parameter	Process Parameter	Ambient Parameter
- Molecular weight of polymer - Type of solvent - Concentration of solution - Viscosity of solution - Conductivity of solution - Surface tension - Dielectric constant - Dipole moment	- Applied electric field - Distance from the tip to the collector. - Flow rate - Nozzle type - Rotation speed of the collecting drum	- Humidity - Temperature

It has been observed that all of the above parameters affect the properties of electrospun nanofibers; therefore, it is important to optimize the various parameters to obtain the good morphology of nanofibers with desired properties. The effect of the various parameters on the properties of nanofibers is summarized in Table 2.

Table 2. The effect of various electrospinning parameters on the properties of nanofibers

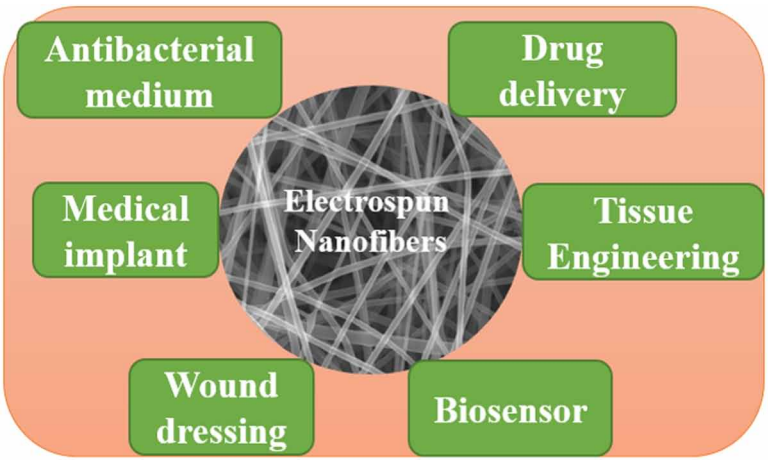
Parameter	Effect
Applied voltage	Fiber diameter is reduced at higher voltage.
Concentration of solution	At higher concentration the nanofibers with higher diameter are produced.
Flow rate	If the flow rate is increased, the fiber diameter also increases.
Conductivity of solution	High conductivity reduces the diameter of fibers.
Solution viscosity	The highly viscous solution forms thick nanofibers. The low viscous solution leads to the fine and short nanofibers.
Tip-to-collector distance	If the distance is too long, thin nanofibers may form. Short distance may help to form a film.
Humidity	High humidity leads to the formation of beaded and porous nanofibers.
Solvent volatility	If the solvent is highly volatile, nanofibers with higher porosity and enhanced surface area will be formed.
Temperature	Nanofibers with uniform temperature can be obtained at higher temperature.

(Casper, Stephens, Tassi, Chase, & Rabolt, 2004; Doshi & Reneker, 1995; Pant, Park, et al., 2019a; Yang et al., 2004).

Biomedical Applications of Electrospun Nanofibers

Electrospun nanofibers have been considered amongst the most promising candidates for biomedical applications. The electrospun nanofibers possess several merits such as high surface area to volume ratio along with tunable diameter, and porosity, suitable flexibility, ease of fabrication, and potential to immobilize various active agents (Pant, Park, Ojha, Kim, et al., 2018; Pant, Park, et al., 2019a). The electrospun nanofibers are structurally similar to the natural extracellular matrix (ECM). Also, the mechanical properties of electrospun nanofibers are suitable for various biomedical applications. So far, the electrospun nanofibers have been used in tissue engineering, wound healing, biosensor, stent coating, drug delivery, implants, cosmetics, facial masks, etc. (Mwiiri & Daniels, 2020; Pant, Park, Ojha, Kim, et al., 2018; Pant, Park, et al., 2019a; Pant, Park, & Park, 2019b; Thenmozhi et al., 2017) Fig. 2 depicts some of the potential areas of biomedical applications of electrospun nanofibers. Till now, many biocompatible polymers (both biodegradable and non-biodegradable) have been successfully electrospun into the fiber form to be applied in the biomedical fields. Several synthetic, semisynthetic, biological polymers and their blends have been electrospun into the nanofibers for biomedical fields (da Silva & Córdoba de Torresi, 2019; Hu et al., 2014). The current research trends in biomedical fields can be categorized into three topics- tissue engineering, drug delivery, and enzyme immobilization (Pant, Park, et al., 2019a).

Figure 2. Some potential areas of biomedical applications of electrospun nanofibers



Drug Delivery Applications of Electrospun Nanofibers

Currently, several diseases are treated with drugs. Such drugs or medicines, can be introduced to the patient's body by several routes. For example, most of the drugs are available in the form of tablets, capsules, or pills and can be swallowed (oral administration). Some drugs are directly sent to the bloodstream by injection (intravenous administration). Due to the susceptibility to degradation and deactivation, more sophisticated drug delivery systems are required. Therefore, it is recommended that the drugs are loaded into a matrix until the moment of release. Over the past decades, numerous carriers for drug delivery have been developed. Electrospinning has appeared as one of the promising technique in drug delivery. In recent years, electrospun nanofibers have been extensively studied for the controlled and sustained release of various drugs. Several types of drugs, including anticancer agents, antiviral agents, cardiovascular agents, anti-inflammatory drugs, analgesic drugs, DNA, RNA, protein, etc have been encapsulated into the nanofibers (Balusamy, Celebioglu, Senthamizhan, & Uyar, 2020; Karthikeyan, Guhathakarta, Rajaram, & Korrapati, 2012; Pant, Park, et al., 2019a; Singh, Garg, Goyal, & Rath, 2016; Son, Kim, & Yoo, 2014; Topuz, Kilic, Durgun, & Szekely, 2021; X. Xu, Chen, Wang, & Jing, 2009; Yu et al., 2009; Zahedi et al., 2012). The electrospinning method offers the benefits of encapsulating both hydrophobic and hydrophilic drugs with high encapsulation and desired release efficiency. Most importantly, the release behavior of the drugs can be controlled by tailoring the morphological features of the electrospun nanofibers such as diameter and porosity, and adjusting the electrospinning parameter such as applied solvents and types of polymers, and the concentration of drugs, etc.

Drug Incorporation Techniques

Several types of electrospinning and drug encapsulation approaches have been developed for successful drug incorporation into the nanofiber membrane. As in Fig. 3, these approaches involve blending, coaxial, emulsion, surface modification (Cornejo Bravo, Villarreal Gómez, & Serrano Medina, 2016; Zamani, Prabhakaran, & Ramakrishna, 2013).

Blending Electrospinning

Blending is a most common method of incorporating drug molecules into the electrospun fibers. In this method, a homogenous drug/polymer solution is prepared and electrospun into the nanofibers with a single phase. In this method, the physiochemical properties of the polymer are important because they affect

the drug-polymer interactions, incorporation of drugs, and release behavior of the drugs (Zamani et al., 2013).

Coaxial Electrospinning

It is a modified version of the conventional electrospinning for preparing core-sheath form of nanofibers. In coaxial electrospinning, a coaxial spinneret needle consisting of an inner and outer nozzle arrangement is used. Two separate solutions are filled in the inner and outer nozzles to obtain a core-sheath structured fibers. In the core-sheath nanofibers, one polymer fiber (core) is surrounded by another (sheath) and hence the sheath fiber effectively controls the release kinetics of the drugs. Coaxial electrospinning is useful for multiple drug delivery systems (Pant, Park, et al., 2019a; Zamani et al., 2013).

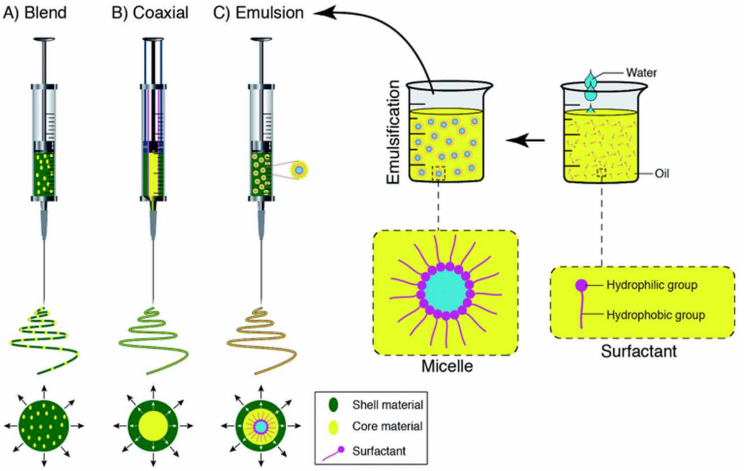
Emulsion Electrospinning

Emulsion electrospinning is a promising method for preparing a core-sheath structured fibers that can encapsulate various drugs. In this technique, an emulsion is the oil phase is created by the emulsion of the drugs (or aqueous solution of protein) in the hydrophobic polymer solution. After carrying out the spinning process, the drug-loaded phase is administrated within the fibers, if a low molecular weight drug is used, or a core-sheath structured fiber is formed when macromolecules are in the aqueous phase. The emulsion technique does not require a common solvent for drugs and polymers. The drugs and polymers can be dissolved in suitable solvents. Hence, several hydrophobic polymers and hydrophilic drugs can be combined (Imani, Yousefzadeh, & Nour, 2018; Nikmaram et al., 2017).

Surface Modification

Surface modification is another simple and promising approach for introducing drug molecules directly into the nanofibers. In this method, the therapeutic agents or drugs are conjugated to the surface of electrospun nanofibers. Several secondary forces such as hydrogen bonding, Van der Waals interactions, electrostatic forces help to retain the drugs onto nanofiber surface. Also, the fiber surface can be functionalized with suitable functional groups such as amine, carboxyl, thiol, hydroxyl, etc and the drugs can be immobilized on its surface. This approach is helpful to avid initial burst release of the drugs (Mohammadian & Eatemadi, 2017).

Figure 3. Schematic representation of the spinneret for blend, coaxial, and emulsion electrospinning. Published by the Royal Society of Chemistry (Nikmaram et al., 2017)



It should be noted that the type of electrospinning and drug loading processes greatly influence the properties of the fibers, which affect the drug release behavior. For example, the drug release rate can be controlled based on the fiber morphology, diameter, porosity, and drug binding mechanism, etc (Agrahari, Agrahari, Meng, & Mitra, 2017). Therefore, the drug loading methods should be chosen accordingly to obtain the desired results. In general, all drug incorporation techniques have their advantages and limitations, which can be summarized as in the Table 3 below.

Table 3. Advantages and limitations of various drug loading methods

Method	Advantages	Limitations
Blending Electrospinning	- Easy and simple method. - Improves the mechanical and other physiochemical properties of fibers. - The drug release rate can be modified.	- A clear understanding of the solvent system as well as the phase behavior of the polymer blend is required.
Coaxial Electrospinning	- The burst release can be controlled. - Enhanced biomolecule functionality. - Sustained release for long time. - Provides a better therapeutic effects and reduces toxicity.	- It requires a special nozzle.
Emulsion electrospinning	- No common solvent is required. - Several hydrophobic polymers and hydrophilic drugs can be combined.	- Only limited drugs can be loaded.
Surface Modification	- Large initial burst release can be controlled. - Biomolecules are surface immobilized.	- Depends on the nature of polymer and drugs. - Functionalization of fibers may be required.

(Cornejo Bravo et al., 2016; Pant, Park, et al., 2019a; Tipduangta et al., 2016)

Drug Incorporated Nanofibers

In recent years, several biocompatible polymers nanofibers have been studied for drug delivery applications. Among them, biodegradable polymers have gained special attention because of some advantages. For example, if the biodegradable polymers are used as drug carrier and implant materials, no secondary surgery is required to remove the implant (Torres-Martinez, Cornejo Bravo, Serrano Medina, Pérez González, & Villarreal Gómez, 2018). Polymers such as poly(α-caprolactone) (PCL), chitosan, poly (vinyl alcohol) (PVA), poly (vinylpyrrolidone) (PVP) have been studied for drug delivery application (Potrč et al., 2015; Torres-Martinez et al., 2018). In the last decades, various types of drugs have been loaded into the electrospun nanofibers to study the release behavior. The biocompatible polymers used for the drug release neither cause harm to cells nor change the drug properties. The electrospun nanofibers go along with diffusion mechanism, thereby showing a good sustained release effects. Table 4 shows some examples of different types of drug incorporated electrospun nanofibers.

Table 4. Various types of drugs incorporated into the polymeric nanofibers

Drug Type	Drug Name	Polymer	Ref.
Anticancer drug	Doxorubicin	PVA-Chitosan (core-sheath)	(Yan et al., 2016)
	Paclitaxel and Doxorubicin	PEG-PLA	(X. Xu et al., 2009)
	Cisplatin	PLA/PLGA	(Xie, Tan, & Wang, 2008)
	Fusidic acid and rifampicin	PLGA	(Gilchrist et al., 2013)
	Cisplatin	PLA	(Zhang et al., 2014)
	Tamoxifen citrate	EC and PVP	(Zheng et al., 2021)
Antibiotic drug	Ciprofloxacin	PVA/PMMA (core-sheath)	(Zupančič, Sinha-Ray, Sinha-Ray, Kristl, & Yarin, 2016)
	Mefoxin	PLGA	(Kim et al., 2004)
	Tetracycline hydrochloride	PLA/PCL	(Zahedi et al., 2012)
	Tetracycline and amphotericin B	PCL-PLA	(Buschle-Diller et al., 2007)
Cardiovascular drug	Carvedilol	PCL	(Potrč et al., 2015)
	Nicorandil	Hyaluronic acid-PVA	(Singh et al., 2016)
	Dipyridamole	PLA	(Bakola et al., 2018)
	Cilostazol	PCL	(Rychter et al., 2018)

continued on following page

Table 4. Continued

Drug Type	Drug Name	Polymer	Ref.
Anti-inflammatory drug	Indomethacin	PVP	(Lopez, Shearman, Gaisford, & Williams, 2014)
	Fenbufen	PLGA/gelatin	(Meng et al., 2011)
	Ibuprofen	PVP	(Yu et al., 2009)
	Naproxen	PVP	(Wu, Yu, Li, & Feng, 2014)
	Ketoprofen	CA	(Yu et al., 2013)
	Aceclofenac	Zein/Eudragit	(Karthikeyan et al., 2012)
Antihistamine drug	Chlorpheniramine maleate	PVA	(Jaiturong et al., 2018)
	Loratadine	PVP	(Akhgari, Ghalambor Dezfuli, Rezaei, Kiarsi, & Abbaspour, 2016)
	Diphenhydramine	PVA	(Dott et al., 2013)
Gastrointestinal drug	Metoclopramide hydrochloride	PCL, PLLA, PLGA	(Tiwari, Tzezana, Zussman, & Venkatraman, 2010)
Contraceptive drug	Levonorgestrrel	PVA	(Blakney, Krogstad, Jiang, & Woodrow, 2014)
	Maraviroc, 3′-azido-3′-deoxythymidine, Acyclovir	PLLA/PEO	(Ball, Krogstad, Chaowanachan, & Woodrow, 2012)
Palliative drug	Donepezil	PVA	(Nagy, Nyul, Wagner, Molnar, & Marosi, 2010)

Ethyl cellulose (EC), Poly(vinyl)alcohol (PVA), polyethylene glycol (PEG), polylactic acid (PLA), poly(lactic-co-glycolic acid) (PLGA), polymethyl (methacrylate) (PMMA), polyacrolactone (PCL), poly(vinylpyrrolidone) (PVP), poly-L-lactic acid (PLLA), cellulose acetate (CA), polyethylene oxide (PEO).

CHALLENGES AND FUTURE PERSPECTIVES

Undoubtedly, electrospinning is a widely accepted strategy for fabricating nanofibers. Although the benefits of electrospinning have been largely demonstrated in drug delivery applications, there are several issues in practical use. For example, implementation of the product in an efficient way is still challenging. So far, many pharmaceutical drugs have been incorporated into the electrospun nanofibers; however, these studies are just limited in drug loadings, characterizations, and release behaviors. Most of the studies have pointed out the initial burst release of drugs as a major problem in the drug delivery system. Despite the tremendous efforts by the researchers, much of the researches conducted are in vitro. In the existing literature,

until now, there is a lack of correct doses and optimized conditions for practical use. In addition, there are several challenges in the electrospinning and drug loading processes that need to be addressed. For example, mass production, reproducibility, and environmental aspects are the issues in electrospinning. Another concern is the toxicity of the solvent in polymer solution as the solvent residue might be present in the nanofibers. Therefore, deep investigations arenecessary to fully understand the interactions among the drugs, polymers, solvents in the solution. The future study should be directed to in vivo. With overcoming the existing challenges, it can be expected that the electrospinning technique will remain a promising strategy for drug delivery applications.

CONCLUSION

In the last decades, the electrospinning technique has made a remarkable contribution in various biomedical applications, including drug delivery. Besides drugs, several biomolecules have also been incorporated into the electrospun nanofibers via various routes. Researches are being carried out to further enhance the drug loading and drug release behavior of electrospun nanofibers. The optimized parameters play a crucial role in the successful encapsulation and release of drugs/biomolecules. By the careful selection of polymers, drugs, and solvents, it is now possible to deliver various therapeutic drugs (or biomolecules) in a desired manner using electrospinning technology.

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Chapter 3
Nanoparticles as a Therapeutic Approach for Tumor Angiogenesis

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ABSTRACT

In cancer, angiogenesis is a hallmark necessary to supply sufficient nutrients for tumor growth and metastasis to distant sites. Therefore, targeting tumor angiogenesis emerges as an attractive therapeutic modality to retard neoplastic cell growth and dissemination using classes of anti-angiogenic drugs. However, multiple administrations of these drugs show adverse effects, precluding their long-term usage. Conventional chemotherapeutic drugs, natural compounds, carbon-based materials, inorganic and metallic elements, genes, siRNAs, shRNAs, and microRNAs can be incorporated into nanovehicles (e.g. polymers) for delivery to specific targets. This chapter reviews angiogenesis and the underlying molecular mechanisms that regulate this process. Furthermore, this chapter provides an overview on different formulations of nanoparticles or nanovectors that employed to combat cancer, with a special focus on their therapeutic potentials in the context of the suppressive effects on tumor angiogenesis process using in vitro and in vivo models of different tumor entities.

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INTRODUCTION

Tumor angiogenesis is a fundamental process consisting of sequential steps for developing cancer (Teleanu, Chircov, Grumezescu, & Teleanu, 2020). In 1971, the father of angiogenesis Judah Falkman, stated that solid tumors require angiogenesis to grow beyond microscopic sizes (Bagley, 2016; Folkman, 1971). Indeed, tumors can only grow 1–2 mm^3 in diameter without angiogenesis due to lack of oxygen. The hypoxic tumor cells then excrete pro-angiogenic molecules, including growth factors, bioactive lipids, cytokines, or extracellular matrix (ECM) degrading enzymes, that specifically interact with receptors on neighboring vascular endothelium. This stimulates the pre-existing vessels to produce new blood vessels toward the tumor cells in order to obtain the needed oxygen and nutrients to survive, proliferate, grow beyond 2 mm3, and metastasize to distant sites (Lugano, Ramachandran, & Dimberg, 2020; Nishida, Yano, Nishida, Kamura, & Kojiro, 2006; Teleanu et al., 2020; Weis & Cheresh, 2011). Many anti-angiogenic approaches, including antibodies and tyrosine kinase inhibitors, have been developed to stop tumor development and reduce mortality. However, the benefits of these anti-angiogenic inhibitors are modest, due to non-response rates being high for some patients and drug resistance (Lugano et al., 2020). (Hanahan & Weinberg, 2011) Developing alternative treatment perspectives are highly warranted. Nanotechnology-based medicine has been progressively advanced in last recent years offering new avenues for cancer-targeted therapies (Edis et al., 2021). Cancer nanomedicine can overcome limitations of stability, poor biocompatibility, and bioavailability exerted by traditional drugs (Edis et al., 2021). Drugs can be either fabricated in nanostructures or loaded alone or in combination with small interfering RNAs (siRNAs), small hairpin RNA (shRNAs), microRNAs (miRNAs), and drugs into nanocarriers. These nanoparticles can be therapeutically used ''pristine'' or functionalized by peptides, monoclonal antibodies, or aptamers to specifically facilitate their cancer targeting (Sindhwani & Chan, 2021).

CIRCULATORY SYSTEM

The fundamental difference in the structure of the circulatory system between vertebrate and invertebrate is the presence of a continuous monolayer of luminal epithelial cells, named as endothelium (Monahan-Earley, Dvorak, & Aird, 2013; Muñoz-Chápuli, Carmona, Guadix, Macías, & Pérez-Pomares, 2005). The circulatory system facilitates transportation and exchange of nutrients, gases, and metabolic wastes to and from body cells. Vertebrates have blood vessels through which blood and its components are transported (Muñoz-Chápuli et al., 2005). The anatomy of the blood vessels is structured based on the size and location into capillary, vein,

artery, arteriole, and venule. Capillaries, the smallest blood vessels, have one layer known as tunica intima. By comparison, the largest blood vessels have three layers. The innermost layer, tunica intima, contains endothelium and basement membrane (BM), whereas the BM encloses the endothelium along the entire blood vessels structure in body. The tunica media, which contains elastic fibers and vascular smooth muscle cells (vSMCs), is centered between the tunica intima and tunica externa layers. The function of the outermost layer, tunica externa, is to anchor the vessels to the surrounding tissue via its fibroelastic connective tissues (McConnell, 2013; Ng, Lee, Kuo, & Shen, 2018; Zuyong Wang et al., 2019).

The cardiovascular system consists of two well-connected circulatory systems that circulate blood in a "closed loop": the systemic circulatory system and the pulmonary circulatory system (Pugsley & Tabrizchi, 2000). In the systemic circulatory system, the heart pumps oxygenated blood through arteries that branch into smaller arteries, called arterioles, until the oxygenated blood eventually reaches the arterial capillaries. As a result of the higher hydrostatic pressure within these capillaries, the oxygenated blood diffuses along these capillaries into the interstitial tissues, where oxygen (O_2) and nutrients can be absorbed by the cells. Carbon dioxide (CO_2) and other toxic waste products secreted by these interstitial tissues are simultaneously diffused back to the venal capillaries due to the higher osmotic pressure within these capillaries. The deoxygenated blood is subsequently returned to the heart through venules and veins. During pulmonary circulation, the heart then pumps the deoxygenated blood to the capillaries of the lung. After that, the deoxygenated blood is diffused from these capillaries to the lung because the oxygen partial pressure (OPP) of CO_2 in the capillaries is greater than that in the surrounding lung tissues. At the same time, O_2 diffuses from the lung tissues into the lung capillaries because the OPP within these capillaries is lower than that in the surrounding lung tissues. Following the binding of O_2 to hemoglobin within the lung capillaries, the oxygenated blood is circulated back to the heart, where a new circulatory system begins (Collins, Rudenski, Gibson, Howard, & O'Driscoll, 2015; Ortiz-Prado, Dunn, Vasconez, Castillo, & Viscor, 2019; Potente & Mäkinen, 2017; Pugsley & Tabrizchi, 2000)

The lymphatic system, which is, in contrast, an open-way circulatory system, consists of an extensive network of vessels and secondary lymphoid organs, including lymph nodes, Peyer's patches, mucosa-associated lymphoid tissue (MALT), and spleens, that are spread all over the body. Lymphatic blood vessels are classified into three types: lymphatic capillaries, pre-collecting lymphatics, and collecting lymphatic ducts. Each type of vessel has specific structural and functional characteristics. The lymphatic capillaries are hollow, thin-walled, blind-ended vessels whose luminal side contains a monolayer of endothelial cells with discontinuous intracellular junctions to allow fluids to enter. In contrast, the collecting lymphatics have continuous intracellular junctions, a basement membrane, and contractile smooth muscle

cells that are responsible for pumping lymph through lymph nodes back into the bloodstream. The collecting lymphatics also have intraluminal bileaflet valves to prevent the backflow of lymph, as well as to ensure unidirectional transport. In the lymphatic system, the lymphatic capillaries collect excess interstitial fluid, white blood cells, and proteins from the interstitial space and circulate them in the form of lymph. The lymphatic capillaries then transport the lymph to the pre-collecting lymphatics and eventually to the collecting lymphatic ducts, which return lymph via lymph nodes to the cardiovascular circulatory system (H. Li et al., 2019; Potente & Mäkinen, 2017; Swartz, 2001).

ENDOTHELIUM

The major components of the endothelium are a monolayer of vascular endothelial cells (VECs) and lymphatic endothelial cells (LECs). These cells interact directly with the neighboring cells that present in the walls of the vessels, as well as the blood and lymph that flow within the vessels (Cahill & Redmond, 2016; Félétou, 2011). The surface area of the human body is covered by 3000–6000 m^2 of endothelium. This monolayer of cells is interconnected by junctional proteins that regulate permeability (J. A. Adams, Uryash, Lopez, & Sackner, 2021). These interconnections are classified into three surfaces. Cohesive surfaces have three main types of junctions (gap, adherent and tight) that collectively link the single layer of ECs together and establish crosslinks with the neighboring cells. The adhesive surfaces serve to adhere the monolayer of endothelium to the basement membrane (BM), while specific binding proteins and other molecules present on the luminal side of the vascular endothelium regulate the circulating blood cells within the blood vessels (Favero, Paganelli, Buffoli, Rodella, & Rezzani, 2014).

The shape and size of the endothelium varies along the vascular network (Setyawati et al., 2015). This intrinsic disparity gives the endothelial cells a heterogeneous characteristic in structure and function between organs, as well as within the same organ (J. A. Adams et al., 2021). The endothelium's heterogeneity exists at the morphological level where there are three categories – discontinuous, continuous fenestrated, or continuous non-fenestrated. The heterogeneity promotes the EC roles in inflammation, fibrinolysis, inflammation, metabolism, angiogenesis, vascular proliferation of the SMCs, vascular permeability, vascular tone, and trafficking of white blood cells (Aird, 2007, 2012; Galley & Webster, 2004; Setyawati, Tay, Docter, Stauber, & Leong, 2015b).

Pericytes, small contractile cells embedded in the BM, together with ECs, control blood flow through capillaries, venules, and arterioles. The pericytes communicate with ECs via paracrine signaling and direct physical interactions. An example is the

exchange of small molecules and ions between the ECs and pericytes' cytoplasm via the gap junctional complex present in the Peg-and-socket contacts. On the other hand, pericytes are anchored to the ECs via the action of adhesion plaques (Armulik, Genové, & Betsholtz, 2011; Bergers & Song, 2005; Gerhardt & Betsholtz, 2003; Munde, Khandekar, Dive, & Upadhyaya, 2014; Rucker, Wynder, & Thomas, 2000; S. Yang et al., 2017).

EXTRACELLULAR MATRIX (ECM)

ECM is a group of molecules organized in a three-dimensional fashion to anchor the embedded ECs. ECM compartments are classified into the interstitial matrix and the BM, also called basal lamina (Iivanainen, Kähäri, Heino, & Elenius, 2003; Theocharis, Skandalis, Gialeli, & Karamanos, 2016; Witjas, van den Berg, van den Berg, Engelse, & Rabelink, 2019). These two distinct compartments are interconnected by anchoring fibrils. The ECs secrete the BMs in a sheet-like structure with a thickness of 50-100 nm. This structure also includes type IV collagen, heparan sulphate proteoglycans (HSPGs), laminin, and entactin/nidogen (Iivanainen et al., 2003; Raghu, 2003; Witjas et al., 2019). The intrinsic deference between these two compartments is that the BM is directly connected with the endothelium in the luminal side of the blood vessels, providing structural support and preventing the blood vessels from rupturing. In contrast, the interstitial matrix is located in the surrounded interstitial space between cells, which mainly has glycoproteins and fibrillar collagens (Iivanainen et al., 2003; Theocharis et al., 2016). The ECM compartments interact with endothelial receptors besides providing the ECs' scaffold architecture. The binding of specific ECM molecules to endothelial cells' receptors in the ECM compartment leads to initiation of intracellular signaling cascades (Iivanainen et al., 2003; Theocharis et al., 2016). The result of these interactions cause enzymatic or non-enzymatic remodeling of ECM (Frantz, Stewart, & Weaver, 2010; Streuli, 1999), which in turn results in the regulation of cell differentiation, migration, proliferation, survival, invasion, angiogenesis and morphogenesis (Akalu & Brooks, 2005; Iivanainen et al., 2003; Theocharis et al., 2016).

Vascular endothelium is also covered with specialized polysaccharide rich ECM, called endothelial glycocalyx, that extends at least 200–400 nm from the endothelial membrane into the lumen of blood vessels (Curry & Adamson, 2012; Moore, Murphy, & George, 2021). The main component of endothelial glycocalyx includes a network mixture of membrane-bound glycosaminoglycans (GAGs), proteoglycans (PGs) and glycoproteins. GAGs are linear chains of carbohydrates with an extraordinary structural diversity that allow them to bind to many biological molecules. They are characterized into five types: heparan sulfate, chondroitin sulfate,

dermatan sulfate, keratan sulfate, and hyaluronan (Tarbell & Cancel, 2016; L. Zhang, 2010). Proteoglycans, such as HSPG, keratan sulfate proteoglycans, chondroitin sulfate proteoglycans (CSPs), keratan sulfate proteoglycans (KSPs), and dermatan sulfate proteoglycans (DSPs), are composed of a core protein linked by one or more glycosaminoglycans. The synthesis of these molecules is primarily occurring by VSMCs, endothelial cells, and other cells of mesenchymal origin. They are involved in regulating the structure of the matrix, including differentiation cell growth and permeability. Glycoproteins, in contrast, are oligosaccharide chains (glycans) covalently attached to proteins through a process called glycosylation (Rek, Krenn, & Kungl, 2009). The major glycoproteins of the ECM are fibronectins, laminins and tenascins (Reitsma, Slaaf, et al., 2007; Tarbell & Cancel, 2016). Fibronectin is made up of two polypeptide chains linked by two disulfide bonds. This type of glycoproteins binds to other extracellular proteins, including proteoglycans, fibrin and collagen, through specific domains. Fibronectin also binds to cells through cellular transmembrane receptors (Hayden, Sowers, & Tyagi, 2005). Laminins are essential glycoproteins for the formation and function of BM, being the most abundant glycoprotein present in the BM. This large cell-adhesive glycoproteins consist of three distinct polypeptide chains, known as α, β, and γ (Hohenester, 2019). Tenascins are a family of four structurally related glycoproteins in vertebrate that oligomerize into hexameric structure (Tenascin C, Tenascin X, Tenascin W) or trimeric structure (Tenascin R) (Jones & Jones, 2000; Kaur & Reinhardt, 2015). The unique structure of Tenascins allow them to interact with transmembrane receptor proteins, cytokines and other ECM proteins (Matsumoto & Aoki, 2020).

BLOOD VESSEL FORMATION

In a vertebrate embryo, the first organ to develop with high functionality is the blood vasculature (Risau & Flamme, 1995). Development of blood vessels during embryogenesis involves two processes- angiogenesis and vasculogenesis. These two vital processes cooperatively and simultaneously generate a complete functional vasculature. The process of the *de novo* development of blood vessels from progenitor cells is known as vasculogenesis. However, angiogenesis involves forming blood vessels from existing capillaries via primary and secondary extensions (Ramazan Demir, Yaba, & Huppertz, 2010; Vailhé, Vittet, & Feige, 2001).

In vasculogenesis, blood islands are developed via the gastrulation process in the mesoderm, which is seen adjacent to the extraembryonic membranous bag, or yolk sac. After proliferation, the mesenchymal cells (pluripotent stem cells) in the blood island differentiate to form hemangioblasts (multipotent stem cells). Subsequent proliferation and differentiation of hemangioblasts lead to the development of

hematopoietic progenitor cells that form different blood cell types. The differentiation also results into angioblasts that form blood vessels, including endothelial cells (Conway, Collen, & Carmeliet, 2001; R Demir, Kayisli, Cayli, & Huppertz, 2006; Failla, Carbo, & Morea, 2018; Kubis & Levy, 2003; Risau & Flamme, 1995). Consequently, vasculogenesis is a vital process during embryonic development to construct the first functional blood vessels, the dorsal aorta (Cox & Poole, 2000; Helker et al., 2015; D. Jin et al., 2017).

ANGIOGENESIS

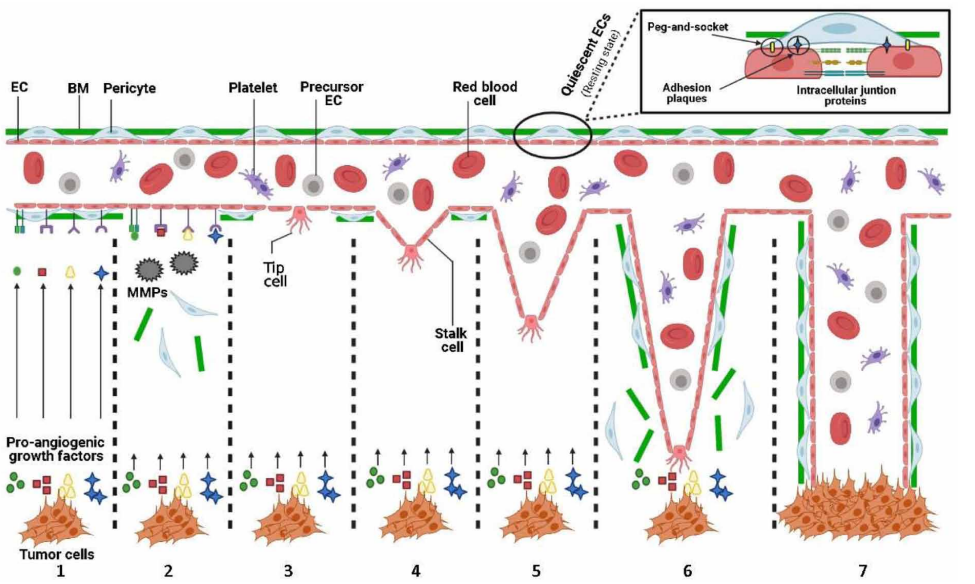
Angiogenesis was first described in 1787 by John Hunter, the founder of scientific surgery, as the development of blood vessels from the already existing one (Natale, Bocci, & Lenzi, 2017; Ribatti & Pezzella, 2021). Angiogenesis is the pivotal mechanism that supplies the required nutrients and oxygen to the hypoxic cancer cells in order to survive, proliferate, migrate and eventually metastasize to distant sites (Hashemi Goradel et al., 2018; Rashidi, Malekzadeh, Goodarzi, Masoudifar, & Mirzaei, 2017; Saman, Raza, Uddin, & Rasul, 2020). Cancer cells cannot exceed the size of 1–2 mm^3 without the physiological mechanism of angiogenesis (Folkman, 1990; Saman et al., 2020). This mechanism could occur either through sprouting angiogenesis, in which endothelial cells protrude, extend and migrate away from an already existing vessel to eventually construct a complete functional vessel or via intussuscepted angiogenesis (tissue pillar insertion mechanism), in which the already existing vessel split to form two complete functional vessels (R. H. Adams & Alitalo, 2007; S. M. Kim, Faix, & Schnitzer, 2017; Ribatti & Pezzella, 2021; Vailhé et al., 2001). The two angiogenesis processes aim to supply the newly formed tissue with adequate blood (Ramazan Demir et al., 2010). Angiogenesis occurs at the embryo development stage following vasculogenesis. However, this process is not present in adults due to the quiescence of blood vessels, except, for example, after an injury where there is healing of the wound or fracture. Additionally, angiogenesis occur in some other conditions such as during muscle exercise, during the formation of corpus luteum and endometrial growth and in some diseases, including tumor growth and diabetes retinopathy (Ramazan Demir et al., 2010; Klagsbrun & Moses, 1999; Kubis & Levy, 2003).

MECHANISM OF SPROUTING ANGIOGENESIS

In sprouting angiogenesis, growth factors from different cells and cellular proteins are utilized in sequential complex stages. In healthy adults, pericytes ensheath and

stabilize the interconnected quiescent ECs, thereby suppressing ECs proliferation and subsequent release of cell survival growth factors, including vascular endothelial growth factor (VEGF) and growth factors angiopoietin 2 (ANG-2). The ECs line the interior surface of the blood vessels; hence they continuously interact with the bloodstream. This monolayer of ECs contains oxygen sensors that control and optimize the rate of the blood flow within the blood vessels. Examples of these sensors include the prolyl hydroxylase domain 2 (PHD2) and hypoxia-inducible factor -2α (HIF-2α). The pericytes and ECs form BMs in a resting state. Removal of pericytes from vessel walls occurs when quiescent ECs mainly sense the presence of VEGFA, and other pro-angiogenetic growth factors such as ANG-2, basic fibroblast growth factor (bFGF), tumor necrosis factor alpha (TNF-α), placental growth factors (PGF), or chemokines. Subsequently, the liberation of ECs from BM occurs, therefore, increases the vessel's permeability and vasodilation. The digestion of the surrounding BM by proteolytic enzymes including MMPs leads to disruption of the intracellular junctions, direct interaction with the ECM components – type I collagen, vitronectin, and Fibronectin, and activation of EC signaling pathways via the transmembrane cell surface proteins. After disrupting the intracellular junctions between ECs, the ECs begin the proliferation, migration and invasion the ECM toward the site that releases pro-angiogenic growth factors and thus stimulates the mechanism of angiogenesis, such as tumor cells. One of the ECs, named a tip cell, is selected to direct the growing sprout during the initial stages of forming a new blood vessel from an already existing one. These processes occur as a response to the release of pro-angiogenic growth factors, mainly binding of VEGFA to the transmembrane VEGF receptors on ECs. Other receptors such as jagged 1 and delta-like ligand 4 (DLL4) also play central roles in the sprouting growth phase of angiogenesis. Importantly, the process of angiogenesis could be pruned following a balance of anti- and pro-angiogenic factors. The division of the stalk cells found behind the tip cells result in elongating the sprout toward the angiogenic stimulus's site. This elongation proceeds until a lumen forms within the endothelial sprout. The anastomoses of sprouts eventually form loops that connect blood flow within the new formed blood vessels. Functional maturity of the vessels is achieved when ECs regain their intracellular junctions and BM by protease inhibitors, tissue inhibitors of metalloproteinases (TIMPs) and plasminogen activator inhibitor-1 (PAI-1). The final stage of angiogenesis involves stabilizing ECs in their quiescent phalanx by mural cells (vSMCS and pericytes), which get recruited by platelet-derived growth factor-B (PDGF-B) and ANG-1 **(Fig. 1)**. The flow of blood leads to increased oxygen delivery within the new formed blood vessels and a reduction in pro-angiogenic attractants (R. H. Adams & Alitalo, 2007; Bai et al., 2021; Ramazan Demir et al., 2010; Elpek, 2015; Raghu, 2003; Senger & Davis, 2011).

Figure 1. Illustration of the sequential stages during tumor angiogenesis



In resting state, ECs are interconnected by intracellular cohesive junctions (gap, adherent and tight), whereas the pericytes ensheath and stabilize the quiescent ECs via Peg-and-socket contacts and adhesion plaques. The mechanism of tumor angiogenesis are illustrated in seven sequential stages: 1) Hypoxic tumor cells mainly secretes VEGF-A, which binds to VEGFR2, and other pro-angiogenic growth factors, including ANG-2, bFGF, TNF-α, PGF, and chemokines; 2) Degradation of BM and removal of pericytes occur in response to proteolytic MMP enzymes, as well as the binding of the pro-angiogenic growth factors to their transmembrane receptors on ECs; 3) and 4) Selection of Tip cell, which guides the new sprout, and the stalk cells via jagged 1 and DLL4 (not shown in the figure); 5) The Tip cell migrates, while the stalk cells behind the tip cells proliferate and elongate the growing sprout toward the tumor cells; 6) BM and intracellular junctions between ECs are re-formed, while pericytes get recruited to stabilize the ECs; 7) the new growing blood vessel is completed allowing the tumor cells obtain the required nutrients and oxygen, and thus increase the tumor size.

VEGFs and VEGFRs

VEGFs, which are described as soluble glycoproteins linked by disulphide double bonds, are the main potent growth factors that stimulate the normal and pathological angiogenesis (Bai et al., 2021; Sherbet, 2011). The VEGFs are classified into:

VEGFA (so-called VEGF), -B, -C, -D and Placenta growth factor (PLGF). The main characteristic of these members is the presence of a cysteine knot structure made from eight conserved cysteine residues (Holmes & Zachary, 2005; Iyer & Acharya, 2011; Muller et al., 1997; Shibuya, 2011). These different classes of VEGFs bind specifically to their transmembrane receptors (VEGFRs), which belong to the receptors of type III tyrosine kinase, to control the pathological and physiological development of lymph and blood vessels (R Demir et al., 2006; Duffy, Bouchier-Hayes, & Harmey, 2004; Nascimento, Gameiro, Ferreira, Correia, & Ferreira, 2021; Smith, Fearnley, Tomlinson, Harrison, & Ponnambalam, 2015). Autophosphorylation of VEGFRs occurs after the binding and dimerization of VEGFs and VEGFRs, respectively. The phosphorylation of these receptors leads to the generation of intracellular signals that induce changes and regulation of different cellular processes (Arroyo & Winn, 2008; Mesquita et al., 2018). Importantly, the signaling pathway associated with binding of VEGF to VEGFR play a pivotal role in regulating the mechanism of angiogenesis (Carmeliet, 2003; Harry & Paleolog, 2003; S. M. Kim et al., 2017). Three transmembrane VEGFRs have been identified: VEGFR1, VEGFR2 and VEGFR3 (Froger et al., 2020). These tyrosine kinase receptors have the same structure as platelet-derived growth factor receptors (PDGFRs). The extracellular region in VEGFR1 and VEGFR2 contain seven immunoglobulins like domains. By comparison, VEGFR3 has six Ig-homology domains in its extracellular region (Ferrara, Gerber, & LeCouter, 2003; Shibuya, 2011).

An experiment on the embryos of mice targeting the genes of VEGFRs demonstrated that knocking out any VEGFR is fatal due to severe abnormality phenotypes in the development of vessels (Costache et al., 2015; Eichmann et al., 1998; Tammela, Enholm, Alitalo, & Paavonen, 2005). Vascular ECs mainly express VEGFR1 and VEGFR2, whereas lymphatic ECs predominately express VEGFR3 (Costache et al., 2015; Shibuya, 2011). Multiple line evidence indicated that VEGF-A/VEGFR2 binding is the pivotal receptor, among the three receptors, that mediate the mitogenic, permeability and angiogenic mechanisms (Achen et al., 1998; Costache et al., 2015; Nascimento et al., 2021). The interaction affinity between VEGFR-A and VEGFR1 is ten folds greater than that in VEGFR2. However, the interaction between VEGF-A and VEGFR2 leads to greater response of angiogenesis than when VEGF-A binds to VEGFR1 (Sadremomtaz et al., 2020; Sawano, Takahashi, Yamaguchi, Aonuma, & Shibuya, 1996). VEGF-C and -D promote downstream signaling pathways through their binding to VEGFR2 or VEGFR3. In contrast, VEGFR1 mediates the downstream signaling only through its binding to VEGF-B or PLGF (Lal et al., 2017). Different isoforms of PLGF, VEGF-A, and -B can be generated via alternative splicing. In contrast, isoforms of VEGF-C and -D are generated only by proteolysis (Tammela et al., 2005).

The dimerization and activation of VEGFR1 get established only through its binding to PLGF or VEGF-B (Klagsbrun & Moses, 1999; Lal et al., 2017). However, genetic ablation studies in mice proposed that knocking out PLGF and VEGF-B genes are indispensable for embryogenesis, as these mice did not have significant angiogenic defects despite lacking these two growths. Nevertheless, some studies evidenced that mice lacking PLGF and VEGF-B genes were found to develop mild phenotypes that included slower myocardial recovery and smaller hearts, especially after ischemia (Bellomo et al., 2000; X. Li et al., 2008; Y. Sun et al., 2004). The expression of VEGF-B is wildly distributed, but its expression in the pancreas, skeletal muscles, and heart is more (Lal et al., 2017; Mesquita et al., 2018), while the level of PLGF in placenta, ovary, lung, and heart is a higher (Tammela et al., 2005). VEGF-A and -B compete for binding to VEGFR1 due to their structural similarities. Additionally, they are able to form heterodimers with VEGFR1 leading to high bioavailability (Iyer & Acharya, 2011). Despite having a high affinity for VEGFR1, PLGF can also bind to VEGFR2 by forming a heterodimer with VEGF-A (Autiero, Luttun, Tjwa, & Carmeliet, 2003).

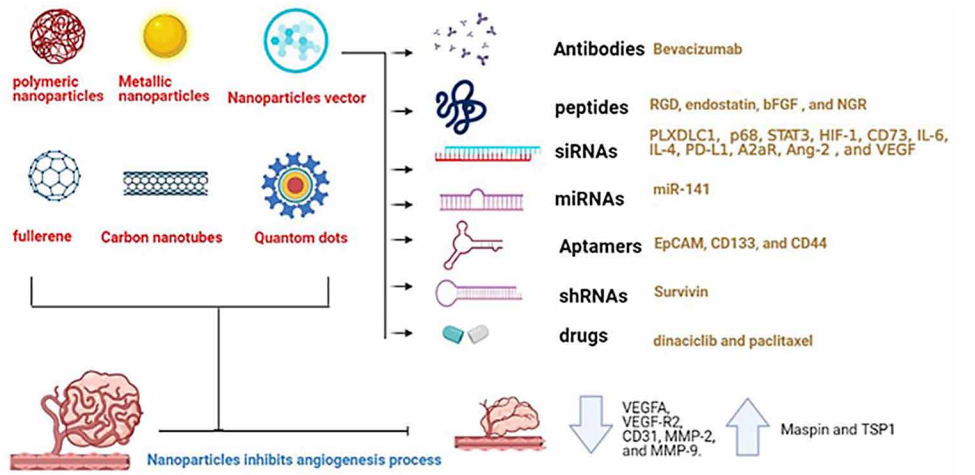
The formation of blood vessels does not require the expression of VEGF-C and -D. However, they are essential in lymph angiogenesis (Tammela et al., 2005). Furthermore, VEGF-C is highly expressed during embryogenesis, while VEGF-D is expressed during postnatal development (Shibuya, 2011). VEGF-D and VEGF-D are produced as pro-proteins possessing long C- and N- terminal amino acids. Then, these two growth factors have to get cleaved via proteolytic processing before binding to VEGFR2 or VEGFR3 (Lal, Puri, & Rodrigues, 2018). VEGF-C and VEGFR3 are highly expressed at the regions of lymphogenesis. Subsequently, their proteins level dropped but remains high only in the lymph nodes (Iyer & Acharya, 2011; Kaipainen et al., 1995). An experiment on the embryos of mice targeting both alleles of VEGF-C is lethal due to a severe abnormality in the lymphatic vessel formation, which indicates that expression of VEGF-C is essential for sprouting of the first lymphatic vessels. In line with previous studies, Shibuya showed an enlargement of lymph nodes when VEGF-C was overexpressed (Shibuya, 2011). However, the deficiency of VEGF-D during embryonic development had no pathologic changes in the development of the lymph vessels (Baldwin et al., 2005).

NANOPARTICLES

Several therapeutic agents are being used to treat cancer. One of the promising therapeutic approaches that recently gained great attention is cancer nanomedicine, where drugs can be formulated in nano-size particles or encapsulated and delivered into tumors through nano vehicles (Edis et al., 2021) as summarized in Fig. 2. In the

following sections, we will describe these nanoparticles (NPs)/nanostructured delivery systems and their potential to combat cancer through disruption of angiogenesis process using *in vitro* and *in vivo* models.

Figure 2. Schematic diagram shows different examples of nanoparticles and nanodelivery systems employed to impair tumor angiogenesis and consequently tumor size and growth via downregulation of angiogenic-related factors (e.g. VEGFA, MMP-2, and MMP-9) and increased expression of anti-angiogenic factors (e.g. Maspin and TSP1). Nanovetcors can be functionalized with monoclonal antibodies, peptides, or aptamers, as well as loaded with siRNAs, shRNA, miRNAs, and chemotherapeutic drugs. Please refer to the text for full details.



Polymeric Nanoparticles-Based Delivery Systems

A set of polymers have been fabricated as nano-sized systems to load and deliver drugs, siRNAs, miRNAs, etc. For instance, chitosan, poly(lactic-co-glycolic acid) (PLGA), poly(lactic acid) (PLA), polycaprolactone (PCL), polyethylene glycol (PEG), gelatin, heparin, and albumin can be used as platforms to exert anti-angiogenesis effect (Kargozar, Baino, Hamzehlou, Hamblin, & Mozafari, 2020; Piperigkou, Karamanou, Afratis, et al., 2016; Piperigkou, Karamanou, Engin, et al., 2016). They can be employed as ‘’pristine’’ or functionalized (Fig. 2). It is worth mentioning that PEG, PCL, PLA, PLGA, and chitosan are food and drug administration)FDA) approved materials (Kargozar et al., 2020). Their copolymers can also be used, e.g., PLA/PGA or PLGA/PEG. We will only discuss here chitosan and PLGA as examples

for polymeric NPs due to their preclinical usage and biomedical applications on wide range.

Chitosan-Based Nanosystems

Chitosan NPs per se have anti-tumor activities (Taher et al., 2019). In a mouse model of hepatocellular carcinoma, chitosan NPs impedes tumor growth and angiogenesis evidenced by reduced microvessel density. Mechanistically, chitosan NPs modulate this effect via VEGFR2 targeting (Xu et al., 2009). Chitosan and its sulfonamide derivatives-based NPs impede *in vivo* angiogenesis in chicken chorioallantoic membrane (CAM) model (Dragostin et al., 2020). Owing to its low toxicity, biocompatibility, and biodegradability, a number of studies placed chitosan in NP formulations as an excellent drug delivery system (Ashrafizadeh et al., 2021; Nagpal, Singh, & Mishra, 2010). Therapeutic applications and efficiency of a wide range of emerging natural or synthetic compounds with promising anti-cancer activities might be limited by their poor water solubility. For example, Ursolic acid regulates tumor growth via inhibition of angiogenesis, but it is poorly soluble in water. Therefore, to improve its solubility and clinical application, Ursolic acid was encapsulated in chitosan NPs forming ursolic acid-loaded chitosan NPs, whose anti-angiogenic activity *in vitro* and in ascites mouse H22 hepatoma cells xenograft model and CAM model has been revealed (H. Jin et al., 2016). Several studies used chitosan-derived NPs as a drug delivery system along with conjugates for targeted therapy in preclinical models. Chitosan NPs can also be used as a delivery platform to siRNAs and miRNAs. Therefore, many interesting studies have been evolved to investigate these approaches on different tumor entities. siRNA against the angiogenesis factor Plexin domain-containing protein 1 (PLXDC1) contained in hyaluronic acid-coated chitosan NPs delayed tumor growth and suppressed angiogenesis evident by decreased blood vessel density in an epithelial ovarian cancer mice model (G. H. Kim et al., 2018). Of note, hyaluronic acid is used to enable NPs to target the endothelial cell receptor CD44. Another study used a combination of siRNAs loaded into (PEG)-trimethyl Chitosan-hyaluronic acid NPs to concurrently silence p68 and signal transducer and activator of transcription-3 (STAT3) and proved repressed tumor growth and angiogenesis *in vitro* and *in vivo* (Hashemi et al., 2020). The co-silencing of hypoxia inducible factor 1 alpha (HIF-1α) and CD73 by siRNAs-loaded superparamagnetic iron oxide nanocarriers entrapped with trimethyl chitosan and thiolated chitosan significantly resulted in reduced tumor growth and angiogenesis using CAM assay. Similarly, the co-silencing IL-6 and its transcription factor STAT3 mediated by siRNAs-loaded NPs had the same inhibitory effect on cancer cell angiogenesis (Masjedi, Ahmadi, Atyabi, et al., 2020). Chitosan NPs coloaded with VEGFA and IL-4 siRNAs (Fig. 2) robustly regressed tumor growth

via angiogenesis blocking in murine model of breast cancer (Şalva et al., 2014). Nanocomplexes formed of chitosan and mimic miR-141 delivered at specific doses exhibits tumor-suppressive and anti-angiogenic effects in breast cancer (Kaban, Salva, & Akbuga, 2019). Immunotherapy as cancer treatment option has gained recently a great attention last few years, where immune checkpoint molecules specifically are targeted. It has been reported that dual silencing of programmed cell death-ligand 1 and the tumor-promoting STAT3 (Fig. 2) by siRNAs-loaded in thiolated chitosan and trimethyl chitosan NPs coupled with hyaluronic acid and HIV-1-derived TAT peptide had an inhibitory effect on angiogenesis of melanoma and breast cancer cells (Bastaki et al., 2021).

Raloxifene delivery can inhibit angiogenesis and tumor growth encapsulated in Arg-Gly-Asp (RGD)-conjugated chitosan NPs (Fig. 2), which exhibit higher stability and greater uptake by $\alpha_v\beta_3$ integrin expressing-breast tumor cells at acidic pH without any cytotoxic effect on normal cells (Yadav et al., 2020). Another recent study showed that docetaxel-loaded chitosan derivative NPs conjugated with the specific gastric cancer vasculature peptide GX1 impairs angiogenesis of human umbilical vascular endothelial cells (HUVECs) cocultured with gastric cancer cells (E. Zhang et al., 2019). Glycol chitosan-Suramin NPs robustly dampen tube numbers and length of HUVECs (Cheng, Gao, Maissy, & Xu, 2019). A very recent exciting report used a combinatorial approach of siRNA, and the prostaglandin E2 receptor antagonist E7046-loaded NPs to examine their effect on tumor progression. HIF-1α siRNA and E7046-loaded HA-trimethyl chitosan-superparamagnetic iron oxide NPs strongly curtail tumor growth and angiogenesis (Karpisheh et al., 2021). Another dual gene/drug delivery strategy to silence HIF-1α- by siRNA and inhibit cyclin-dependent kinase (CDK) activity by dinaciclib in angiogenesis suppression was reported (Izadi et al., 2020). Another efficient modality of combination treatment used was the dendritic cell-based vaccine along with siRNA-loaded NPs to enhance the cytotoxic T lymphocyte functions against breast cancer. In this context, PEG-chitosan-lactate (PCL) NPs incorporated with adenosine 2a receptor (A2aR) siRNA act synergistically with dendritic cell vaccine to profoundly regress tumor growth, metastasis, and angiogenesis via decreased VEGFA, VEGF-R2, and CD31 expressions, and in turn, a prolonged survival rate in a 4T1 breast cancer mice model (Masjedi et al., 2020). Another group of researchers applied the same approach of dendritic cell-based cancer immunotherapy, but with the delivery of specific siRNA to downregulate the expression of cytotoxic T-lymphocyte antigen 4, inhibitory immune checkpoint molecules expressed on tumor-infiltrating T lymphocytes. Similar findings were obtained for their anti-angiogenic potential (Esmaily et al., 2020). Regarding gene therapy, further research reported the synthesis of a delivery system consisting of graphene oxide-reinforced chitosan festooned with carbon dot to deliver tumor

necrosis factor α (TNF-α). This system resulted in the suppression of angiogenesis using CAM assay (Jaleel, Ashraf, Rathinasamy, & Pramod, 2019).

Apart from siRNAs and miRNAs, chitosan NPs are able to deliver and control the release of the endostatin peptide drug, which significantly exhibited potent toxicity against endothelial cells *in vitro* (Ebrahimi Samani et al., 2017).

We further summarize different genes, siRNAs, shRNAs, aptamers, monoclonal antibodies, and/or drug-loaded chitosan-based NPs as suppressors for angiogenesis process in Table 1.

Table 1. Chitosan as delivery nanoplatforms to block tumor angiogenesis

Therapeutic Agent/ Modified Nanoparticles	Therapeutic Targeting/Drug Delivery	Model(s) Used	References
Chitosan lactate conjugated with RGD	ZEB-1 and CD73 siRNAs	Mouse models of murine breast (4T1) and colorectal (CT26) carcinomas	(Alzamely et al., 2021)
hyaluronic acid PEG-Chitosan-Lactate (H-PCL)	IL6 siRNA and BV6 to block inhibitor of apoptosis (IAP)	Mouse models of murine breast (4T1) and colorectal (CT26) carcinomas	(Salimifard et al., 2020)
Chitosan magnetic NPs	Ang-2 siRNA	mice model of Melanoma	(Shan et al., 2020)
Lipid-core nanocapsules coated with chitosan- and modified with gold-III and bevacizumab (MLNC-Au-BCZ)	VEGFA using monoclonal antibody	CAM assay	(de Cristo Soares Alves et al., 2020a)
Mucin1 aptamer-conjugated chitosan NPs	cMET siRNA and docetaxel	mucin1+ SKBR3 vs. mucin1- CHO cells (MMP2, MMP9, IL8, VEGFA, and STAT3)	(Zolbanin et al., 2018)
Fe3O4-bLf-AEC-CP nanocarrier	locked nucleic acid (LNA) modified aptamers against EpCAM, CD133, and CD44	xenograft mice model injected with colon cancer stem cells	(Roy, Kanwar, & Kanwar, 2015)
Galactose modified trimethyl chitosan-cysteine (GTC) NPs	Oral Survivin shRNA- and VEGFA siRNA	Mice model of human hepatoma	(L. Han, Tang, & Yin, 2014)

PLGA-Based Nanosystems

PLGA is biodegradable and biocompatible, and its nanoparticle formulation has been proved to be efficient for drug delivery in different studies (Lü et al., 2009). Notably, it is well established an overexpression of FGFR1 on tumor cells and tumor microvessels. Therefore, PLGA NPs (D/P-NPs) loaded with the truncated bFGF peptide (tbFGF) and paclitaxel (PTX) resulted in massive impairment in the tube formation by HUVECs and exerted an anti-angiogenic activity *in vivo* using the alginate-encapsulated tumor cell and the transgenic zebrafish models (B. Xu et al., 2016). Based on the knowledge of homing sequences and internalizing receptors, tumor-penetrating peptides were used as effective strategy to enhance drug or NP penetration, e.g., Asn-Gly-Arg (NGR) sequence, which is able to bind endothelial CD13 (Alberici et al., 2013; Sugahara et al., 2009). The principle of NGR peptide action is similar to iRGD peptide. The iRGD peptide consists of 2 peptides motifs: RGD, which binds to αvβ3/5 integrins on tumor vasculature and neoplastic cells, and CendR motif. Once integrins interact with RGD, proteolytic cleavage occurs with subsequent exposure of the cryptic CendR motif. This results in binding of truncated peptide to neuropilin-1, enhancing penetration of peptide conjugated or co-administered with drugs into tumors. The tumor vasculature homing efficacy and tumor penetration ability of NGR peptide was enhanced by embedding its sequence in the CendR motif, and this sequence was placed in the iRGD framework to form iNGR. Several studies have exploited the mechanism of action of iRGD and iNGR to target different tumors, and that can be achieved through selective delivery and accumulation of the drug in tumors *in vivo* and the expression of both integrin and neuropilin-1 on neoplasm vasculatures. A study demonstrated that iNGR functionalized-PTX-loaded PEG-PLGA NPs have recognized tumor vessels and penetrated the tumor upon intravenous administration, leading to reduced angiogenesis activity and increased survival time in a mice model of glioma (Kang et al., 2014). Another study showed that cotreatment of PTX-loaded PLGA (PLGA-PTX) NPs with iRGD peptide enhanced treatment of colorectal tumors in mice model (Zhong et al., 2019). Other several studies reported PLGA as a delivery system for gene (Yu et al., 2016), siRNAs/shRNAs (Chuntang Sun et al., 2011; Zou et al., 2013, 2014), and aptamers (T. Duan et al., 2019) to inhibit tumor angiogenesis (Fig. 2).

Carbon-Based Nanomaterials

Carbon Nanotubes

Carbon nanotubes (CNTs) are synthetic scaffolds discovered in 1991 and characterized by excellent chemical mechanical and electrical properties. They can act as nanovectors

for drug or gene delivery (Cao & Luo, 2019) CNTs can be divided into single-walled (SW) or multi-walled CNTs (MWCNTs). Codelivery of the chemotherapy candesartan and VEGFA-targeted siRNA (siVEGFA) loaded into polyethylenimine (PEI)-modified SWCNTs synergistically dampens tumor growth and angiogenesis *in vitro* and *in vivo* using HUVECs and pancreatic cancer mouse models, respectively, with no remarkable toxicity on normal cells (X. Ding et al., 2017) Delivery of NGR peptide-linked SWCNTs loaded with anti-angiogenesis 2-methoxyestradiol were able to inhibit neoangiogenesis in a mice model of sarcoma (C. Chen et al., 2013) Another study developed plasmid angiotensin II type 2-packaged MWCNTs, which are functionalized with iRGD peptide and conjugated with candesartan forming nanocomplex to dual target αvβ3-integrin and angiotensin II type 1 receptor and subsequent angiogenesis suppression in xenograft mice model of lung cancer (Su et al., 2017). In contrast, it has been shown that MWCNTs have little impact on the capacity of human brain microvascular endothelial cells (HBMECs) to form rings as read out for angiogenesis. This suggests that MWCNTs alone may not suffice to inhibit angiogenesis, and their effect is cell culture model-dependent (Eldridge et al., 2017). A nanohybrid consisting of (+)-catechin, gelatin and CNTs completely abolished neo-angiogenesis in zebrafish xenotransplants (di Leo et al., 2017). The disruption of angiogenesis in CAM model by MWCNTs was augmented when modified with pachymic acid via downregulation of metalloproteinase-3 (MMP-3) (Ma et al., 2015). Coloading of curcumin and doxorubicin (DOX) hydrochloride into CNTs functionalized with pH and thermo responsive polymer resulted in a synergistic anti-tumor effect via suppression of growth factors-mediated angiogenesis in CAM model and reversal of multidrug resistance in hepatocellular carcinoma mice model (Das et al., 2020). Interestingly, functionalized SWCNTs can be exploited for their photothermal effect near-infrared irradiation to eradicate solid cancers *in vivo*. Indeed, treatment of mouse model of S180 ascites with NGR peptide-linked SWCNTs incorporated with docetaxel and exposed to thermal therapy resulted in synergistic regression of tumor mass via angiogenesis disruption (Lei Wang et al., 2011) Further, a SWCNT platform can be used in radioimmunotherapy when they radiolabeled by covalently linking to 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid and the tumor neovascular (vascular endothelial-cadherin epitope)-targeting antibody E4G10. Administration of a single intravenous dose of targeted radiolabelled SWCNTs significantly diminished tumor volume and enhanced the survival rate in a xenograft mice model of colon adenocarcinoma (LS174T) via targeting tumor neovasculature (Ruggiero et al., 2010) The effect of CNTs has been extended to the main immune effector cells of tumor microenvironment, namely macrophages. A study by Yang M et al., showed that oxidized MWCNTs decrease tumor-associated macrophages and tumor vasculature, resulting in delayed tumor progression and lung metastasis in a mice model of breast cancer (M. Yang et al., 2012).

Although an *in vitro* study showed that "pristine" and functionalized SWCNTs had limited cytotoxicity to endothelial cells (Albini et al., 2010). A study by Chaudhuri P et al., reported that DOX-loaded-SWCNTs promoted tumor angiogenesis *in vitro* and *in vivo* in zebrafish and murine models. Mechanistically, SWCNTs stimulated integrin clustering in endothelial cells and elicited activation of phosphoinositide-3-kinase (PI3K) and focal adhesion kinase (FAK). Additionally, SWCNTs mitigated the cytotoxic effect of DOX and increased endothelial tubulogenesis, This is in contrast to the action of fullerenols or DOX-conjugated fullerenols, where anti-angiogenesis activity was observed in the same *in vivo* models (Chaudhuri et al., 2010).

The usage of CNTs should be applied with cautions, as the neoplastic-like transformation effect of SWCNTs and MWCNTs has been previously shown (L. Wang et al., 2014). This has been further confirmed in another study, where single pulmonary exposure to MWCNTs markedly promotes angiogenesis and metastasis of breast carcinoma into lungs. This led the authors to raise concerns and to point out the risks of the long-term exposure to airborne NPs that may prepare the pre-metastatic environment and contribute non-lung cancer progression (Lu et al., 2019). Besides their adverse effects on normal development of embryo (Al Moustafa et al., 2016) MWCNTs triggered elevated reactive oxygen species (ROS), actin filament remodeling, and increased migration of human microvascular endothelial cells (HMVECs) via increased intercellular adhesion molecule 1 (ICAM-1) and monocyte chemoattractant protein-1 (MCP-1) (Pacurari et al., 2012).

Carbon Quantum Dots

Similar to CNTs, carbon quantum dots (CQDs) and CQDs-based composites hold anti-cancer potential by radio- and phototherapy. For instance, in comparison with the commercial anti-angiogenic inhibitor semaxanib (SU5416, a selective VEGFA inhibitor), a composite of (CQDs/Cu_2O) had a higher anti-angiogenic capacity in ovarian cancer SKOV3 cells via decreased expression of VEGFR2, MMP-2, and MMP-9 (Fig. 2), besides increased expression levels of the anti-angiogenesis-related factors Maspin, and TSP1 (D. Chen et al., 2021). CAM treated with CQDs showed significantly reduced vessels associated with downregulation of VEGFA, FGF, VEGFR2, and hemoglobin (R. Shereema et al., 2015).

Fullerene

Rice University researchers discovered fullerenes, also known as buckyballs, in 1985. Fullerenes, such as C60, C70, and C82, are carbon-based molecules that exhibit the shape of ellipsoid, hollow sphere, or tube (Fig. 2). It is also called metallofullerene when a metal atom is inserted into a fullerene, and the metal atom is usually a

Group III transition element or a lanthanide (Jiang, Wu, & Wang, 2017; Peng et al., 2017; Saleem, Wang, & Chen, 2018). These NPs are apparently biocompatible and demolish tumor blood vessels, with subsequent tumor starvation and regression (Zhou, Deng, Zhen, Li, Guan, Jia, Li, Zhang, Yu, Zou, et al., 2017). It has been reported that C60(OH)20 are able to inhibit the expression of angiogenesis-related factors, including VEGFA, PDGF, and TNF-α. In a dose-dependent manner, C60(OH)20 retard tumorgenesis and metastatic potential in a mouse breast cancer model. The number of tumor microvessels have been substantially decreased upon NPs' treatment, and that effect was attributed to lower VEGFA expression (Jiao et al., 2010). C60(OH)22 inhibited tube formation and inhibited MMP2 and MMP9 activities, as well as histone deacetylase 1 (HDAC1), histone deacetylase 2 (HDAC2), HIF-1, and VEGFA expression levels were decreased in vitro and in HUVEC xenograft mice, where all factors are required for tumor growth, angiogenesis, and metastasis (Chengdu Sun et al., 2016). Interestingly, silencing of HDAC1 or HDAC2 exerted the same inhibitory effect of C60(OH)22 on angiogenesis of HUVECs, suggesting that C60(OH)22 is a HDAC inhibitor (Chengdu Sun et al., 2016). Together, this suggests that fullerenes with several hydroxyl groups can effectively inhibit angiogenesis. Another study showed that gadolinium incorporated with fullerenol NPs have been shown to inhibit 10 angiogenesis-promoting factors at transcriptional and posttranslational levels. These NPs decreased microvessel density by 40% in a human microvascular endothelial cell (HMEC) xenograft model as compared to the controls. Notably, gadofullerenol NPs had no obvious harmful effects on mice as compared to PTX (Meng et al., 2010). In hepatoma H22 mice model, gadofullerene functionalized with β-alanine has been shown to specifically target blood vessels within tumors (Y. Zhou et al., 2017).

Graphene

Graphene is a stunning new nanocarbon with six-membered rings formed by single, bi-, or few (< 10) layers of carbon atoms (Rao, Biswas, Subrahmanyam, & Govindaraj, 2009). Being easily processed, costly effective, thermal stable, biocompatible, highly electrical conductive, and able to bind aromatic and hydrophobic compounds, graphene is an appealing polymer for drug delivery and gene therapy (Z. Singh, 2016; B. Zhang, Wei, Zhou, & Wei, 2016). As an example for a dual gene/drug targeting nanosystem, carboxylated graphene oxide (GO) coupled with trimethyl chitosan and hyaluronic acid NPs and loaded with both (HIF)-1α-siRNA and dinaciclib (known to inhibit cyclin-dependent kinases family) was able to significantly inhibit angiogenesis, cell growth, and cell motility (Izadi et al., 2020). In a recent study, GO, hyaluronic acid, and copper sulfide were conjugated in a nanostructure which markedly inhibited angiogenesis in squamous cell cancer (SCC-7) xenograft mice

model (Izadi et al., 2020). Another study by Cibecchini et al., reported that GO exhibited anti-angiogenic effect on HUVECs (Cibecchini et al., 2020). A GO-based nanocarrier has recently been developed to target the VEGF mRNA using VEGF-siRNA. GO functionalized to improve its electropositivity and targeting efficiency and loaded with VEGF siRNA suppressed tumor growth and angiogenesis via downregulation of VEGFA mRNA and protein expression levels in HeLa cells and in a mice model (J. Li et al., 2018). Notably, in a coculture of HUVECs with glioblastoma cancer cells of wild type p53 (U87) in the presence of graphite NPs and graphene oxide nanoplatelets, angiogenesis was reduced, whereas in case of glioblastoma cells with mutant p53 (U118) angiogenesis was not affected. The anti-angiogenesis process of the nanostructures can be explained by diminished ROS and reactive nitrogen species (RNS) levels, associated with a reduced NFkB activation in p53 status-dependent manner (Wierzbicki et al., 2018). Another research found that bovine serum albumin-conjugated GO (BSA-GO) has a high affinity for VEGF-165, which is the primary receptor for angiogenesis. As a result of competing binding, angiogenesis was repressed. The treatment of HUVECs with BSA-GO nanosheets resulted in reduced cell proliferation and tube formation. Furthermore, *in-vivo* findings revealed that BSA-GO interferes with angiogenesis in a CAM model and in corneal neovascularization in rabbit (Lai et al., 2016). Reduced GO (rGO) nanosheets coated with the anti-angiogenic low-molecular-weight heparin (LMWH) derivative displayed stable dispersion and tumor distribution relative to uncoated nanosheets. Relative to untreated group, when human oral squamous cancer (KB) cells-bearing mice were intravenously injected with the coated rGO nanosheets encapsulating DOX, tumor volume was reduced via increased apoptosis (Shim et al., 2014).

Natural Compounds-Based Nanoparticles

Curcumin

Curcumin is a polyphenolic phytochemical yellow pigment and a component of the Indian turmeric spice (Anand et al., 2008). Several studies have been addressed the multifaceted functions of curcumin as a safe and a promising therapeutic or a preventive agent against inflammation and a wide range of diseases, including cancers (Slika & Patra, 2020). However, poor water solubility and, consequently, relatively low systemic bioavailability due to the rapid metabolism and conjugation in the liver narrows the therapeutic efficiency window of curcumin. Therefore, the formulation of curcumin as nanoparticle or encapsulation in a nano-sized system will overcome this limitation. Curcumin-loaded chitosan/poly(butyl cyanoacrylate) NPs suppress angiogenesis and tumor growth in a murine xenograft model of hepatocellular carcinoma (J. Duan et al., 2010). Curcumin encapsulated into biodegradable polymeric

micelles (MPEG-PCL) reduced embryonic angiogenesis and tumor angiogenesis in the transgenic zebrafish model and tube formation of HUVECs, respectively (Gong et al., 2013). Further, curcumin- and DOX-co-loaded MPEG-PCL micelles inhibit tumor angiogenesis in a lung cancer mouse model (B. L. Wang et al., 2013) and in a diethylnitrosamine-induced hepatocellular carcinoma mice model (Zhao et al., 2015). The biodegradable MPEG-PLAs micelles enhanced the anti-angiogenic effect of curcumin in the glioma xenograft mice model (Zheng et al., 2016). Upon loading with organically modified silica NPs, phototoxicity of curcumin in human oral cancer cells was improved over free curcumin via downregulation of NF-κB-regulated VEGFA levels, (S. P. Singh, Sharma, & Gupta, 2014) . Similar findings were obtained when curcumin-loaded polyester amine (PEA) NPs were used in the alginate-encapsulated tumor cells and transgenic zebrafish model (Ding et al., 2014). Dendrosome/curcumin micelle displays a chemoprotective activity against breast cancer metastasis via downregulation of NF-κB-regulated VEGFA, cyclooxygenase 2 (COX-2), and MMP-9 expressions, and in turn angiogenesis (Farhangi et al., 2015). However, curcumin-capped copper NPs did not show a superior anti-angiogenic effect than native curcumin in breast cancer (Kamble et al., 2016). Dual treatment of docetaxel and curcumin-loaded nanofibrous microspheres resulted in inhibition of abdominal metastases of colorectal cancer in a mice model via inhibition of tumor angiogenesis (Fan et al., 2016). Another strategy of treatment exploited the acidic environment of cancer cells. For example, DOX and curcumin-co-encapsulated in the pH-sensitive amphiphilic poly β-amino ester NPs massively inhibited *in vitro* and *in vivo* angiogenesis via repression of HUVEC proliferation, invasion, migratory potential, and tube formation, as well as modulation of VEGFA pathway (J. Zhang et al., 2017). The *in vivo* anti-tumor and potent anti-angiogenic effect of curcumin was greatly increased upon conjugation either with LMWH to formulate LMWH-curcumin-nanodrugs (Xiao et al., 2018) or with gold NPs (AuNPs) to form biosynthesized AuNPs tested against breast cancer cell lines (Vemuri et al., 2019a). For targeted therapy, co-delivery of curcumin and folate by PEG-PLA micelles effectively repressed glioma in mice via angiogenesis inhibition (He et al., 2020).

Resveratrol

Resveratrol is a non-flavonoid polyphenolic natural compound found in many nutrients. Numerous studies have demonstrated that resveratrol exerts anti-cancer effects, namely anti-proliferative, anti-angiogenesis, and apoptotic activities, on different tumor entities (Delmas, Cornebise, Courtaut, Xiao, & Aires, 2021). The potent anti-angiogenic properties of resveratrol can be synergistically enhanced when combined with the chemotherapeutic DOX drug *in vitro* and *in vivo* using HUVECs and CAM models (Uvez et al., 2020). Mechanistically, resveratrol treatment

inhibits VEGF and ERK1/2-AKT signaling, as well as reduces ROS production and downregulates the pro-angiogenic factor expression, such as VEGFA, interleukin 8 (IL-8), and CXCL8 (Y. Han, Jo, Cho, Dhanasekaran, & Song, 2019). Interestingly, expressions of angiogenesis-related miRNAs miRNA-34a, miRNA-424, miRNA-503, miRNA-155 are regulated by resveratrol (Varghese, Liskova, Kubatka, Samuel, & Büsselberg, 2020). Few nanotechnological studies either formulated or encapsulated resveratrol in NPs to enhance its bioavailability and overcome its chemical instability. The chemotherapeutic agent pemetrexed and resveratrol co-delivery by lyotropic liquid crystalline NPs repressed tumor growth via angiogenesis suppression in a mice model of urethane-induced lung cancer (Abdelaziz et al., 2019). Another study used the phospholipid complex resveratrol to facilitate its physical incorporation into albumin NPs, being coupled with quantum dots (QDs) and mannose moieties, as well as conjugated with the chemotherapeutic pemetrexed drug. This nanohybrid platform induced tumor regression via inhibition of VEGFA-induced angiogenesis with non-immunogenic effect in Ehrlich-Induce mammary tumor-bearing mice (Zayed et al., 2019).

Paclitaxel

PTX is one of the taxane families of naturally occurring alkaloids. It has potent anti-cancer effects via targeting the microtubules by β-tubulin-binding resulting in cell cycle arrest. It is used as the first-line chemotherapy to treat different tumor entities (Mikuła-Pietrasik et al., 2019; Vacca et al., 2002). It was reported that PTX has a suppressive effect on angiogenesis, and this can be attributed to its extensive accumulation in endothelial cells relative to other cell types (Merchan et al., 2005). Furthermore, PTX treatment decreased vasculogenesis and angiogenesis-related factors VEGFA and FGF-2, whereas it increased expressions of an endogenous inhibitor of angiogenesis TSP1 (Hata et al., 2004). PTX in the nano-sized formulation or encapsulated in nanoparticle delivery systems markedly enhances its anti-tumor and anti-angiogenic potency. PTX loaded in emulsifying wax NPs (PX-NPs) as colloidal carriers showed potent anti-tumor growth and anti-angiogenic efficacy compared to Taxol in colon adenocarcinoma mouse xenograft model (Koziara, Whisman, Tseng, & Mumper, 2006). Dual treatment also holds great potential as an efficient combinatorial therapy compared with monotherapy. In this regard, a nanocapsule of PTX-conjugated amphiphilic polyester entrapped with the FDA-approved inhibitor of neovasculature combretastatin A4 was able to be sequentially released to dampen tumor angiogenesis and liver metastasis in tumor xenograft models, and intrasplenic liver metastasis model (Wang & Ho, 2010). Similar anti-tumor and anti-angiogenesis findings were observed when both drugs were co-loaded into PLGA solid nanoparticulate decorated with RGD peptide as targeted

therapy (Zhe Wang, Chui, & Ho, 2011). Another approach for targeted therapy is using folate receptor-targeted NPs to circumvent chemotherapy resistance. These NPs encompassing a heparin-folate-PTX platform loaded with additional PTX profoundly diminished tumor growth. This nanosystem decreased angiogenic activity in the resistant squamous cancer xenograft model (X. Wang et al., 2011). Interestingly, a very recent study reported that co-loading of the FDA-approved drugs PTX, combretastatin, and verteporfin in polymer-lipid hybrid NPs markedly inhibits triple-negative breast tumor growth and stemness, as well as angiogenesis in patient-derived xenograft (PDX) and *in vivo* zebrafish models (El-Sahli et al., 2021). Since platelets are involved in angiogenesis and interact with circulating tumor cells (CTCs), a platelet membrane protein-coated nanostructured lipid carrier and loaded with PTX has been engineered. This lipid-based nano-sized drug delivery system has an anti-tumor effect against the ovarian cancer cell line SK-OV-3 (Bang et al., 2019).

Inorganic and Metallic Elements-Based Nanoparticles With Anti-Angiogenic Activity

Normal diet contains several inorganic and metallic elements, which are indispensable for metabolism and many physiological functions within the human body. Some of these elements are of therapeutic relevance exerting anti-angiogenic functions in cancer upon their delivery in nanosystems (Fig. 2). In this regard, we will discuss some examples of these elements.

Cerium Nanoparticles

Cerium is a rare earth metal and has two oxide forms. Cerium oxide NPs (CNPs) or nanoceria have two coexisting oxidation states caused by the partial reduction of Ce^{3+} to Ce^{4+} (Dhall & Self, 2018). Therefore, nanoceria has a pivotal scavenging role for ROS and RNS in turn, emerging as a promising therapy in many pathological diseases (B. H. Chen & Stephen Inbaraj, 2018; Walkey et al., 2015). For example, treatment with nanoceria suppressed VEGFA (165)-induced cell growth, activation of VEGFR2, MMP2, and capillary tube formation of HUVECs. Further, it significantly blunted tumor growth and attenuated angiogenesis, evidenced by reduced immunohistochemical staining of CD31 and apoptosis of vascular endothelial cells in nude mice of ovarian cancer (Giri et al., 2013). Heparin functionalized nanoceria mitigated endothelial cell proliferation and, in turn, angiogenesis (Lord et al., 2013). A study by Hijaz M et al. showed that folic acid-conjugated nanoceria markedly retarded tumor growth and angiogenesis in an ovarian cancer xenograft mouse model (Hijaz et al., 2016). It is noteworthy that nanoceria possesses multifaceted anti-cancer

activity via a redox-independent radio-sensitizing effect on human keratinocytes (Corsi, Caputo, Traversa, & Ghibelli, 2018). In contrast, it appears that nanoceria has dual roles, where it serves as bioactive scaffolds to enhance angiogenesis (Z. Xu et al., 2020). Therefore, this should be taken in consideration when nanoceria is being employed in clinical settings.

Gold Nanoparticles

The fascinating bioactivity of gold NPs (AuNPs) renders it a promising therapeutic and diagnostic tool. AuNPs are inorganic nucleus encircled by an organic monolayer (Arvizo, Bhattacharya, & Mukherjee, 2010). AuNPs can form different structures such as clusters, plasmonic crystals, or catalytic particles with a variety of nano-based structures depending on their size ranges (Mori & Hegmann, 2016; Seo & Song, 2012). Several biomolecules can be used for the surface functionalization of AuNPs, such as peptides, proteins, and oligonucleotides (T. Sun et al., 2014; Webb & Bardhan, 2014). A wide range of studies has been performed to reveal the most efficient Au nanoformulations to curtail angiogenesis. Lipid-core nanocapsules coated with chitosan and functionalized with Bevacizumab (BCZ) and Au III showed strong anticancer activity against C6 glioma cell line *in vitro* and anti-angiogenic capacity in CAM model, with a remarkable decrease of BCZ dose used in nanoformulation relative to BCZ in aqueous solution (de Cristo Soares Alves et al., 2020b). Hollow gold nanoshell coated with anti-programmed death ligand-1 and loaded with DOX (T-HGNS-DOX) was designed for chemo- and photothermal therapies. T-HGNS-DOX had a marked anti-cancer activity due to substantial absorption of DOX post nonionizing radiation caused by elevated programmed death-1. The proliferative marker Ki-67 and the angiogenesis marker CD31 expressions were mitigated, with a subsequently drastic reduction in locally advanced melanoma (Banstola et al., 2021). A conjugate of AuNPs with folic acid inhibited tumor angiogenesis and showed reduced tumor vasculature (Huang et al., 2020). AuNPs conjugated with anti-angiogenic peptides inhibited the angiogenesis by modulating VEGFA intrinsic pathway in a CAM model induced by exosomes isolated from chronic myeloid leukemia k562 cells (Roma-Rodrigues, Fernandes, & Baptista, 2019). AuNPs interferes with the crosstalk between the tumor niche and endothelial cells. Endothelial cells conferred decreased tubes formation and migratory phenotype when cultured with condition media isolated from AuNPs-treated ovarian cells or cocultured with cancer cells and cancer-associated fibroblast pretreated with AuNPs. The AuNPs exerted their effect by reducing VEGF-165 mRNA expression, thus decreasing the activation of VEGFR2 (Y. Zhang et al., 2019). Biosynthesis of AuNPs conjugated with naturally occurring compounds, such as, quercetin, PTX, curcumin, and turmeric, showed significant inhibition of angiogenesis when tested against the

human breast cancer cell lines MCF-7 (low metastatic potential) and MDA-MB-231 (highly aggressive cells), without showing cytotoxic effect against the normal human embryonic kidney cells (HEK293) (Vemuri et al., 2019b) AuNPs used to treat human colorectal cancer (SW620)-xenograft nude mice showed a significant decrease in the anterior gradient 2 (AGR2, a protein that is secreted by the malignant tumor) together with vascular normalization (F. Pan et al., 2018). AuNPs also had been used as a delivery system for human endostatin (Anti-angiogenic agent used in the treatment of tumor); this nanocarrier was tested in colorectal metastatic cancer-xenograft mice model and HUVEC cells *in vitro* and showed inhibition of VEGFR2 and obstructed AG2-mediated angiogenesis and decreased formation of tubes and cell motility (F. Pan et al., 2017). AuNPs were also integrated with tetrasodium salt meso-tetrakis (4-sulfonatophenyl) porphyrin. This nanosystem was capable of invading selectively the cancer cells and transported anti-tumor drug DOX to the cancer cells' nucleus in multidrug resistance brain cancer. This delivery system enhanced cellular apoptosis and showed a strong inhibition of metastasis, invasion, and angiogenesis (Bera, Maiti, Maity, Mandal, & Maiti, 2018). The biosynthesized AuNPs showed a significant decrease in the Ang-1/tie2 pathway, thus reducing angiogenesis in a CAM model (Vimalraj, Ashokkumar, & Saravanan, 2018). AuNPs were also investigated against two types of cancer cells, the mouse fibroblast L929 and human cervix adenocarcinoma Hela cells. Results showed that AuNPs were linked to the cell membrane and localized in cytoplasmic vesicles or the cytosol. AuNPs inhibited angiogenesis in a CAM model (Tan & Onur, 2018). A hybrid-NP composite of quinacrine and Au (QAuNPs) was used to treat oral squamous cell carcinoma and showed a significant inhibition of cell growth and angiogenesis in a xenograft mice model. Action of QAuNPs caused a downregulation in the angiogenic-related markers, such as Ang-1, Ang-2, VEGFA, and MMP-2. So, QAuNPs demonstrated an efficient treatment against angiogenesis and metastasis of oral squamous cell carcinoma (Satapathy et al., 2018). When AuNPs were loaded with anti-angiogenic peptide and combined with laser irradiation exhibited a localized angiogenesis blockade effect in a CAM model via 4-fold downregulating VEGFA expression, thus inhibiting the VEGFR pathway (Pedrosa, Heuer-Jungemann, Kanaras, Fernandes, & Baptista, 2017). AuNPs confirmed its anti-angiogenic effect and showed normalization of tumor vasculature and revert the epithelial-mesenchymal transition (EMT) inducing lung metastasis. As a result, AuNPs reduced metastasis of melanoma tumor (W. Li et al., 2017). AuNPs were also conjugated with gum arabic with a diameter of 15-18 nm. This nanocomposite administration followed by laser irradiation caused a significant downregulation of VEGFA leading to decreased angiogenesis in mice model of lung cancer induced by a chemical substance (Gamal-Eldeen et al., 2017). Quercetin (a potent anti-malignant and anti-oxidant flavonoid) conjugated to AuNPs blocked epithelial growth factor receptor (EGFR)/

VEGFR-2 pathway leading to a decrease in tube formation of HUVECs, reduced the formation of new vessels in a CAM model, and inhibited the tumor progression in mammary carcinoma induced by dimethylbenzanthracene (DMBA) in rats (Balakrishnan et al., 2016). PEGylated Au nano semi-cubes treatment followed by laser activation downregulated VEGFA and was associated with decreased VEGFR2, PDGFR, and HIF-1 expression levels in skin cancer-bearing mice (Abo-Elfadl et al., 2016). Nanogold was also used as a drug carrier for human endostatin (an inhibitory factor of angiogenesis) for non-small cell lung cancer treatment. Besides, nanogold conjugated with human endostatin improved the cytotoxic effect of 5-fluoro uracil (W. Li et al., 2016). Oligo-ethylene glycol-capped AuNPs were conjugated with peptides that can associate with cellular receptor involved in angiogenesis regulation. This AuNP-peptide composite displayed a specific inhibition of angiogenesis using CAM assay (Roma-Rodrigues, Heuer-Jungemann, Fernandes, Kanaras, & Baptista, 2016). Popovtzer et al., combined cetuximab (an inhibitor of EGFR) with AuNPs reduced significantly radio resistance and the tumor growth in head and neck cancer bearing mice via angiogenesis supersession evidenced by decreased CD34 expression (Popovtzer et al., 2016). AuNPs linked with captopril and VEGFA-siRNA reduced the VEGFA expression *in vitro* and decreased the tumor progression in MDA-MB-435 xenograft mice model (M. Li, Li, Huang, & Lu, 2015). Changing the chemistry of the surface of AuNPs also can change its bioactivity as reported by Grzincic E et al., who coated the AuNPs with four different coatings: citrate, lipid alkanethiols, lipid poly allylamine hydrochloride PAH, or PAH alone, showed a downregulation in angiogenesis genes in both human dermal fibroblasts and prostate cancer PC3 cells with a change in the levels of expression and the pathways involved according to the chemistry of coated surface (Grzincic, Yang, Drnevich, Falagan-Lotsch, & Murphy, 2015). AuNPs blocked HUVEC motility and tube formation evoked by VEGF-165-mediated Akt pathway resulting in disruption of the cell surface ultrastructure and destabilization of cytoskeleton (Y. Pan, Wu, Qin, Cai, & Du, 2014). AuNPs was also conjugated to snake venom NKCT1 toxin and exhibited a potent inhibition of angiogenesis through reduced VEGFA mRNA level in solid Ehrlich carcinoma (Bhowmik, Saha, DasGupta, & Gomes, 2014). Radiolabeled 177Lu AuNPs conjugated with RGD showed a significant decrease in tumor progression and reduced metabolic processes, as well as lowered the mRNA levels of VEGFA genes associated with reduced the tumor vascularization (Vilchis-Juárez et al., 2014). AuNPs repressed VEGFA expression and reduced the migration of HUVECs that were cultured with condition medium isolated from human hepatocarcinoma cells (Y. Pan, Wu, Liu, et al., 2014). AuNPs showed inhibitory effect on the interactions between VEGFA (165)-VEGFR2 and inhibited the phosphorylation of Akt in HUVECs and reduced tumor volume and angiogenesis exemplified by immunohistochemical staining of CD34 in H22 xenograft mice

model (Y. Pan et al., 2013). AuNPs conjugated with tunicamycin (a strong inhibitor of N-acetylglucosaminyl 1-phosphate transferase) linked to peptide nanotubes decreased the endothelial cells proliferation and thus inhibiting the angiogenesis by 50% (Banerjee, Johnson, Banerjee, & Banerjee, 2013). Reduction of AuNPs by diaminopyridinyl (DAP)-derivatized heparin inhibited the angiogenesis process mediated by fibroblast growth factor (FGF-2) (Kemp et al., 2009). AuNPs suppress HUVEC and fibroblast proliferation caused by inhibition of VEGFA (165) and bFGF (basic fibroblast growth factor), respectively. AuNPs binds to heparin-binding growth factors and cause a blockade to growth factor–mediated signaling, probably by cysteine residues in the heparin-binding domain (Mukherjee et al., 2005).

Silver Nanoparticles

Silver nanoparticles (AgNPs) are small clusters of silver atoms used as anti-bacterial and anti-microbial agents in medicine (Chaloupka, Malam, & Seifalian, 2010). Having distinct physical and optical properties and biochemical versatility, AgNPs appear to have tremendous importance in a wide variety of biomedical applications (Lee & Jun, 2019). AgNPs exerted various activities inducing loss of membrane integrity, formation of free radicals, and promoting DNA damage demonstrated by comet assay against human microvascular endothelial cells. In addition, a cytotoxic effect against the endothelial colony-forming cells which is important in angiogenesis was also observed (Zhu et al., 2015).

Conjugation of AgNPs with plant extract from palm pollen downregulated VEGFA and its receptor VEGFR and decreased the vasculature in a CAM model (Homayouni-Tabrizi et al., 2019). Quinacrine (QC) conjugated to AgNPs and encapsulated in PLGA in CAM model showed a significant anti-angiogenic effect (Satapathy, Siddharth, Das, Nayak, & Kundu, 2015). Not only the silver conjugated nanoparticles have a biological effect, but also the naked AgNPs synthesized either by green methods or by other chemical methods showed anti-angiogenic bioactivity as reported in several studies. The biosynthesized AgNPs using the extract isolated from rapeseed flower pollen downregulated the VEGFA in MDA-MB-231 cells (Hajebi, Tabrizi, Moghaddam, Shahraki, & Yadamani, 2019). Another biosynthesized AgNPs using the aqueous isolated from *Clitoria Ternatea* flower showed anti-angiogenic properties in Ehrlich ascites carcinoma *in vivo* model via reduced VEGFA protein levels assessed by ELISA. Counts and densities of microvessels were also reduced in tumors and in a CAM model (Srinivas, Shivamadhu, Siddappaji, Krishnappa, & Jayarama, 2019). AgNPs biosynthesized using *Saliva Officinalis* significantly reduced the vessel number and length in the CAM assay compared with untreated group (Baharara, Namvar, Mousavi, Ramezani, & Mohamad, 2014). AgNPs significantly inhibited VEGFA and glucose transporter 1 (GLUT1) expression under the hypoxic

conditions in the MCF-7 cells (T. Yang et al., 2016). AgNPs biosynthesized using *Bacillus licheniformis* resulted in inducing apoptosis and DNA fragmentation in bovine retinal endothelial cells (BRECs) and hampered the cell survival mediated by PI3K/Akt signaling pathway (Kalishwaralal et al., 2009). In another study, AgNPs also caused inhibition of angiogenesis through reducing VEGFA, cell motility, and formation of tubes in BRECs and blocked the formation of new vasculature in Matrigel plug assay *in vivo* (Gurunathan et al., 2009).

On the contrary, AgNPs exerted a pro-angiogenic effect when coated with polyvinylpyrrolidone. They caused endothelial cells to form tubes, produce ROS, and induce expression of angiogenic-related factors, such as VEGFA and NO. AgNPs facilitated the activation of signaling pathways regulating VEGFR, such as FAK, Akt, ERK1/2, and p38. *In vivo*, angiogenesis was induced by Ag in the B16F10-induced melanomas xenograft mice model (K. Kang et al., 2011).

Zinc Oxide Nanoparticles

Zinc oxide nanoparticles (ZnO-NPs) are a vital and important commodity because of their multifunctional properties, stability, low cost, and widespread use (Rahman, Harunsani, Tan, & Khan, 2021). For example, ZnO.is used in Pharmaceutics, cosmetics, and glass industries. It is also a bio-friendly substance that have photo-catalytic and photo-oxidizing potentials (Ansari et al., 2013; Mirzaei & Darroudi, 2017; Sirelkhatim et al., 2015). Numerous studies were conducted to underscore the anticancer properties of ZnO-NPs synthesized by green methods. ZnO-NPs biosynthesized by *Ceratonia siliqua* extract showed a significant VEGFR downregulation and high VEGFA mRNA expression levels in MCF-7 and MDA-MB-231 cells, leading to inhibiting angiogenesis (Pouresmaeil, Haghighi, Raeisalsadati, Neamati, & Homayouni-Tabrizi, 2020). ZnO-NPs showed a promising anti-angiogenic effect on HUVECs by inducing cell apoptosis and DNA damage. Besides, reduced VEGFA expression and impairment of tube formation leading to blockade of angiogenesis (Poier et al., 2020). ZnO-NPs biosynthesized by *Hyssops officinalis L.* decreased the number of vessels and their length in a CAM model. Also, ZnO-NPs downregulated VEGFA and its receptor on the MCF-7 cells (Rahimi Kalateh Shah Mohammad, Homayouni Tabrizi, Ardalan, Yadamani, & Safavi, 2019). Synthesis of ZnO-NPs in a green manner using algae *Sargassum muticum* showed reduced angiogenesis in a CAM model and induced apoptosis in the human liver cancer HepG2 cells (Sanaeimehr, Javadi, & Namvar, 2018). ZnO-NPs functionalized with biopolymer gelatin showed a remarkable anti-angiogenic activity in chick embryos (Divya et al., 2018).

FUTURE RESEARCH DIRECTIONS

During last few years, progress has been made toward NPs' manufacturing. This makes them appealing choice for wide biomedical applications, especially cancer treatment. It is very crucial to determine NPs' acute and chronic toxicity, pharmacokinetics, pharmacodynamics, toxicity to and interactions with immune system, biodegradability, and safety to the environment. These challenges can be overcome to some extent by green biosynthesis method as a good alternative over the chemical method for NPs' synthesis, where properties of reduced toxicity, cost effective, and ecofriendly can be achieved. Although results of cancer nanomedicine in clinical trials are very encouraging, applications of nano therapy to target tumor angiogenesis in clinical settings are very limited and under-investigated. Therefore, more research is required to fully examine the therapeutic efficacy of nanomedical drugs against tumor angiogenesis in clinical trials. Further, dual roles of NPs in promoting or suppressing angiogenesis based on their size, shape, and dosage should be very carefully considered before clinical translation.

CONCLUSION

In this chapter, we provide an overview on physiological and pathological angiogenesis process. Different types of drugs have been developed to target tumor angiogenesis. However, these therapeutic agents have toxicity and became ineffective due to developing drug resistance. Recent advances of nanotechology used for nanoparticulate drug formulation or nanocarrier delivery system fabrication hold promising hopes to target tumor vasculature. These nano-based treatment perspectives (e.g., polymer-based nanosystems, carbon-based nanomaterials, natural compounds-derived NPs, and inorganic and metallic elements-based NPs encapsulating siRNAs, shRNA, miRNAs, and/or chemotherapeutic drugs, and functionalized with peptides, aptamers, or monoclonal antibodies) targeting tumor angiogenesis have been proved to be efficient in preclinical models of numerous tumor entities. Therefore, these findings can open new horizons for clinical translation in the near future.

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Chapter 4
Nanophytotherapeutics for Cancer

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ABSTRACT

Phytochemicals have been attributed beneficial health properties, mainly their anticancer potential. Cancer treatment seeks to shrink the tumor and kill cancer cells; however, the conventional treatment available frequently fails due to the emergence of drug-resistant cell lines. Plant-derived compounds have been studied for their potential anticancer effects or as adjuvant drug to conventional treatment. However, some of the physicochemical properties and stability characteristics of the phytocompounds generate biopharmaceuticals difficulties that limit their efficacy and clinical applications in oncology. In this sense, nanomedicine offers an alternative for the development of biocompatible, biodegradable, safe, and efficacy phytoformulations. Nanostructured delivery systems show immense potential in the bioavailability of phytodrugs by providing better alternatives to conventional dosage forms, through improving physicochemical and biopharmaceutical properties of the phytocompounds and along with it to enhance the therapeutic efficacy.

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INTRODUCTION

The importance of natural products in medicine, agriculture and industry has led to numerous studies on the synthesis, biosynthesis and biological activities of these substances (Huang et al., 2016). Obtaining molecules of natural origin have been used for several centuries to prevent and treat various chronic ailments. These bioactive constituents are described as phytochemicals, and are secondary metabolites made by plants for their own defense purposes. They have been attributed beneficial health properties for being antioxidants, anti-inflammatory, antiallergic, hepatoprotective, neuroprotective, dermatoprotective, antimicrobial, antifungal, antispasmodic/antidiarrheal Agents, hypolipidemic, hypotensive, antidiabetic, analgesic, immunomodulating, and anticancer (Patel, 2017).

Cancer is noncommunicable disease with incidence of 19 million of new cases and responsible for nearly 10 million deaths worldwide in 2020. The World Health Organization estimates that these values will increase by about 60% for 2040 (IARC, 2020). The Cancer treatment is aimed at achieving sustained reductions in tumor and the elimination of cancer cells, however, the conventional treatment available such as chemotherapy, laser therapy, and cell-directed surgery, frequently fails due to the emergence of drug-resistant cell lineages (Hansen and Read, 2020). On the other hand, the side effects of systemic chemotherapy are often severe (Schirrmacher, 2019). Therefore, emerging strategies of Cancer therapy are still being studied with the aim of increasing long-lasting efficacy and reducing side effects.

The plant derived compound have been studied for their *anticancer effects* or *potential adjuvants* for conventional treatment, taking into consideration their low toxicity, low costs, affordable acquisition and multitargeting properties that allow the modulation of different signaling pathways (Lin et al., 2020). Between these, alkaloids, diterpenoids, flavonoids, polyphenolic compounds, and sesquiterpenes attained from medicinal plants, fruits, and vegetables possess immense anti-cancer potential (Banik et al., 2019). In fact, approximately, 50% of approved anticancer drugs are phytochemical or directly derived therefrom, which belong to four major classes of clinically used plant-derived anticancer compounds: vinca alkaloids, taxane diterpenoids, camptothecin derivatives, and epipodophyllotoxin (Choudhari et al., 2020). Considering that approximately the 10% of the plant species with therapeutic potential have been studied, there is still much to study on the way to the discovery anticancer agents based on phytochemicals (Subramaniam et al., 2019).

Many natural products such as curcumin, genistein, and others, exhibit anti-cancer activity through inhibition of proliferation, induction of apoptosis, induction of cell cycle arrest, inhibition of invasive behavior, and suppression of tumor angiogenesis *in vitro* and *in vivo* models (Agbarya et al., 2014). Among these, curcumin has been recognized as the most promising phytochemical in the treatment of several cancer

types for its ability by targeting different cell signaling pathways including growth factors, cytokines, transcription factors, and genes modulating cellular proliferation and apoptosis (Giordano and Tommonaro, 2019).

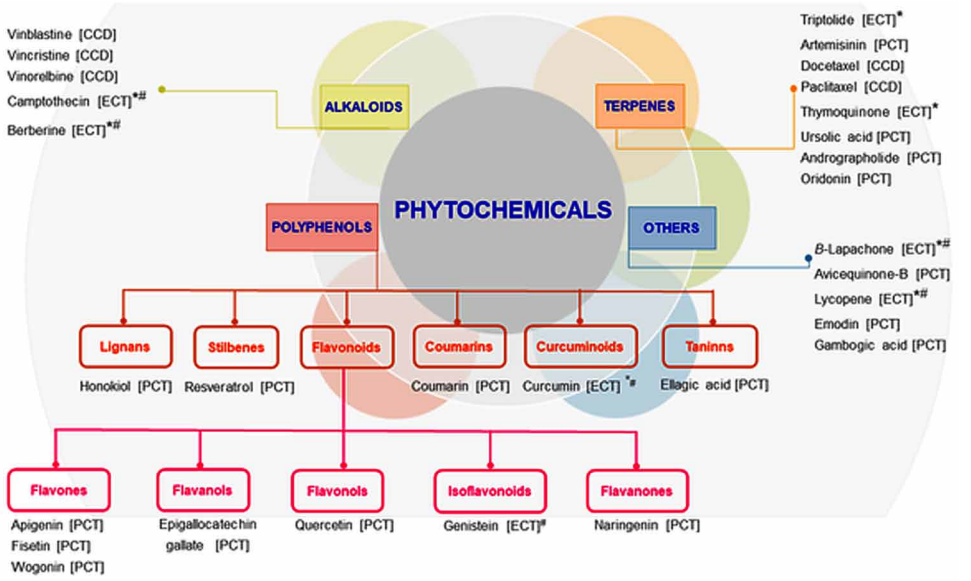
On the other hand, the adjuvant action of phytochemicals is based on 1) Direct potentiating tumoricidal effect or sensitizing cancer cells to be more responsive to chemotherapeutic drugs; 2) Reversing chemoresistance, through diminishing drug efflux or overcoming other mechanism to increase the accumulation of chemotherapeutic drugs in cancer cells; and 3) Alleviating toxicity induced by chemotherapeutic drugs, promoting the repairing mechanism in normal cells against damage of chemotherapeutic drugs (Lin et al., 2020). Phytochemicals such as curcumin, silymarin, allicin, lycopene, ellagic acid, resveratrol and among others, have showed additive/synergic effects, improving the activity of the anticancer drugs and reducing their collateral and side effects (Zhang et al., 2021). For example, Resveratrol could enhance anticancer therapies by regulating multidrugresistant protein expressions and interfering with cell signaling pathways include cellular cycle and apoptosis (Zhang et al., 2021).

However, applications of phytochemicals as anticancer and adjuvant therapy, have been limited due to poor oral bioavailability, poor aqueous solubility, rapid metabolism, and systemic elimination that limit its efficacy in cancer treatment (Yadav et al., 2020). In this sense, the nanomedicine is the solution to promote the development of nanoformulations biocompatible, biodegradable and stable. In short, optimized nanophytherapeutics would contribute to increase efficiency, improve drug specificity, enhance absorption rates, reduce drug degradation and diminish systemic toxicity in cancer therapy (Wei et al., 2019).

PHYTOCHEMICALS FOR CANCER THERAPY (PHYTOCHEMICALS AS ANTICANCER DRUG)

The Fig. 1 shows the main phytochemical groups employed as Current Clinical Drug (CCD), Evaluated in Clinical Trials (ECT) (only Clinical Trials with completed status and Phase II and III were included) and studied in Pre-clinical Trials (PCT). The selection of the compound is based on a bibliographic search on Pubmed using the keywords: “Nanoformulation” “Nanoparticle” “Phytochemical”, “Anticancer Drug”, “Natural Compound”, “Cancer Therapy”. Next, a brief description of the prototype compounds of each group will be made.

Figure 1. Group of phytochemicals with anticancer activity and delivered by nano-structured systems. [CCD] Current Clinical Drug; [ECT] Evaluated in Clinical Trials (only Clinical Trials with completed status and Phase II and III were included) and [PCT] Pre-clinical Trials



Alkaloids

Alkaloids have a wide range of biological activities and diverse chemical structure dependent on precursor amino acid (phenylalanine, tyrosine, tryptophan, ornithine, or lysine) (Verpoorte, 2004). Chemically, alkaloids correspond to cyclic compounds that contain one or more basic nitrogen atoms in ring system, which in turn, some hydrogen atoms are replaced by various oxy-alkyl radicals (Habli et al., 2017). Most of the known alkaloids have been isolated from plants, mainly from plant families Leguminosae, Menispermaceae, Ranunculaceae, Loganiaceae and Papaveraceae (Mondal et al., 2019). The significant biological activities, such as the analgesic action, bronchodilation and the anticancer effects make these compounds serve as an attractive reservoir for drug discovery (Lu et al., 2012). Alkaloids, such as Vincristine, Vinblastine, Vinorelbine, Camptothecin and Berberine have already been successfully developed into anticancer drugs, but only vincristine, vinblastine and vinorelbine have been approved by Food and Drug Administration (FDA) as pharmaceutical strategy against different tumors (Lee et al., 2015).

The Vinca alkaloids (VAs) (Vincristine, Vinblastine and Vinorelbine) are phytochemicals isolated from the leaves of the Madagascar periwinkle plant,

Catharanthus roseus, formerly known as Vinca rosea (Agrawal, 2007). The VAs are current cancer therapy indicated in hematologic malignancies, leukemia, Hodgkin's and non–Hodgkin's lymphoma, rhabdomyosarcoma, neuroblastoma, Non-small-cell lung carcinoma (NSCLC), breast, lung and testicular carcinoma, Kaposi's sarcoma, and second-line transitional cell carcinoma of the urothelium (TCCU) (Choudhari et al., 2020). These phytochemicals, constitute the first class of mitotic inhibitor, acting as tubulin targeting anticancer drugs. Specifically, the VAs interact with GDP-α/β-tubulin dimers blocking the microtube formation required to anaphase onset and consequently to generate a prolonged arrest state. Additionally, the VAs interact with GTP-α/β-tubulin eliciting the microtubular that determines the accumulation of chromosomes in unnatural forms, leading to cell death through activation of p53-dependent and/or -independent apoptotic pathways (Martino et al., 2018). On the other hand, the VAs have non-mitotic toxic effects including inhibition of axon transport, secretion processes and structure disorders and impairment of platelet functions, actions related with their toxicological profile and side effect reported, in particular, neurotoxicity (Choudhari et al., 2020).

On the other hand, Camptothecin and its derivatives, topotecan and irinotecan approved by FDA, act by targeting Topoisomerase I (TOP1) function (Effect also known as TOP1 inhibition). TOP1 is enzyme responsible of change the topological state of nucleic acids by forming Topoisomerase Cleavage Complexes (TOP1CCs), a TOP1-DNA interface required for DNA replication and transcription. Camptothecin target TOP1CCs causing DNA synthesis damage by replication run-off and inducing the cell death pathways by engaging p53 (TP53) and Schlafen 11 (SLFN11) (Thomas and Pommier, 2019). Camptothecin registers phase II clinical trial for the treatment of solid tumor, Advanced Gastric, Gastroesophageal, or Esophageal Squamous or Adenocarcinoma and Non-Small Cell Lung Cancer (https://www.clinicaltrials.gov).

Finally, Berberine has been used in Traditional Chinese Medicine as antineoplastic, radiosensitizing, anti-inflammatory, anti-lipidemic, anti-oxidant, antimicrobial and anti-diabetic therapy (Miguel et al., 2014). Diverse pharmacological actions of Berberine have been reported, between these, the apoptosis induction through up-regulate p53 expression, by suppressing the inner inhibitor MDM2 at the post-transcriptional level TP53 and via activation of AMPK pathway. Besides, Berberine has exhibited the ability to overcome multidrug resistance, to increase efficacy of drug such as Cisplatin, Tomoxifen and to suppress tumor metastasis (Zhang et al., 2020). Recently, Berberine to be safe and effective in reducing the risk of recurrence of colorectal adenoma in Phase II and III Clinical Trials (Chen et al., 2020).

Polyphenols

Among the secondary metabolites present in plants, the group corresponding to polyphenols is the one with the greatest diversity of compounds, characterized by having within their chemical structure at least one aromatic ring with hydroxyl groups. According to their number of phenolic groups and structural elements, they are mainly divided into phenolic acids, flavonoids, stilbenes, lignans, lignins, coumarins, anthraquinones, xanthones, tannins, curcuminoids, quinones and others (Huang et al., 2010). The polyphenols have multiples health benefits, especially with regard to chronic diseases (Fraga et al., 2019). For example, the polyphenols have shown antioxidant (Luo et al., 2021), anticancer (Zhou et al., 2016), neuroprotective (Spagnuolo et al., 2016), anti-inflammatory (Joseph et al., 2016), antiviral {Formatting Citation}, antidiabetic (Haddad and Eid, 2017), antifungal and antibacterial (Zorofchian Moghadamtousi et al., 2014) effects.

Given the great diversity of compounds, twelve polyphenols have been selected in the present work based on the advances in research carried out as anticancer agents and potential nanophytotherapeutics (Fig. 1). This way, ten of the selected polyphenols have pre-clinical studies about their anticancer activity (Apigenin, Coumarin, Ellagic acid, Epigallocatechin, Fisetin, Honokiol, Naringenin, Quercetin, Resveratrol and Wogonin) and only two have already been part of Clinical Trials (Genistein and Curcumin). A summary with the basic pharmacotherapy of the polyphenols of the TCP group is presented in the Table 1.

Table 1. Basic Pharmacotherapy of polyphenols with pre-clinical studies in cancer

Polyphenol	Cancer Type	Action Mechanism
Apigenin	Bladder, Prostate, Lung, Pancreatic and Colon Cancer, among others (Imran et al., 2020).	Apigenin modulate different hallmarks of cancer such as cell proliferation, apoptosis and autophagy through enhanced expression of pro-apoptotic proteins, activation of caspase cascades, inhibiting PI3K/Akt/FOXO, MAPK/ERK, NF-κB, JAK/STAT, and Wnt/β-catenin signaling pathways (Ahmed et al., 2021).
Coumarin	Breast Cancer, Leukemia, Melanoma and Prostate Cancer (Akkol et al., 2020).	Coumarins target a number of pathways in cancer such as kinase inhibition, cell cycle arrest, angiogenesis inhibition, heat shock protein (HSP90) inhibition, telomerase inhibition and antimitotic activity (Thakur et al., 2015).
Ellagic acid	Prostate, colon, pancreatic, breast, ovarian, bladder, and glioblastoma cancers, as well as lymphoma (Ceci et al., 2018).	Ellagic acid induce apoptosis (Upregulation Bax and downregulation Bcl-2), generate DNA damage (Oxidative stress) and Cell cycle arrest G0/G1 via TGF-β/Smads pathway (Ríos et al., 2018).

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Table 1 Continued

Polyphenol	Cancer Type	Action Mechanism
Epigallocatechin	Cervix, liver, Prostate, Lung, Pancreatic and Colon Cancer among others (Almatrood et al., 2020).	Epigallocatechin can induce apoptosis through the activation of the apoptosis-related molecules and modulation of multiple molecular pathways as well as decreasing the mitochondrial membrane potential in cancer cells and activating caspase-9, Procaspase-3, -6, -7, Procaspase-8, -10. Additionally, Epigallocatechin can arrest cancer cell cycle in G1 phase by regulating cell cycle related proteins (Aggarwal et al., 2020).
Fisetin	Breast, Prostate, Pancreatic Lung Cancer (Imran et al., 2021).	Fisetin activate caspase-9, caspase-3 and upregulate p53, Bax, Bak and down regulate NF-κB and Bcl-2 to generate apoptosis. Besides, Fisetin produces G0/G1 phase arrest through increase in p53 and p21 proteins, and decrease cyclin D1, cyclin A, Cdk- 4 and Cdk-2 (Kashyap et al., 2018).
Honokiol	Colorectar, breast, lung, skin, brain, bone Cancer (Ong et al., 2020).	Honokiol induces apoptosis, suppresses the proliferation, expression of cancer stem cell marker protein, P-glycoprotein number reduction, and radiosensitization through pathways as STAT3, NF-κB, mTOR, EGFR, MAPK, SHH among several others (Rauf et al., 2018b).
Naringenin	Breast, prostate, lung, gastric, colon, bladder, cervical cancers and leukemia (Memariani et al., 2020).	Naringenin inhibite survival signaling pathways such as NF-κB, MAPK and AKT and suppresses MAPK activation to induce cancer cells apoptosis (Zeng et al., 2018).
Quercetin	Breast, gastric, colon, pancreatic, prostate ad Lung Cancer (Rauf et al., 2018a).	Quercetin promotes loss of cell viability, apoptosis and autophagy in cancer by reducing β-catenin and HIF-1α stabilization, inducing caspase-3 activation and inhibiting of Akt, mTOR, and ERK phosphorylation. Quercetin also prevents metastasis by reducing VEGF secretion and MMP levels. By interfering in PI3K/Akt/mTOR pathways, quercetin exerts its metabolic effect on cancer, inhibiting key enzymes of glycolysis and glucose uptake (Reyes-Farias and Carrasco-Pozo, 2019; Tang et al., 2020).
Resveratrol	Breast, Skin, Liver and Prostate Cancer (Ko et al., 2017).	Inhibition Sirt-1/PTEN/PI3K/AKT Upregulation p21/p53 Inhibition AMPK/YAP Inhibition NF-κB/STAT3 Downregulation HIF-1α (Berretta et al., 2020; Elshaer et al., 2018).
Wogonin	Ovarian, colorectal and breast Cancer (Feng et al., 2018; D. Yang et al., 2020; Zhao et al., 2019).	Wogonin induces apoptosis via different mechanisms including DNA fragmentation, PARP degradation, activation of Caspase-3 (but not Caspase-1), induction of Caspase-9 or Caspase-8 cleavage, reduction of Bcl2 family proteins and via ER-stress pathway. Besides, wogonin interferes with the cell cycle, arresting the cells in G1 phase and induces differentiation leading to decreased malignant cell growth (Huynh et al., 2017).

Within selected polyphenols, Curcumin and Genistein have completed phase II and III clinical studies as monotherapy for the treatment of cancer and only Curcumin has also been evaluated as an adjuvant combination therapy to chemotherapy. In this way, Curcumin have been studied to breast and pancreatic cancer and in combination with Plaquitaxel in Advanced Breast Cancer. Moreover, Genistein have been studied to breast, prostate and metastatic Colorectal Cancer and as adjuvant with decitabine in Lung cancer (https://www.clinicaltrials.gov).

Curcumin causes death of cancer cells by cell cycle arrest sequentially in the G1/S and G2/M phases and induce apoptosis through upregulate the expression and activity of p53, inhibition the activity of NF-κB, attenuate the regulation of anti-apoptosis PI3K signaling and decreases anti-apoptotic Bcl-2 protein expression (Liczbiński et al., 2020). Furthermore, curcumin also increase the expression of MAPKs to induce endogenous production of ROS and inhibition of 26S proteasome activity in the context of treatment of cancer (Hassan et al., 2019). On the other hand, Genistein has multitarget activity on cancer pathway (inducing apoptosis, cell cycle arrest, antiangiogenic activity) and antimetastatic potential. Thus, the main molecular targets of genistein include caspases, Bcl-2, Bax, nuclear factor-κB, inhibitor of NF-κB, phosphoinositide 3-kinase/Akt, extracellular signal-regulated kinase 1/2, MAPK, and Wingless and integration 1/β-catenin signaling pathway (Tuli et al., 2019).

Terpenes

Terpenoids are natural hydrocarbons made up of isoprene units (five carbons) as their basic components. Different terpenes include hemiterpenes (C5), monoterpenes (C10), sesquiterpenes (C15), diterpenes (C20), sesterterpenes (C25), triterpenes (C30), and polyterpenes (> C30). This group of metabolites are produced predominantly by plants, particularly conifers (Brahmkshatriya and Brahmkshatriya, 2013). The terpenoid family of natural products has been a valuable source of medical discoveries, for example, currently is known the anti-microbial action of monoterpenes or the psychoactive, anxiolytic and anesthetic effect of derived Meroterpenes such as Cannabinoids (Bergman et al., 2019). We found eight representatives terpenes studied in anticancer nanophytotherapy (Fig. 1).

Docetaxel and Paclitaxel with FDA approbation, Docetaxel for breast, prostate, and non-small cell lung as single agent and in combination with chemotherapy, and Paclitaxel for breast cancer (https://www.fda.gov/ - Drug Approvals and Databases). Both phytochemicals are antimicrotubule agent, whose primary mechanism of action is to bind beta-tubulin, enhancing the action of tubulin dimers and stabilizing current microtubules while inhibiting their disassembly, producing cell cycle arrest during G2/M (Phillips and Petrylak, 2010; Wang and Du, 2018).

Triptolide and Thymoquinone have pre-clinical studies for patients with refractory pancreatic cancer and as chemopreventive on oral potentially malignant lesions, respectively (https://www.clinicaltrials.gov). The activation of apoptosis is one of the major mechanism associated to anticancer effect of Triptolide through different pathways such as activation of caspases and HSP70, NF-kB, ERK1/2, Bcl-2 signaling inhibition (Noel et al., 2019). Otherwise, Thymoquinone has reported antiproliferative activity by means of p53- independent pathway and arrest of cells in the progression of the cell cycle (Banerjee et al., 2010).

Finally, Artemisinin, Ursolic acid, Andrographolide and Oridonin have been studied in diverse pre-clinical assays. For example, Artemisin acts in a multi-specific manner also against hematological malignancies (Mancuso et al., 2021); Ursolic acid inhibits breast cancer cell proliferation (Jaman and Sayeed, 2018); Andrographolide has shown anticancer and preventive effect (Farooqi et al., 2020; Mishra et al., 2015) and Oridonin has been studied as potential antiangiogenic and antimetastatic pharmacology alternative (Abdullah et al., 2021).

Even though the diverse groups of phytochemicals described shown broad anticancer properties, some factors do not contribute to good bioavailability. For example, the polyphenols are associated with low absorption from the gastrointestinal tract, transformation in the intestine, rapid metabolism, and systemic elimination. The action of salivary proteins rich in proline, make polyphenols become insoluble complexes (Adrar et al., 2019). Besides their stability is affected by the action of acidic pH in the stomach and alkaline in the small intestine and as product of their metabolism can present methylations, sulphations and glucuronidations, generating changes in its structure and as a consequence in its biological activity (Mithul Aravind et al., 2021; Squillaro et al., 2018). The alkaloids also do not escape of pharmaceutical challenges. The physicochemical properties presented by this group of compounds have been unfavorable for good bioavailability, due to their low solubility and stability (Zheng et al., 2018). For example, in the case of berberine, a pentacyclic isoquinoline alkaloid, presents poor intestinal absorption and / or bioavailability (Habtemariam, 2020).

NANO-STRUCTURED DELIVERY SYSTEM FOR PHYTOMEDICINE IN CANCER TREATMENT

As mentioned in the previous section, most of the biologically active constituents of plants, such as, alkaloids, polyphenols, flavonoids, tannins, and terpenoids are poorly absorbed from the gastrointestinal tract because of their large molecular weight, high lipophilicity, low water solubility, poor permeability, instability, high first pass metabolism or low which caused problems in clinical trials (Choudhari et al., 2020).

Therefore, sometimes these active constituents need to be given in large quantities, which brings associated problems with its potential toxicity (Martino et al., 2018).

Based on the biopharmaceutical challenges involved with phytochemicals and their delivery, recent advancements in the field of nanotechnology can help to solve many of them by improving solubility, stability (protecting them from degradation and increasing residence time), absorption, targetability, safety, dosage (due to allow sustained drug release) and therefore, their activity, efficacy and even efficiency because allow combination therapy or co-delivery of two or more phytoconstituents or drugs enhancing the therapeutic index (Bagheri et al., 2018; Din et al., 2017; Yang et al., 2020). The Table 2 show the potential of different nano-structured carriers for anticancer phytochemicals delivery.

The Fig. 2 summarizes the most used nano-structured systems and their main advantages for phytomedicine delivery in cancer therapy. As we can see, there are multiple advantages in the use of nanocarriers for nanophytomedicine, particularly in cancer treatment these strategies of delivery, in addition have shown an enhanced permeation and retention (EPR) effect, which improves permeation through barrier due to nano size carrier and the retention caused due to poor lymphatic drainage at the tumor sites. The preferential accumulation of the nanoparticles into the cancer cells, allow a passive targeting without addition of any of ligand moiety, extending half-life of the phytocompound, decreases side effect due to avoid unwanted effects in non-target organs and reduces dosages (Kim et al., 2021). Besides, nanotechological approaches allow flexibility in routes of administration such as oral, transdermal, and parental, among others (Table 2).

Figure 2. Schematic representation of the most commonly nano-structured systems used for phytochemicals delivery in cancer treatment and their main advantages
(Modified from Bagheri et al., 2018; Din et al., 2017; Yang et al., 2020)

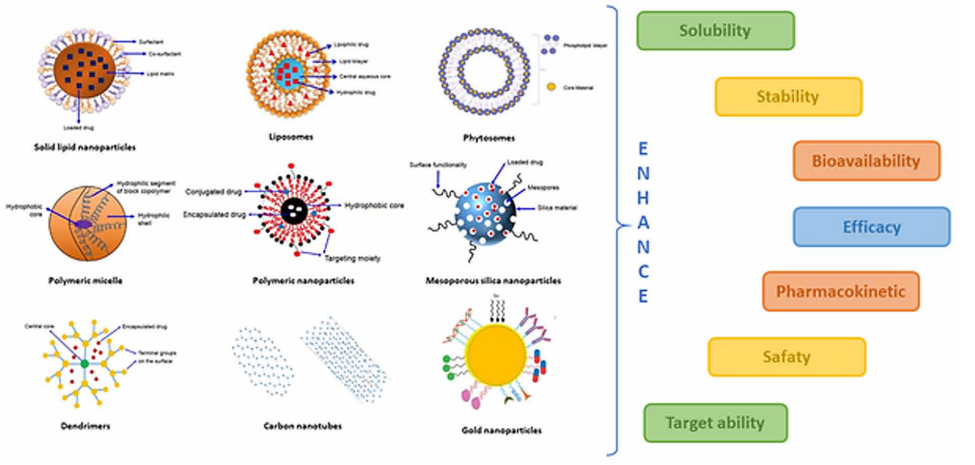

Table 2. List of phytochemicals formulated in nanocarriers for Cancer therapy

Phytochemicals	Nanocarrier Formulation	Route of Delivery	Biopharmaceutical Advantages	Pharmacological Advantages	Reference
ALKALOIDS					
Berberine https://www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=11353 https://go.drugbank.com/drugs/DB04115 Class: benzylisoquinoline alkaloid **Pharmaceutical Problem:** – Poorly soluble due its hydrophobic properties. – Poor stability Low bioavailability.	Nanoemulsion	*in vitro*	↑ stability ↑ oral bioavailability ↑ permeability	-	(Hua et al., 2018)
		in vitro	-	↑ phototoxicity in cervical carcinoma	(Floriano et al., 2021)
	Self-nanoemulsifying drug delivery system	*in vitro*	Approach for improving oral absorption	-	(Ke et al., 2015)
	Folate acid modified chitosan nanoparticle	*in vitro / in vivo*	sustained release	↓ proliferation and migration Promoted apoptosis and necrosis	(Y. Wang et al., 2018)
	Lyotropic liquid crystalline nanoparticles	*In vitro*	↑ solubility ↑ cell uptake	-	(Loo et al., 2020)
Berberine + Diosmin	Casein micelles	*in vitro / in vivo*	↑ targeting ability sustained release ↑ cellular uptake	↓ NF-κB and TNF-α ↓angiogenesis ↑apoptosis.	(Abdelmoneem et al., 2018)
Camptothecin **Class:** Quinoline alkaloid https://go.drugbank.com/drugs/DB04690 **Pharmaceutical Problem:** – Lactone hydrolysis. – Poor aqueous solubility. – Low oral efficacy due to poor absorption and bioavailability. – Some toxic effects.	Solid lipid nanoparticles	*in vitro*	↑ stability	-	(Martins et al., 2012)
	PEGylated Liposomes coated with human serum albumin	*in vivo*	↑ stability ↑ circulation time in the plasma and AUC ↑ accumulation in tumor tissue	↓ Tumor growth (colon adenocarcinoma)	(Watanabe et al., 2008)
	Polymer conjugated	in vitro / in vivo	↑ stability Prolonged intra-tumor retention and sustained release. Improved pharmacological profile.	Tumor regressions (HT29 human colon carcinoma) No toxic deaths	(Caiolfa et al., 2000)
	Hydrophobically modified glycol chitosan nanoparticles	*in vivo*	↑ stability (prolonged blood circulation) ↑ accumulation in tumors ↑ tumor targeting	↓ Tumor growth (MDA-MB231 human breast cancer xenografts subcutaneously implanted in nude mice)	(Min et al., 2008)
	Poly(lactic-co-glycolic acid) microspheres	*In vitro*	↑ stability Sustained delivery	-	(Ertl et al., 1999)
	Self-microemulsifying drug delivery system	*in vitro / in vivo*	↑ oral bioavailability (AUC)	↓ Tumor growth (SKOV-3 human ovarian cancer xenograft in nude mice)	(Lu et al., 2008)
	Microparticles	*In vivo*	↓ dose size	↓ Tumor growth (orthotopic rat model of lung cancer)	(Chao et al., 2009)

continued on following page

Table 2. Continued

Phytochemicals	Nanocarrier Formulation	Route of Delivery	Biopharmaceutical Advantages	Pharmacological Advantages	Reference
Vinblastine https://www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=6851 https://go.drugbank.com/drugs/DB00570 **Class:** alkaloid **Pharmaceutical Problem:** Margins of safety reduced (Toxicity)	Aptamer-nanoparticle bioconjugates	*in vitro*	↑ cellular uptake and internalization capability	↑ Cytotoxicity (Breast Cancer Cells)	(Zhou et al., 2014)
	Liposomes	*in vitro / in vivo*	Sustained release	↓ cells survival ↓ cell proliferation G0/G1 and G2/M arrest (ovarian cancer celis)	(Shah et al., 2018)
	Cationic liposomes	*in vitro / in vivo*	↑drugs across the blood-brain barrier ↑accumulation selective in tumor site	↑ Apoptosis ↓Tumor metastasis through downregulation of PI3K, MMP-2, MMP-9 and FAK. (Glioma cells) In vivo: ↓Toxicity	(Xiao et al., 2018)
	Poly(ethylene glycol)–folate nanoparticles	*in vivo*	↑Tumor-Targeting ↓Toxicity ↓ low release ↓ toxicity	-	(Zhu et al., 2019)
Vincristine https://www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=6785 https://go.drugbank.com/drugs/DB00541 **Class:** alkaloid **Pharmaceutical Problem:** – Margins of safety reduced (Neurotoxicity)	Polymeric nanoparticles (F56 peptide conjugated nanoparticles)	*in vitro / in vivo*	Slower and sustained release ↑nanoparticle distribution	↑ Cytotoxicity ↓proliferation, migration, and tube formation (Colon cancer cells) In vivo assay: ↑Mouse survival ↓lung metastasis in mice Survival	(Lee et al., 2015)
	Liposomes	*in vitro*	↑ site specific drug release ↑ uptake into the tumor	↓ IC_{50} (Lung cancer cell line)	(Thakkar et al., 2012)
	Polymeric magnetic: Dextran shell, with superparamagnetic iron oxide core and was conjugated with folate	*in vitro*	↑ entrapment efficiency ↑ skin permeation Controlled release of drug	↑ Apoptosis through increase of Caspase-9 and P53 expression. ↑ Apoptosis through decrease P21 and AKt1 expression. (Testicular tumor cells)	(Al-Musawi et al., 2021)
POLYPHENOLS					
Coumarin https://go.drugbank.com/drugs/DB04665 **Class:** Coumarins **Pharmaceutical Problem:** – Hidrophobicity	Poly(lactic-co-glycolic acid) nanoparticles	*in vitro*	↑ cellular uptake ↑ bioavailability	↑ apoptotic through down-regulation of cyclin-D1, survivin and Stat-3, and up-regulation of p53 and caspase-3. (melanoma cancer cells)	(Khuda-Bukhsh et al., 2010)

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Table 2. Continued

Phytochemicals	Nanocarrier Formulation	Route of Delivery	Biopharmaceutical Advantages	Pharmacological Advantages	Reference
Curcumin **Class:** Curcuminoid https://www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=7000 https://go.drugbank.com/drugs/DB11672 **Pharmaceutical Problem:** – Low aqueous solubility due to its high hydrophobicity. – Low oral bioavailability due to poor absorption and rapid metabolism.	Monomethoxy poly(ethylene glycol)-oleate micelles	*In vitro*	↑ water solubility ↑ bioavailability	↓ IC_{50} (Brain Cancer cells) ↑ Apoptosis	(Erfani-Moghadam et al., 2014)
	Monomethoxy poly(ethylene glycol)- poly(ε-caprolactone) micelles	*In vivo*	↑ $t_{(1/2)}$ and AUC	↓ Angiogenesis (Zebrafish)	(Gou et al., 2011)
	Copolymeric nanoparticles	*In vitro*	↑dispersion in aqueous medium.	None	(Bisht et al., 2007)
	poly(lactic-co-glycolic acid) nanospheres	*In vitro*	↑ uptake of the nanospheres in prostate cancer cell lines.	↓ IC_{50} (Prostate Cancer cells) ↓ NF-κB activation	(Mukerjee and Vishwanatha, 2009)
	poly(lactic-co-glycolic acid) nanoparticles	*in vitro / in vivo*	↑ water solubility ↑ bioavailability (enhanced absorption by improved permeability, inhibition of P-glycoprotein-mediated efflux, and increased residence time in the intestinal cavity)	-	(Xie et al., 2011)
	Liposomes	*in vitro*	↑ bioavailability	↑ anticancer effects ↓ adverse effects	(Feng et al., 2017)
	Nanostructured lipid carrier	*in vitro / in vivo*	↑ oral bioavailability	↑ cytotoxicity ↑ cellular uptake (HCT116 and HT29)	(Vijayakumar et al., 2019)
	Phytosomes	*in vitro / in vivo*	-	↓ cell growth ↓ tumor number ↓tumor size (colorectal-cancer model)	(Marjaneh et al., 2018)
	Meriva® Curcumin formulated with phosphatidylcholine	*in vivo*	↑ bioavailability	↓ MMP-9 expression ↓ Lung metastasis	(Ibrahim et al., 2010)
	Polymeric micelles	*in vitro*	↑ cellular uptake	↓ Proliferation ↑ Apoptosis (Breast cancer cells)	(Karimpour et al., 2019)
	Micellar nanoparticles	*in vitro*	↑Aerosolization property ↓Side effects	↑ cytotoxicity on lung cancer cells G2/M arrest ↓Interleukin-8 (Lung cancer cells)	(Lee et al., 2016)
	Ethosomes	*in vitro / ex vivo*	↑transdermal permeation Controlled-release	Melanoma skin cáncer	(Krishna Kollipara et al., 2019)
	Dendrimers	*in vitro*	↑ solubility ↑ bioavailability	↑ inhibition of tumor cell proliferation	(Ghaffari et al., 2020)

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Table 2. Continued

Phytochemicals	Nanocarrier Formulation	Route of Delivery	Biopharmaceutical Advantages	Pharmacological Advantages	Reference
	Self-microemulsifying drug delivery system	*in situ* / *in vivo*	↑ solubility ↑ oral absorption	-	(Cui et al., 2009)
	Solid lipid nanoparticles	*in vitro*	↑ uptake efficiency	↑ cytotoxicity ↑ Apoptosis (breast cancer cells) ↑ Bax/Bcl-2 ↓ cyclin D1 and CDK4	(Wang et al., 2018)
	PEGylated solid lipid nanoparticles	*in vivo*	↑ oral bioavailability	-	(Ban et al., 2020)
	Solid lipid nanoparticles with mesoporous silica shells	*in vivo*	↑ Oral delivery ↑ Cell-uptake	-	(Kim et al., 2016)
	Solid lipid nanoparticles	*in vivo*	Enhanced pharmacokinetic (C_{max}, AUC)	-	(Kakkar et al., 2011)
	Immunoliposomes	*in vitro*	↑ uptake at intracellular level ↑ selectivity	↓ IC_{50} (breast cancer cell lines).	(Catania et al., 2013)
	Chitosan nanoparticles	*in vitro / in vivo*	↑ bioavailability	-	(Kar et al., 2009)
Curcumin + Camptothecin **Class:** Polyphenol + Alkaloid	Cationic polymeric nanoparticles	*in vitro*	-	Enhances synergistic effects of anticancer activity in colon-26 cells	(Ruttala and Ko, 2015; Tan and Norhaizan, 2019)
Curcumin + Paclitaxel **Class:** Polyphenol + Terpene	Liposomes	*in vitro*	-	Effectively kills the breast cancer cells compared to individual treatment	Ruttala and Ko, 2015; Tan and Norhaizan, 2019)
Curcumin + Rutin **Class:** Polyphenols	Chitosan nanoparticles	*in vitro / in vivo*	↑ oral bioavailability	-	(Ramaswamy et al., 2017)
Curcumin + Resveratrol **Class:** Polyphenols + Polyphenols	Immunoliposomes	*In vitro*	↑ uptake at intracellular level ↑ selectivity	↑ Antiproliferative activity ↓ IC_{50} (breast cancer cell lines)	(Catania et al., 2013)
Honokiol https://pubchem.ncbi.nlm.nih.gov/compound/72303 **Class:** Lignane **Pharmaceutical Problem:** High hydrophobicity prevents vascular administration	Monomethoxy poly(ethylene glycol)- poly(lactic acid) nanoparticles	*in vitro*	Sustained release	↓ viability of human (ovarian cancer cells)	(Zheng et al., 2010)
	Polymeric nanoparticles (nanoparticles based on epigallocatechin gallate functionalized chitin)	*in vitro / in vivo*	↑Tumor selectivity	↑citotoxicity ↓ cell proliferation of by inhibiting more cells in the G2/M phase ↓ mitochondrial membrane potential. (Liver cancer and lung cancer cell lines).	(Tang et al., 2018)

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Table 2. Continued

Phytochemicals	Nanocarrier Formulation	Route of Delivery	Biopharmaceutical Advantages	Pharmacological Advantages	Reference
Resveratrol **Class:** Stilbenes https://www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=8741 https://go.drugbank.com/drugs/DB02709 **Pharmaceutical Problem:** – Low water solubility – Low oral bioavailability due to poor absorption and rapid metabolism – Low selectivity	Self-nanoemulsifying drug delivery system	*in situ*	Improved release ↑ absorption ↑ permeability ↑ bioavailability	-	(Singh and Pai, 2015)
	Solid lipid nanoparticles	*In vitro*	↑ solubility ↑ stability ↑ intracellular delivery	↓ G2/M phase ↑ S-arrest	(Teskač and Kristl, 2010)
	Immunoliposomes	*in vitro*	↑ uptake at intracellular level ↑ selectivity	↓ IC_{50} (breast cancer cell lines)	(Catania et al., 2013)
	Gold nanoparticles	*in vitro*	↑ cellular uptake	↓ IC_{50} (breast, prostate and pancreatic cancer cell lines)	(Golonko et al., 2019)
Ellagic acid https://go.drugbank.com/drugs/DB08846 **Class:** Tannin **Pharmaceutical Problem:** – Low water solubility	Solid lipid nanoparticles	*in vitro*	↑ targeting ability	↓ proliferation ↓ cell growth (liver, breast and prostate cancer cell lines)	(Badawi et al., 2018)
Ellagic acid + pemetrexed **Class:** Tannin + chemotherapeutic	Lactoferrin coated mesoporous silica nanoparticles	*in vitro*	↑ water solubility ↑ cellular uptake	Synergistic effect in breast cancer cells ↑ cytotoxicity	(Ali et al., 2020)
Anthocyanin **Class:** Flavonoid **Pharmaceutical Problem:** – Highly susceptible to degradation in high pH, light, heat, and oxygen. – Poor bioavailability.	Nanoemulsion and nanoliposome	*in vitro*	↑ physicochemical stability	-	(Chen and Inbaraj, 2019)
Apigenin https://www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=4136 https://go.drugbank.com/drugs/DB07352 **Class:** Flavonoid **Pharmaceutical Problem:** – Low water solubility – Poor bioavailability	Nanogel	*in vitro*	↑concentration and exposure time	↑ apoptosis	(Hashemi and Samadian, 2018)
Fisetin https://www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=5182 https://go.drugbank.com/drugs/DB07795 **Class:** Flavonoid **Pharmaceutical Problem:** – Low water solubility	Monomethoxy poly(ethylene glycol)- poly(ε-caprolactone) micelles	*in vivo* (CT26 animal model)	↑ water solubility. ↑ cellular uptake Sustained release	↑ cytotoxicity ↑ apoptosis ↑ antiproliferation ↑ angiogenesis	(Chen et al., 2015)
	Liposomes	*in vitro / in vivo*	↑ bioavailability ↑ antitumor efficacy	↓ tumor growth (lung carcinoma)	(Seguin et al., 2013)
	Ethosomes	*in vivo*	Improved pharmacokinetic. Improved dermal delivery	↓TNF-α and IL-1α ↓ Tumor incidences (skin cancer)	(Moolakkadath et al., 2019)
Wogonin **Class:** Flavonoid **Pharmaceutical Problem:** – Low water solubility – Low oral bioavailability	Glycyrrhetinic acid modified liposome	*in vitro / in vivo*	↑uptake of liposome in the tumor ↑ bio-distribution	↓ IC_{50} (Liver cancer cell lines) ↓ Liver tumor weight	(Tian et al., 2014)

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Table 2. Continued

Phytochemicals	Nanocarrier Formulation	Route of Delivery	Biopharmaceutical Advantages	Pharmacological Advantages	Reference
Epigallocatechin https://www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=7002 https://go.drugbank.com/drugs/DB03823 **Class:** Flavonoid **Pharmaceutical Problem:** – Instability (very prone to oxidation in aqueous solutions) – Poor intestinal absorbance Reduce efficacy *in vivo.*	Cationic solid lipid nanoparticles	*in vitro*	↑ stability Intrinsic toxicity, due to the surfactant used in its production.	↑or ≈ antiproliferative effect depend on cell lines: Caco-2, HepG2, MCF-7, SV-80 and Y-79).	(Silva et al., 2019)
	Liposomes	*in vitro*	↓ degradation	↑ basal cell carcinomas (BCCs) death	(Fang et al., 2006)
	Chitosan nanoparticles	*In vivo*	↑ efficacy	↓ tumor growth ↑ prostate-specific antigen	(Khan et al., 2014)
	Polymeric nanoparticles	*In vitro*	↑ targeting ability. ↑ efficacy	↓ cell proliferation ↓IC50	(Zeng et al., 2017)
Quercetin **Class:** Flavonoid https://www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=5346 https://go.drugbank.com/drugs/DB04216 **Pharmaceutical Problem:** – Low water solubility – Low oral bioavailability	Polyethylene glycol 4000 liposomes.	*in vitro / in vivo*	↑ solubility ↑ bioavailability	↓ tumor growth *in vivo* ↓ tumor angiogenesis ↑ apoptosis	(Chen et al., 2006)
	polymer-lipid hybrid nanoparticles	*in vitro / in vivo*	↑ bioavailability ↑ cellular uptake and internalization capability ↑ therapeutic index	↑ cytotoxic *in vitro* ↑ antileukemic effects *in vivo*	(Yin et al., 2019)
	Solid lipid nanoparticles	*in situ*	Improved pharmacokinetic. ↑ GI absorption ↑ bioavailability	-	(Li et al., 2009)
	Solid lipid nanoparticles	*in vitro*	-	↓ Colony numbers ↓ IC_{50} ↑ apoptotic and necrotic indexes ↑ Bax expression ↓ Bcl-2 expression ↑ ROS and MDA (Breast cells)	(Niazvand et al., 2019)
	Poly(lactic-co-glycolic acid) nanoparticles	*in vitro / in vivo*	-	In liver cancer cells: ↓ Proliferation ↑ apoptosis through Cyto-c/caspase pathway ↓ colony formation ↓ cell growth through Akt/ERK1/2 and AP-2β/hTERT pathway inactivation In xenograft tumor model: ↓ Tumor volumes ↓ Tumor weights	(Ren et al., 2017)
	Ethylcellulose nanoparticles	*ex vivo*	Sustained release ↑ skin retention ↓ dose and administration frequency	-	(Sahu et al., 2013)
Quercetin + Doxorrubicin **Class:** Polyphenols + Chemotherapeutics	Phytosomes (nano-quercetin)	*in vitro*	↑ therapeutic efficacy	↑ apoptosis	(Minaei et al., 2016)

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Table 2. Continued

Phytochemicals	Nanocarrier Formulation	Route of Delivery	Biopharmaceutical Advantages	Pharmacological Advantages	Reference
Quercetin + Vincristine **Class:** Polyphenols + Alkaloid	Liposomes	*in vivo*	Prolonged plasma circulation of the two drugs	Maintained the synergistic drug ratio. Effective tumor growth inhibition in human breast tumor xenograft	(Wong and Chiu, 2011)
Quercetin + alantolactone **Class:** Polyphenols + Terpene	Micelles	*in vivo*	Synergistic effect ↑ therapeutic efficiency	↓Tumor growth	(Zhang et al., 2019)
Genistein https://www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=2826 https://go.drugbank.com/drugs/DB01645 **Class:** Flavonoid **Pharmaceutical Problem:** – Low water solubility – Low bioavailability – Low stability (instability to high temperatures, pH, oxygen)	PEGylated silica nanoparticles	*in vitro*	↑ aqueous dispersibility	Antiproliferative effects on colon cancer cells: ↑ apoptosis ↑ autophagy	(Pool et al., 2018)
	Biodegradable nanoparticles	*in vitro / in vivo*	↑ cellular uptake	↑ cytotoxicity ↓ tumor cell growth	(Zhang et al., 2015)
Naringenin https://www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=10298 https://go.drugbank.com/drugs/DB03467 **Class:** Flavonoid **Pharmaceutical Problem:** – Poor solubility in water and slow dissolution rate. – Low bioavailability at the tumor site.	Polymeric biodegradable nanoparticles	*in vitro*	-	↑ anticancer potential	(Fuster et al., 2020)
	Multi-Walled Carbon Nanotubes	*in vitro*	Prolonged release in the tumor pH environment.	↑ anticancer effect on skin and lung cell line	(Morais et al., 2020)
	Poly(lactic-co-glycolic acid) nanoparticles	*in vitro*	Sustained release behavior	↑cytotoxic effect	(Akhter et al., 2020)
TERPENES					
Andrographolide https://www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=9675 https://go.drugbank.com/drugs/DB05767 **Class:** Diterpenoid **Pharmaceutical Problem:** – Clinical efficacy by oral administration is contrasted by its biopharmaceutical properties.	Biodegradable nanoparticles	*in vitro*	Improved biopharmaceutical Properties: Sustained release	-	(Chellampillai and Pawar, 2011)

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Table 2. Continued

Phytochemicals	Nanocarrier Formulation	Route of Delivery	Biopharmaceutical Advantages	Pharmacological Advantages	Reference
Artemisinin https://www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=9954 https://go.drugbank.com/drugs/DB13132 **Class:** Sesquiterpene **Pharmaceutical Problem:** – Low bioavailability due to its low solubility. – Rapid metabolisms produce an initial burst effect and high peak plasma concentrations. Not very stable (opening of the lactone ring)	Nanocapsule	*in vitro*	↑ hydrophilicity ↑Sustained drug release	-	(Chen et al., 2009)
Dihydroartemisinin (Artenimol) https://www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=9957 https://go.drugbank.com/drugs/DB11638 **Class:** Sesquiterpene **Pharmaceutical Problem:** – Insoluble in water and poorly soluble in lipid – Short half-life	Magnetic nano-liposomes	*in vitro / in vivo*	Improved targeting antitumor efficiency ↑ bioavailability	Cycle G1 block ↑Apoptosis (Head and neck squamous cell carcinoma). ↓ Tumor size ↓ Tumor weight	(Li et al., 2019)
Docetaxel https://www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=6809 https://go.drugbank.com/drugs/DB01248 **Class:** Taxane **Pharmaceutical Problem:** Low solubility and high lipophilicity	Polymeric nanoparticles: NGR-PM–docetaxel. Asn-Gly-Arg motif with PEG-b-PLA copolymer.	*in vitro / in vivo*	↑ sustained drug release	↑ in vivo antitumor activity ↓ IC_{50} (Prostate cancer cell lines)	(Zhao and Astruc, 2012)
	Chitosan microspheres	*in vitro / in vivo*	↑accumulation in lung cancer cells Sustained release	-	(Wang et al., 2014)
Docetaxel + Nicotinamide **Class:** Terpene + Vitamin	Nanostructured lipid carrier	*in vitro / in vivo*	↑ solubility ↑ skin permeation ↑ skin retention	-	(Fan et al., 2013)
Paclitaxel https://www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=2770 https://go.drugbank.com/drugs/DB01229 **Class:** Taxane **Pharmaceutical Problem:** Toxicity	Nanoparticles coated with polydopamine and grafted by alendronate as ligand.	*in vitro / in vivo*	Sustained release in vitro Targeted delivery in vivo ↑ accumulate in tumor. ↓ side effects in vivo	↑ Cytotoxicity (Osteosarcoma cells) ↓ Tumor tumor volumen	(Zhao et al., 2019)
	Biotin functionalized PEGylated poly(amidoamine) dendrimer	*in vitro*	Efficient targeted drug delivery	↑ Cytotoxicity on A549 cell line (human non-small cell lung cancer) ↓ growth tumor	(Rompicharla et al., 2019)
	PEGylated phospholipid particles	*in vitro*	↑ encapsulation efficiency	-	(Meenach et al., 2013)
	chitosan hollow nanoparticles	*in vitro*	↑cellular uptake	↓Proliferation ↑Apoptosis (Lung cancer cells)	(Jiang et al., 2017)

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Table 2. Continued

Phytochemicals	Nanocarrier Formulation	Route of Delivery	Biopharmaceutical Advantages	Pharmacological Advantages	Reference
	Chitosan-modified poly(lactide-co-glycolic acid) nanoparticles	*in vitro*	↑cellular uptake	↑Citotoxicity (Lung cancer cells)	(Yang et al., 2009)
Paclitaxel + β-Lapachone **Class:** Terpene + Naphthoquinone	Micelles	*in vitro*	↑ solubility ↑ half-life ↑ delivery efficiency	Synergistic cytotoxicity effect against the NQO1 overexpressing cancer cells, including A549 NSCLC cells, and several pancreatic cancer cells.	(Rompicharla et al., 2019)
Oridonin https://pubchem.ncbi.nlm.nih.gov/compound/5321010 **Class:** Diterpenoid **Pharmaceutical Problem:** – sPoorly water-soluble	Self-nanoemulsifying drug delivery system	*in vitro / in vivo*	Enhanced pharmacokinetic (C_{max} and AUC) ↑oral bioavailability	-	(Zhang et al., 2008)
Thymoquinone https://go.drugbank.com/drugs/DB16447 **Class:** Diterpenoid **Pharmaceutical Problem:** – Poorly water solubility. – Low bioavailability after oral administration.	Nanostructured lipid carrier	*in vitro*	-	↑ apoptosis cell cycle arrest (breast cancer and cervical cancer cell lines)	(Ng et al., 2015)
	Self-nanoemulsifying drug delivery system	*in vivo*	Enhanced pharmacokinetic (C_{max} and AUC) ↑ absorption ↑ oral bioavailability ↓ side effects	Improved anticancer activity. Hepatoprotective effect	(Kalam et al., 2017)
	Nanoemulsion	*in vivo*	↓ toxicity after acute exposition	-	(Tubesha et al., 2013)
	pH-dependent mesoporous silica core-shell nanoparticles	*in vitro*	controlled release	↑ caspase-3 activation cell cycle arrest at G2/M ↑ apoptosis	(Shahein et al., 2019)
	Polymeric micelles	*in vitro*	controlled release	↓ IC_{50}	(Shaarani et al., 2017)
Triptolide https://go.drugbank.com/drugs/DB12025 **Class:** Diterpenoid triepoxide **Pharmaceutical Problem:** – Poor water solubility. – High toxicity	Cationic liposomes	*in vitro / in vivo*	↑ uptake into the tumor ↓ toxicity	↑ apoptosis ↓ volume and weight of the tumor (breast cancer)	(Zheng et al., 2019)
	Polymeric pH-sensitive nanoparticles coated with folate	*in vitro / in vivo*	↑ solubility ↑ site specific drug release ↑ uptake into the tumor ↓ toxicity	Orthotopic Mouse Models-liver cancer: ↓ Tumor size ↑ Survival Mice Liver Cells: ↑ apoptosis	(Ren et al., 2017)
	PEGylated nanoparticles	*in vitro / in vivo*	-	None	(Wang et al., 2018)

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Table 2. Continued

Phytochemicals	Nanocarrier Formulation	Route of Delivery	Biopharmaceutical Advantages	Pharmacological Advantages	Reference
	Polymeric nanocarrier	*in vitro / in vivo*	-	↓ Cell viability (Pancreatic cancer cells) In vivo assay: ↑cell necrosis and inflammatory cell infiltration ↑ inhibition cancer cells.	(Wang et al., 2016)
Ursolic acid https://pubchem.ncbi.nlm.nih.gov/compound/64945 https://go.drugbank.com/drugs/DB15588 **Class:** triterpene **Pharmaceutical Problem:** – Low solubility – Poor bioavailability	Poly(lactic-co-glycolic acid) nanoparticles	*in vitro* (cervial cancer cell) and *in vivo*		↓ proliferation ↑ apoptosis ↓ tumor size	(Wang et al., 2017)
	Chitosan nanoparticles	*in vitro / in vivo*	-	↓proliferation, migration, and tube formation of human umbilical vascular endothelial cells	(Jin et al., 2016)
	pH-Sensitive mesoporous silica nanoparticles	*in vitro*	↑ cellular uptake Controlled release	↓ proliferation G2/M arrest ↑apoptosis	(Li et al., 2017)
	Liposomes	*in vitro*	-	↓ proliferation in breast and prostate cells. ↓IC_{50}	(Caldeira De Araújo Lopes et al., 2013)
	PEGylated liposomes	*in vitro*	↑ stability than conventional liposomes Sustained release ↑ Uptake in tumor tissues	↓ cytotoxic effect	(Zhao et al., 2015)
OTHERS					
Avicequinone-B https://pubchem.ncbi.nlm.nih.gov/compound/79740 **Class:** Furanonaphthoquinone **Pharmaceutical Problem:** Hydrophobic compound with poor aqueous solubility	Liposomes	*in vitro*	↑ aqueous solubility	↑ cytotoxic effect on cutaneous squamous cell carcinoma cells	(Hu et al., 2019)
β-Lapachone https://go.drugbank.com/drugs/DB11948 **Class:** Naphthoquinone derivative **Pharmaceutical Problem:** – Low water solubility – Short blood half-life – Non-specific distribution – Narrow therapeutic window	Gold nanoparticles	*in vivo*	↑ targeting ability	↑radiotherapeutic efficacy	(Jeong et al., 2009)
	Poly(ethylene glycol) and polylactide acid micelles	*in vitro*	-	↑ cytotoxicity on lung, prostate, and breast cancer cells.	(Blanco et al., 2007)

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Table 2. Continued

Phytochemicals	Nanocarrier Formulation	Route of Delivery	Biopharmaceutical Advantages	Pharmacological Advantages	Reference
	Polymeric micelles	*in vitro*	↓ side-effects (preferential accumulation in tumors) ↑ maximum tolerated dose ↑ stability ↑ blood circulation time	↑ antitumor efficacy in treating orthotopic non-small cell lung tumors that overexpress NQO1.	(Ma et al., 2015)
	Cationic solid lipid nanoparticles	*in vitro*	↑ stability Intrinsic toxicity, due to the surfactant used in its production.	↑or ≈ antiproliferative effect depend on cell lines: Caco-2, HepG2, MCF-7, SV-80 and Y-79).	(Silva et al., 2019)
	Liposomes	*in vitro*	↓ degradation	↑ basal cell carcinomas (BCCs) death	(Fang et al., 2006)
	Chitosan nanoparticles	*In vivo*	↑ efficacy	↓ tumor growth ↑ prostate-specific antigen	(Khan et al., 2014)
	Polymeric nanoparticles	*In vitro*	↑ targeting ability. ↑ efficacy	↓ cell proliferation ↓IC50	(Zeng et al., 2017)
Emodin https://go.drugbank.com/drugs/DB07715 **Class:** Anthraquinone **Pharmaceutical Problem:** – Poor solubility	Solid lipid nanoparticles	*in vitro*	↑ aqueous solubility Sustained release	↑ cytotoxicity on human breast cancer cell line G2/M arrest ↑ apoptosis	(Wang et al., 2012)
Gambogic acid https://pubchem.ncbi.nlm.nih.gov/compound/9852185 **Class:** Xanthonoid **Pharmaceutical Problem:** – Poor solubility – Inadequate oral bioavailability	Graphene and single-walled carbon nanotubes	*in vitro*	-	No toxicity ↑ antiproliferative effects in breast and pancreatic cancer cells	(Saeed et al., 2014)
Gambogic acid + Indocyanine green **Class:** Xanthonoid + fluorescent dye	Red cell membrane coated bovine serum albumin nanoparticles	*in vitro / in vivo*	long-term circulation	Synergistic chemo-photothermal therapeutic efficacy.	(Wang et al., 2020)
Lycopene https://go.drugbank.com/drugs/DB11231 **Class:** Carotenoid **Pharmaceutical Problem:** – Stability (susceptible to oxidants, light, and heat)	Niosomes	*in vitro / in vivo*	Sustained release Improved pharmacokinetic (C_{max} and AUC) ↑ oral bioavailability ↑ entrapment efficiency	↑ apoptosis *in vitro*	(Et Al, 2016)

In this sense, developing of new drug delivery system based on nano-structures such as polymeric systems: nanoparticles, nanocapsules, micelles, dendrimers and nanogels; lipid-based nano-systems such as solid lipid nanoparticles, liposomes, phytosomes, niosomes, nanoemulsions; inorganic nanostructures as carbon nanotubes and mesoporous silica nanoparticles or gold nanoparticles, among others, have shown many advantages to deliver phytochemicals in cancer therapy (Table 2).

Nano-structured systems help in the modulation of physicochemical and biopharmaceutical characteristics of the phytochemicals since they are known to modify the hydrophobic surface of the drugs (Cui et al., 2009). As far as solubility

improvement is concerned, most work are focused on improving the aqueous solubility of the high hydrophobic or poorly aqueous soluble phytoactives, such as curcumin, resveratrol, fisetin, quercetin, triptolide, artemisin, avicequinone, emodin and genistein, among others (Table 2). At this point, is important to mention that solubility is not an isolated parameter. It is always associated with drug dissolution, distribution, local availability, and bioavailability. Therefore, improvements in solubility are also associated with pharmacokinetics parameters as absorption, permeability, and bioavailability.

Pharmacokinetic properties get affected by different routes of administration and the amount of drug administered. Nano-structured systems for phytochemicals are designed to alter the pharmacokinetic pattern of the isolated natural compounds. The incorporation in a nano-structured system by encapsulation, conjugation, or other mechanism, involves surface modification of the molecule and hence modifies the rate of absorption of the less absorbed drugs. In this context, the utility of nanostructured lipid carriers as nanoemulsions, liposomes, solid lipid nanoparticles and many more have demonstrated to improve solubility, which also improve absorption, permeability and in consequence bioavailability and efficacy (Chen et al., 2016). In the case of curcumin, liposomes, solid lipid nanoparticles and self-microemulsifying drug delivery system (SMEDDS) have shown to improve considerably its solubility and oral absorption (Table 2). Other lipophilic drugs as paclitaxel, docetaxel and camptothecin have shown to improve their bioavailability when are formulated in nano-structured systems (Table 2).

Due to bioavailability also depends on various factors (ie drug solubilization at blood pH, absorption of the drug, distribution of the solubilized drug into systemic circulation, first-pass metabolism, gastrointestinal stability, molecular weight of the drugs, etc.), many efforts have been made in enhancing stability of phytochemicals. Examples of phytomolecules very prone to chemical unstability (hydrolisis and oxidation) are camptothecin, anthocyanin, lycopene, epigallocatechin and ursolic acid, whilst curcumin, resveratrol and artemisinin are examples of phytocompound which suffering from extensive first-pass metabolism. In both cases, after being formulated in nanocarrier systems have demonstrated to improve their stability. The nanoformulations tend to reduce extent of hepatic first pass metabolism, and gastric pH mediated degradation, so overall enhancing bioavailability of orally administered drugs (Table 2).

According to Fig. 2, formulations of phytochemicals based on nano-structurated systems improve efficacy prolonged blood circulation, EPR effect and high deposition in tumors, example of this are camptothecin nanoformulations (Caiolfa et al., 2000; Min et al., 2008). In addition, in most nanoformulations have been possible to observe a sustained release effect that significantly decreases the dose size, improving its

safety profile, good examples are nanoformulations of camptotecin (Chao et al., 2010) and quercetin (Sahu et al., 2013).

Regarding to toxicity, triptolide, vincristine and paclitaxel are some examples of phytocompounds that have reduced their toxicity by improving targeting antitumor efficiency when are loaded into nano-structurated delivery systems (Table 2). Improved target ability is meant to specify a drug target and help them achieve highest concentration of drug for optimum therapeutic effect at the desired site of action and avoid their distribution in other tissues and organs, which also helps reduce toxic effects. In general, to improve target ability leads to increase efficacy and reduce toxic effects. In this regard, dihydroartemisinin, honokiol, lapachone, camptothecin and triptolide are some examples of phytocompund that have shown specific distribution and accumulation in tumors when are formulated in nano-structured carriers, which makes them safer for potential clinical use (Table 2).

The delivery of nano-structured systems containing anticancer drugs as camptothecin and paclitaxel has been investigated with significant success. In this way, a completed phase II study was performed with cyclodextrin-based polymer-camptothecin [CRLX101] for advanced gastric, gastroesophageal, or esophageal squamous or adenocarcinoma and non-small cell lung cancer. On the other hand, liposomal paclitaxel has demostred clinical efficacy (phase II) in advanced or metastatic esophageal carcinoma (https://www.clinicaltrials.gov). Considering this, is important to mention that the research in phytonanoformulations is moving from pre-clinical assays to clinical trials. In fact, nowadays there are commercial formulations based on nano-phytotherapeutics approved by the FDA for cancer therapy (Table 3). For example, vincristine was approved in a liposomal formulation, which demonstrated enhanced efficacy with reduced toxicity. Paclitaxel in albumin nanoparticle formulation showed to increase the solubility and the bioavailability resulting in a higher concentration of the drug in the tumor and simultaneously to reduce its toxicity. Table 2 shows some additional nanosystem based strategies for this purpose. Finally, a semisynthetic derivative of camptothecin liposomal formulations (Irinotecan) was approved in combination with fluorouracil and leucovorin, as therapy for metastatic pancreatic cancer in patients when gemcitabine-based chemotherapy failed (Table 3).

FUTURE RESEARCH DIRECTIONS

This chapter has described the advances in the use of nanophytoformulations as drug in cancer therapy at the level of pre-clinical and clinical trials, and in addition discussed the application of the nano-structured systems in the optimizing their formulations and how this help to enhance their physicochemical and biopharmaceutical properties and hence their therapeutic efficacy.

Table 3. Nanophytotherapeutics for cancer approved for the FDA

Phytocompound	Nano-structured System	Indication	FDA Approval	Reference
Paclitaxel	Protein based nanoparticles (Abraxane®)	Lung cancer and metastatic breast cancer	2013	(Anselmo and Mitragotri, 2016; Harshita et al., 2019; Ventola, 2017).
Vincristine	Non-PEGylated liposomes (Marqibo®)	Acute lymphoblastic leukaemia	2012	
Irinotecan	PEGylated liposomes (Onivyde®)	Metastatic pancreatic cancer	2015	

(https://www.fda.gov/)

We believe that, in the coming years, the continuous development of nanotechnology in the field of the nanocarriers and the increasing interest in the use of natural products in wester (traditional) medicine, will allow us to have a wide range of optimized nanophytotherapeutics, which will generate greater efficacy and safety of pharmacological therapies for the routine management of cancer patients.

Nanomedicine will become in a solution that will promote the development of phytoformulations more biocompatible and much more stables and effectives, due to the optimized nanophytherapeutics would contribute to improve the specificity of the phytochemicals, improve their absorption rates, reduce their degradation, and decrease their systemic toxicity in cancer therapy.

Increasingly there will be a greater interaction between the area of phytochemistry and nanotechnology, aimed at improving oral bioavailability, aqueous solubility, metabolism, and its systemic elimination (physicochemical and biopharmaceutical properties). This improvement should be aimed at ensuring that most of the biologically active components of plants, such as alkaloids, flavonoids, tannins, terpenoids and particularly polyphenols are better absorbed, have better feasibility to be used in clinical trials.

CONCLUSION

Nano-structured delivery systems show immense potential in delivering phytomedicine by providing better alternatives than conventional dosage forms compared to isolated conventional phytocompounds. This is due to their tremendous ability in the improvement of solubility, pharmacokinetic parameters such as absorption, distribution, metabolism and excretion, bioavailability, targeting ability, efficacy, and safety. In addition, they itself have therapeutic benefits such as cationic solid

lipid nanoparticles used for delivering epigallocatechin gallate has shown intrinsic toxicity, due to the surfactant used in its production (Silva et al., 2019). Particularly, in cancer therapy, phytomedicine based on nanocarrier systems has been development to address them to tumor site, because nano-systems allow to modify physicochemical properties of the drugs and offer targeting ability additional to their specificity. However, despite of all tremendous advantages mentioned, very few phytomedicines have reached clinical use. This could be explained considering the follow still existing challenges: scaling-up for production, the high cost of preparation and the low shelf life of this type of formulations associated to their stability problems (i.e. particle aggregation) (Hua et al., 2018).

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Chapter 5
Potential Cancer Biomarkers

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ABSTRACT

Extensive studies in the field of oncology are able to identify potential cancer biomarkers with tumor-specific molecular characteristics that exceed or complement those of existing biomarkers. However, there are challenges in the development and clinical validation of the cancer biomarkers due to the complexity of the biological process involved. Standalone or integrative approach of broad range of biomolecules, their expression pattern, epigenetic alterations, and metabolic effects are well studied in the cancer research. The potential cancer biomarkers need to be studied extensively with advanced technologies to bring about a great change in cancer screening and therapy. This chapter provide an overview on recent studies about potential cancer biomarkers. Also, specific characteristics of potential biomarkers in three common types of cancer are discussed.

INTRODUCTION

Cancer remains the second leading cause of death around the world (Nalejska, 2014; Wild, 2014). Though cancer affects almost every organ system; most affected organs are lung, breast, prostate, colon and rectum, stomach and skin. Effective cancer treatment strategies depend on many factors such as assessment of individuals susceptibility and early-stage detection. Effective cancer screening strategies

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depend on less labor-intensive, economical, and non-invasive methods. Cancer detection in their early stages of development is very crucial in providing therapies efficiently. Biological molecular markers are commonly used for cancer screening. A biomarker is described with a "characteristic that it is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" (Biomarkers Definitions Working Group 2001). Biomarkers detected using molecular biology tools provide evidence that are crucial for molecular characterization of cancer phenotypes and personalized treatment. Based on the purpose, they can be useful in diagnostic, prognostic, treatment and prevention (Nalejska, 2014). Diagnostic biomarkers are used for screening and early detection. Prediction biomarkers are staging markers for risk stratification. Prognostic biomarkers help to understand the cancer recurrence and metastatic. Treatment biomarkers are used in selection and therapy response prediction (Hoseok, 2015).

Identifying potential cancer biomarkers as a tool in diagnostic, prognostic, or therapeutic information has been challenging. Biomarker-based personalized cancer therapy helps in treatment decisions based on tumor genotypes and genetic profiles (Kalia, 2015; Maruvada 2005). Main challenge is the criteria to select, interpret, and apply these new genetic and genomic assays (Li, 2013). Currently, some available biomarkers with clinical applications (e.g., prostate-specific antigen for prostate cancer, alpha-fetoprotein for liver cancer, carcinoembryonic antigen for colorectal cancer, cancer antigen 125 for ovarian cancer, and cancer antigen 19–9 for pancreatic cancer) are less sensitive. Therefore, there is a need for more reliable biomarkers that act as precise indicators of tumorigenesis at the cellular levels and for better therapeutic outcome.

POTENTIAL CANCER BIOMARKERS

Any biomolecule or biological processes which may lead to a cancer prognosis, screening, risk assessment or therapy are potential candidates as cancer biomarkers (Mishra, 2010). There is an abnormal expression of specific biomolecules such as peptides, proteins, and nucleic acids in cancer tissues that can be considered as potential candidates for biomarkers. A biomarker can also be a collection of alterations that leads to change in the gene expression or variant protein or metabolic product (Henry, 2012). Types of potential biomarkers may include micro RNAs (miRNAs), circulating long non-coding RNAs (lncRNAs), extracellular vesicle (EV)-associated proteins, circular RNAs (circRNAs), messenger RNAs (mRNAs), enzymes, genetic variants and epigenetic modifications (Fig. 1).

Circulating miRNAs are small, non-coding RNA molecules that can regulate gene expression and may act as potential oncogenes or tumor suppressors. Thus, they are considered as potential biomarkers for cancer screening. Abnormal expression profiles of regulated miRNAs in both tumor paraffin sections and body fluids with high specificity, sensitivity, and stability shows its potential as cancer biomarkers (Matsuzaki, 2017). Moreover, miRNA microarrays and high-throughput techniques are being used in understanding altered miRNA expressions to correlate it with occurrence of human carcinogenesis (Biomarkers Definitions Working Group 2001).

Extracellular vesicles (EV) are small membrane-bound structures that helps in local and distant cell-to-cell communication. Tumor-derived EVs modifies the microenvironment and evades the immune system. Thus, facilitate metastasis and angiogenesis (Matsuzaki, 2017). Micro-RNAs contained within EVs are functionally associated with cancer phenotypes. Understanding the physiological alterations in EVs during tumorigenesis helps to design better therapeutic approach. Considering these factors and their stability in body fluids, investigations are being carried out to elucidate the role of EV-derived miRNAs as tumor biomarkers (Kinoshita, 2017).

Circulating long non-coding RNAs (lncRNAs) regulate gene expression but lack protein-coding potential. They play important role in modulating mRNA stability and maintaining nuclear architecture. Specific combinations of lncRNAs with other circulating markers have been studies as potential biomarkers for cancer detection as it can be involved in tumorigenesis and tumor metastasis. They are uniquely expressed in differentiated tissues or specific cancer types. However, extensive studies may be required to demonstrate their reproducibility in the clinical applications (Matsuzaki, 2017).

Circular RNAs (circRNAs) are novel class of endogenous noncoding RNAs with diverse cellular functions. circRNAs can function as cancer diagnosis biomarker as it plays an important role in cancer development and progression. circRNAs could be molecular markers of cancer associated with stomach, liver, lung, colon and circulatory system (Henry, 2012).

Messenger RNAs (mRNAs) could be considered as noninvasive biomarkers for tissue or organ specific biomarkers for diagnosis and prognosis of cancer. For example, in many cancer types, the ubiquitin-conjugating enzymes 2C (UBE2C) mRNA and/or protein expression was abnormally high. Functional studies demonstrated that UBE2C variant expression was associated with spontaneous tumors and carcinogen-induced tumor with evidence of chromosome aneuploidy. Cell proliferation and anchorage-independent growth was stimulated by overexpression and accumulation of UBE2C (Xie, 2014).

Mitochondrial DNA (mtDNA) mutations have been associated with different types of cancer. It has been reported that there is no single mutational hotspot associated with the wide spectrum of cancer phenotypes; hence, sequencing and characterization

of the entire mitochondrial genome is required to detect the precise mutation load (Jakupciak, 2006). Mitochondrial microarray technology and real-time PCR can be used to detect variations in the entire mitochondrial genome that which has predictive potential for cancer detection and prognosis. mtDNA mutation analysis may provide a molecular tool for the early cancer detection as the mutations occur as recurrent events in primary tumor tissues and can be analyzed from non-invasively collected body fluids though validation need to consider.

Integration of methods, technologies and data set may enrich the understanding and application of such novel biomarker in cancer studies (Matsuzaki, 2017). The clinical studies and basic research findings in a large scale helps in the broader decoding of the interactive pathways in the biological system.

POTENTIAL BIOMARKERS IN THREE MOST COMMON TYPE OF CANCERS

Lung Cancer

Protein biomarkers studied with regard to lung cancer diagnosis, prognosis and therapy shows great significance. An *in vitro* carcinogenesis model identified PGP9.5 (protein gene product 9.5/ ubiquitin COOH-terminal esterase L1), TIMP-2 (Tissue inhibitors of metalloproteinases-2), TCTP (translationally controlled tumor protein), and TPI (triosephosphate isomerase) as potential lung cancer biomarkers. PGP9.5 is an enzyme (ubiquitin hydrolase) that is commonly expressed as neuron cytoplasmic protein during neuronal differentiation. PGP9.5 expression was strongly associated with lung cancer pathology. In addition, mutations leading to alterations in the expression of cell-cycle regulators may indicate multiple cancer types. TIMP-2 protein is involved in regulating cellular functions such cell growth, differentiation, and apoptosis and its expression was decreased in human malignancies. TCTP is a highly conserved protein expressed in various tissues and is associated with cell cycle and apoptosis. TCTP protein expression is increased in various human tumor tissues that are mainly a part of digestive and reproductive systems. It has IgE-dependent histamine releasing activity and can be studied for potential therapeutic application leading to tumor reversion. TPI is a highly conserved enzyme that plays a major role in glycolysis and other metabolic pathways and it was significantly overexpressed in lung cancer tissues (Kim, 2008). Other potential lung protein biomarkers include serum amyloid, haptoglobin, plasma kallikrein protein fragments, complement component 9, complement fragment C4d, matrix metallopeptidase 9, insulin-like growth factor binding protein, peroxiredoxin, progesterone receptor

membrane component 1 protein, nuclear protein-Ciz1, and cell surface receptor-uPAR1 (Hoseok, 2015).

Micro RNAs (miRNAs) are studied widely and considered as promising biomarkers for noninvasive lung cancer screening. For example, miRNA-34 was studied to understand the early stage lung cancer detection (Bianchi, 2011). miRNAs such as miR-7, miR-21, miR-200b, miR-210, miR-219-1, miR-324 were upregulated; and miR-126, miR-451, miR-30a, and miR-486-5p were downregulated in lung cancer tissues compared to the normal. These miRNAs expression was found to be highly sensitive and specific (Boeri, 2011; Gayosso-Gomez, 2021; Shen, 2011).

Epigenetic modification of certain genes was studies as potential markers in lung carcinoma. Atypical methylation pattern of many gene promoters has been reported to be strongly associated with lung cancer risk. Studies shows that methylation of p16, SHOX2, BRMS1, Septin 9, TMEFF2 genes in the plasma were also associated with lung cancer. It was reported that lung cancer survivors, the hypermethylation of the certain enzymes and proteins such as O(6)-methylguanine DNA methyltransferase (MGMT), ras effector homologue 1 (RASSF1A), death-associated protein kinase (DAPK), and PAX5α in sputum was significant compared with smokers (Constancio, 2020).

Circulating tumor cells (CTCs) are defined as cells shed by a primary tumor; that shows a significant high concentration in plasma of lung cancer patients. Cancer cells metastasize through the bloodstream as single CTC or cluster in a consistent manner and it may be less invasive method for lung cancer screening (Huang, 2018). Thus, CTCs may be studies as a promising biomarker for lung cancer with good sensitivity and specificity.

Breast Cancer

Micro RNAs are studied as potential candidates for screening breast cancer in early prognosis or diagnosis. The expression pattern of seven miRNAs (miR-10b, miR-21, miR-125b, miR-145, miR-155 miR-191 and miR-382) in the serum breast cancer patients has been demonstrated. In this study, miR-145, miR-155 and miR-382 profiles showed a better sensitivity and specificity (Mar-Aguilar, 2013). Breast cancer miRNA profiling studies showed consistent upregulation of miR-21 and miR-210; and downregulation of miR-145, miR-139-5p, miR-195, miR-99a, miR-497 miR-205 and miR-622. Metastasis of breast cancer cells were associated with modulation of miR-622 expression profile and its functional target enzyme (NUAK1 kinase/threonine-protein kinase) which is associated with cell proliferation and tumor progression. In breast cancer patients, miR-622/NUAK1 axis is deregulated and affects the motility phenotype of breast cancer cells (Orlandella, 2020). Studies reported that circulating tumor associated miRNAs have the potential to detect breast

cancer and can differentiate tumors according to histologic features. Higher levels of miR-21 was associated lymph node metastasis and advanced cancer stage (Heneghan, 2010). miR-10b is highly expressed in metastatic breast cancer cells and play a part specifically in the tumor metastasis. In addition, there is a significant association between miR-10b and the hormonal status of breast cancers (Ma, 2007). Moreover, multiple gene expression associated with tumor phenotype such as miR-622/NUAK1 expression and miR-10b are studied as potential biomarkers for breast cancer.

Many potential protein biomarkers are studied with regard to breast cancer diagnosis, prognosis and therapy. Ki67 (cellular marker for proliferation) is a nuclear non-histone protein expressed during cell growth and DNA synthesis phases of cell cycle. Evaluation of Ki67 showed that it is expressed among proliferating cells and absent in quiescent cells. Another cell cycle protein, cyclin D1 is overexpressed in over 50% of breast cancer. Cyclin E acts as a positive regulator of cell cycle transition and its increased levels may be significant in association with the response to cancer therapy. Estrogen receptor-beta (ERb) expression has been linked to the expression of Estrogen receptor-alpha (ERa) and progesterone receptors (PgR). In breast cancer tissues, ERb was significantly downregulated, is correlated positively with Ki67, and is also associated with human epidermal growth factor receptor 2 (HER2) overexpression. These factors could be studied standalone or in a complement with each other for prognostic or therapeutic value in invasive breast cancer for better outcome (Weigel, 2010).

Immunohistochemical biomarkers are used to classify breast cancer into biologically distinct subtypes that helps in a guided treatment. Programmed death-ligand 1 (PD-L1) are transmembrane protein receptors that is overexpressed in certain type of breast cancers as its expression mainly occurs on tumor-infiltrating immune cells than on tumor cells. Tumor immune system interaction may be influenced by many molecular pathways as a response to immunotherapy. High level of microsatellite instability is considered a predictive factor of response to immune checkpoint blockade, showing mismatch repair deficiency. Vascular endothelial growth factor (VEGF) is a signaling protein that acts as an endothelial cell survival factor/angiogenetic factor promote blood supply to the tumorous cells. VEGF level alteration may be correlated to clinical prognosis or associated pathologies (Ronchi, 2020). In addition, blood-based biomarkers such as serum protein biomarkers (SPBs) and tumor-associated autoantibodies (TAbs) may improve the sensitivity of breast cancer screening. These molecules are highly specific, and biochemically stable. Hence, they have greatest potential in screening assays that helps to correlate with tumor metastasis (Hollingsworth, 2014).

A DNA microarray allows gene expression profiling of tumors that measure thousands of mRNA transcripts. In breast cancer, existence of tumors originated from different cell types has been studied with this bulk expression profiling (Weigel,

2010). Breast cancer genes such as BRCA1 and BRCA2 have been studied extensively as a biomarker in screening. Functional variations in BRCA1 are studied as novel predictive markers in response to chemotherapy (James, 2007). Furthermore, certain developmental control genes are critical in tumor development and progression. Beta protein 1 (BP1) is expressed in 80% of invasive ductal breast carcinomas and its overexpression is implicated in aggressive phenotype. BP1 could serve as both a novel prognostic biomarker for breast cancer and a therapeutic target (Lang, 2021; Lou, 2018).

Colorectal Cancer

Potential protein biomarkers for the prediction of tumor progression have been studied. E-cadherin is a transmembrane glycoprotein that acts like an adhesion encoded by the CDH1 gene. It is involved in cell-cell interactions is downregulated during certain types of tumors and is associated with cancer cell phenotypes. Mutations, epigenetic silencing, increased endocytosis and proteolysis mechanisms may lead to E-cadherin inactivation in cancer. Progressions of multiple cancer types have been associated with suppression on E–cadherin expression. In addition, epigenetic modification such as promoter hypermethylation has been reported with the loss of E-cadherin expression in cancer (Christou, 2017).

All clinical stages of colorectal cancer (CRC) may be associated with expression of the inflammatory response genes. Expression of tyrosine kinase-LCK, granulysin -GNLY, taurine transporter- SLC6A6 and lysosome-associated membrane protein-LAMP2 genes are studied in early stage of colorectal cancer. LCK gene is a proto-oncogene involved in immune cell differentiation and GNLY gene is involved in antimicrobial immune response. LCK and GNLY are both lymphocytic inflammatory response genes that are elevated in stage I and reduced in stage IV CRC. In contrast, SLC6A6 and LAMP2 genes were showing decreased expression in stage I, and over expressed in stage II (Janikowska, 2018). In addition, tubby-like-3 protein/TULP3 (transcription regulator) expression levels were elevated associated to lymphatic and vascular invasion in CRC (Sartor, 2019). Thus, it shows a possible role of these genes as a diagnostic and prognostic biomarker in CRC.

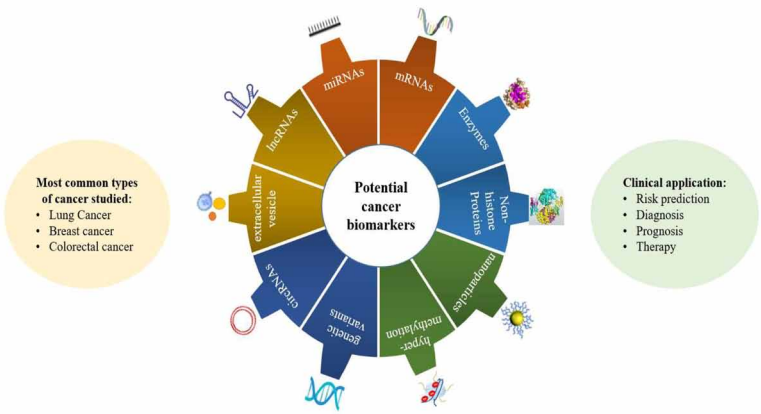
Few other gene expression profiles were studied in association in CRC screening. Altered expression of vitamin D catabolizing enzyme coded by CYP24A1 gene was reported to be associated with CRC progression and in several cancer types. CRC phenotypes such depth of tumor invasion, lymph node metastasis, venous permeation, and apoptosis were correlated with CYP24A1 protein expression (Sun, 2016). Tyrosine phosphatase coded by DUSP4 gene was upregulated and its transcript variants are individually overexpressed in early-stage CRC tissue. Hence, DUSP4 transcripts elevated expression could distinguish all tumor stages from

normal tissues and have the potential to serve as diagnostic biomarkers for CRC (Varela, 2020). Hypermethylation of the secreted frizzled-related protein (SFRP) genes might serve as indicator for early CRC. A study that identified that SFRP2 gene (tumor suppressor) is inactivated by the epigenetic hypermethylation which leads abnormal molecular signaling in CRC. Thus, SFRP2 has been studied as potential biomarker in early CRC progression events (Wang, 2009). Furthermore, down-regulation of HOTAIRM1 (HOXA transcript antisense RNA, myeloid-specific 1) - a long non-coding RNA that regulates gene expression during myelopoiesis- act as tumour suppressor in CRC. HOTAIRM1 and CEA (carcinoembryonic antigen) based combined assay might provide a promising diagnosis for CRC (Wan, 2016).

Altered miRNAs expression are studied as potential diagnostic, prognostic and therapeutic markers at different stages of CRC. Co-expressed miRNAs in CRC phenotypes may have a collective role in associated cellular events (Arndt, 2009). Crucial pathways of CRC carcinogenesis include epidermal growth factor receptor signaling pathway, DNA mismatch repair and aberrant DNA methylation of miRNA genes (Pellino, 2018). Clinical and functional studies demonstrated that 11 common miRNAs (miR-20a, miR-19a, miR-17-5p, miR-93, miR-25, miR-31, miR-106a, miR-143, miR-145, miR-125a, miR-1) that were differentially expressed between normal colon and CRC (35). Another research finding show that miR-92a, miR-103a-3p, miR-127-3p, miR-151a-5p, miR-17-5p, miR-181a-5p, miR-18a-5p and miR-18b-5p was significantly elevated in colorectal cancer plasma samples compared to normal (Yang, 2014; Zhang, 2019). In addition, miR-92a is among the best characterized miRNA oncogenes whose abnormal alteration are frequently observed in a variety of tumor types (Yang, 2014). Response to adjuvant chemotherapy studies on miR-150 expression of CRC patients shows that tumor tissue had reduced levels of miR-150 expression compared with paired non-cancerous tissue (Ma, 2012). These findings suggest that miRNAs expression in standalone or in combinations could be potential non-invasive molecular biomarkers for CRC screening or to study therapeutic outcome.

Specific and sensitive biomarkers can provide great insights into tumorigenesis and facilitate the development of improved therapies (Lan, 2015). The practicality of clinical use of the biomarker depends both on the level of application and the feasibility. The potential cancer biomarkers need to be studied extensively with advanced technologies to bring about a great change in cancer screening and therapies by improving risk analysis, early detection, diagnosis, and prognosis where these biomarkers will be used either as stand-alone tests or to complement existing approaches.

Figure 1. Potential cancer biomarkers studied for clinical application



NANOTECHNOLOGY FOR THE DEVELOPMENT OF NOVEL BIOMARKERS IN CANCER THERAPY

In cancer nanotechnology, nanometer-sized particles linked with tumor targeting ligands with high affinity and specificity are used to target tumor pathophysiology (Zhang, 2019; Nie, 2007). It is an interdisciplinary area of research in medicine and technology. Metals like gold or silver nanoparticles have great electromagnetic, optical, or structural properties that are used in photothermal therapy (Song, 2010). Metal oxide nanoparticles and semiconductor quantum dots includes other examples that are like acts like an immunogenic cargo along with biomolecules to capture cancer biomarkers, such as exosomes and cancer-associated proteins (Jia, 2017). The large surface area to the volume ratio or the size is the crucial factor in applying nanoparticles for cancer detection because its surface can be covered by the biological targets efficiently and densely which then recognizes the targeted tumor (Song, 2010). Thus, improving the specificity and sensitivity of an assay designed with this principle (Zhang, 2019).

FUTURE RESEARCH DIRECTION

A panel of highly specific, sensitive and effective biomarkers could play a great in the cost-effective prediction, detection and treatment of cancer. Predictive cancer biomarkers could be the future of cancer management at various molecular staging of disease. Oncology research should focus on more reliable, accurate, simple and non-invasive diagnostic methods. Technology-driven research approach and "omics"

technologies (genomic, proteomic, metabolomics and interactomics) with the efficient molecular techniques and bioinformatic tools shows a great promise in biomarker discovery and clinical application. In addition, from developing a biomarker in the research laboratory to using it as a clinical tool is a long complex journey which would need a collaborative effort of the experts in the field. Moreover, there are still scope for innovative approaches when it comes to efficient clinical application of cancer biomarkers.

CONCLUSION

The research and development in the field of oncology is growing at a phenomenal rate that keeps a high pace with the evolving disease pathophysiology at the molecular level. Although there are scientific and technological challenges in the translation from academic research to clinical application, these developments increase opportunities for personalized oncology. Genetic and metabolic biomarkers based on the molecular profiles of individual patients brings a promising approach to this aspect. Interdisciplinary research in nanotech and genetic engineering are looked up to in the field chemotherapeutic development.

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KEY TERMS AND DEFINITIONS

circRNAs: Circular RNAs.
CRC: Colorectal cancer.
CTCs: Circulating tumor cells.
EV: Extracellular vesicle.
lncRNAs: Circulating long non-coding RNAs.
miRNAs: Micro RNAs.
mRNAs: Messenger RNAs.
mtDNA: Mitochondrial DNA.

Chapter 6
CNT-Based Nano Medicine From Synthesis to Therapeutic Application

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ABSTRACT

Carbon nanotubes (CNTs) are allotropes of carbon consisting of cylindrical tubes, made up of graphite with a diameter of several nm to a length of several mm. They had extraordinary structural, mechanical, and electronic properties due to their small size and mass, high mechanical resilience, and high electrical and thermal conductivity. Their large surface area made them applicable in pharmacy and medicine and adsorb or conjugate a broad variety of medical and diagnostic agents (drugs, genes, vaccines, antibodies, biosensors, etc.). They are often used to deliver drugs directly into the cells without going through the metabolic process of body. In addition to drug delivery and gene therapy, CNTs are also used for tissue regeneration, diagnostic biosensors, chiral drug enantiomer separation, drug extraction, and drug or pollutant analysis. CNTs have recently been discovered as effective antioxidants. The ADME and toxicity of different types of CNTs have also been documented here, as well as the prospects, advantages, and challenges of this promising bio-nano technology.

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INTRODUCTION

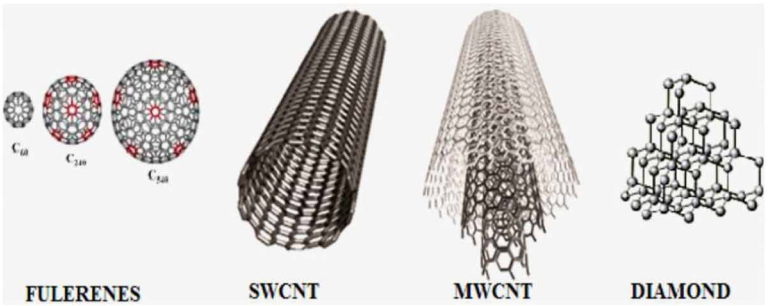
Carbon nanotubes (CNTs), first discovered by Japanese scientist Iijima in 1991 (Iijima, 1991), are now considered the top focus in research and industries. These are allotropes of carbon consisting of cylindrical tubes made up of graphite with a diameter of several nanometers to a length of several millimeters (Hirlekar et al., 2009; Singh et al., 2012; Zhang et al., 2010). Due to their small size and mass, immense mechanical strength, and high electrical and thermal conductivity. They have remarkable structural, mechanical, and electronic properties (Usui et al., 2012; Zhang et al., 2010). Carbon nanotubes are used chiefly as a substitute for different structural components for electronics, optics, plastics, and other products in the field of nanotechnology. Since the beginning of the twenty-first century, they have been used in pharmacy and medicine for drug delivery systems in therapeutics. CNTs can adsorb or conjugate with a wide range of therapeutic materials such as drugs, proteins, antibodies, DNA, and enzymes due to their high surface area, excellent chemical stability, and rich electronic poly-aromatic structure. They are a perfect vehicle for drug delivery by reaching directly into cells and by preserving the drug's integrity during metabolism through the body (Hirlekar et al., 2009; Zhang et al., 2010). Many studies have shown that when drug molecules are bonded to CNTs, they are delivered into cells more efficiently and safely than the conventional methods (Singh et al., 2012; Zhang et al., 2010). This fantastic innovation has brought a new age of drug preparation that is entirely different from the existing techniques used in the pharmaceutical industry and has drastically altered previous pharmacology principles (Singh et al., 2012; Usui et al., 2012). It was first used to bind antibiotic drugs to carbon nanotubes to treat cancer and particular infection, respectively. Then, for gene therapy, immunotherapy, tissue regeneration, and diagnosis of various diseases, other biomolecules such as genes, proteins, DNA, antibodies, vaccines, biosensors, and cells, etc., were attached to CNTs and assayed for their pharmacological application (Bekyarova et al., 2005; Kateb et al., 2010; Zhuang et al., 2007; Rosen & Elman, 2009; W. Zhang, Zhang, & Zhang, 2011). As a result, CNTs have attracted the interest of scientists from a variety of fields in a relatively short period of time. They may be useful antioxidants in the future for health protection and disease prevention (Galano, 2010). All these advances in medicine, however are only in the developmental stage and are not being used in humans. CNTs can also be used for enantiomer isolation of chiral drugs and chemicals in the drug industry as well as in the laboratory, and for solid phase extraction of drugs from impurities before analysis (El-Sheikh, 2011; Yu et al., 2011). Many scientific groups have recently led to the development of novel functionalization method of CNTs for drug delivery and evaluation, as well as to the study of CNT-albumin interactions (He et al., 2020). The area of pharmacy and medicine is the subject which describes

various CNT applications. It focuses on some of the most effective approaches for using carbon nanotubes as a drug delivery system for drugs and biomolecules in the treatment and diagnosis of various diseases. It also explains Pharmacokinetics, metabolism, and toxicity of CNTs.

CARBON NANOTUBES: CLASSIFICATION AND METHODS OF SYNTHESIS

Carbon, the primary component of all organic materials, is widely acknowledged as one of the world's most available elements. It can develop allotropes, as shown in **Fig. 1**. Diamond, which has sp3 hybridization, and graphite, which has sp2 hybridization, are two well-known forms (Heimann et al., 1997). The physical and chemical properties of carbon allotropes are defined by valence bond hybridization. Diamond, for example, is the hardest known substance on the planet, and graphite is weak in one direction but hard in others. Carbon nanotubes have unique properties for various engineering applications that make them attractive. Because of their chemical inertness, carbon nanotubes must be functionalized to achieve additional physicochemical properties. Single-walled carbon nanotubes and fullerenes are not the same as multi-walled.

Figure 1. Allotropes of carbon: fullerenes, nanotubes, and diamond, respectively



Fullerenes

In 1985, Rice University's Smalley research group discovered a new carbon source, Buckminsterfullerene, while performing tests on carbon vaporization using laser pulses (Kroto, 1993). This structure is also identified as buckyball or fullerene, and it has a bonding between sp2 and sp3 hybridization (Pierson, 1993). Fullerenes with

a varying number of carbon atoms were discovered later. The formula C2n, where n is an integer, represents the number of carbons in any cluster of fullerenes. Each fullerene has (n-10) hexagons (Ajayan, 1999; Ebbesen, 1996). The discovery of fullerenes motivated scientists to explore other types of carbon.

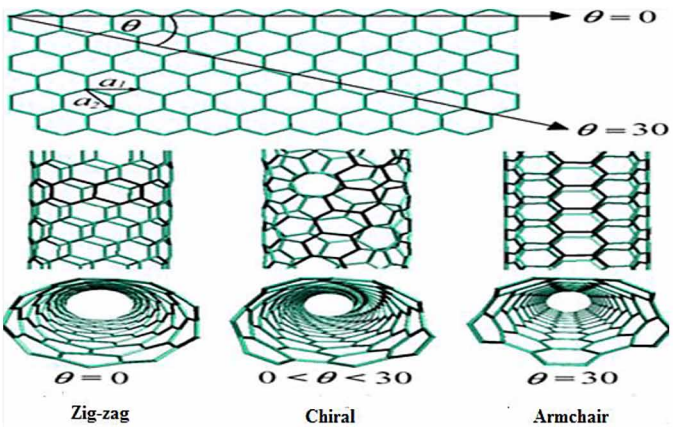
Nanodiamonds

Nanodiamond is yet another carbon nanostructure that has gained significant interest in recent years. In 1950, the first artificial diamonds were created using a high-pressure/high-temperature process. Then, in 1960, low-pressure chemical vapor deposition (CVD) was developed as a method for producing polycrystalline films (Shenderova et al., 2002).

Carbon Nanotubes

The discovery of graphitic tubules, a new form of carbon, was ignited by the discovery of fullerenes (Iijima, 1991). First, carbon nanotube (CNT), discovered and identified by Iijima, had two to fifty sheets of graphene walls, so they were referred to as multi-walled carbon nanotubes (MWNT) (Thostenson, 2001). CNTs are made up of rolled-up graphene sheets with a buckyball-shaped hemisphere at one end. Types of CNTs are determined by the direction in which this graphene sheet is rolled up. The angle between C-C bonds and the tube's axis can alter, and thus the chirality of a CNT is defined by this angle (Hernadi et al., 1996); Iijima and Ichihashi (1993); (Thostenson et al., 2001) .The various types of CNTs are described by a chiral vector, as explained in **Fig. 2**

Figure 2. A graphene sheet customized honeycomb structure



By folding the sheet along the vectors, SWCNT can be established. The two basic vectors are shown: a1 and a2. The folding of the vectors ($\boldsymbol{\theta} = 0$), ($0<\boldsymbol{\theta}<30$) and ($\boldsymbol{\theta} = 30$) leads to nanotubes of zig-zig, chiral and armchair structure.The common possibilities are "zigzag" and "armchair" CNTs, the former having $\theta = 0$, and the latter with $\theta = 30°$, and all the CNTs with $0° < \theta < 30°$ are defined as chiral tubes. The electronic properties of nanotubes vary depending on their shape; therefore, armchair nanotubes are metallic; however, zigzag and chiral nanotubes may be either metallic or semiconducting. Multi-walled CNTs are considered to be metal conductors, while SWCNTs are usually a combination of metal and semiconducting material (Katz & Willner, 2004)[REMOVED HYPERLINK FIELD].

METHOD OF SYNTHESIS

Various synthetic techniques have been modified to improve the yield and properties of CNTs, such as Electric-arc discharge (EAD), laser ablation (LA), and another cost-effective process for producing extremely pure carbon nanotubes (CNTs) is chemical vapor deposition (CCVD).

Electric-Arc Discharge (EAD)

In this process, the catalytic decomposition of hydrocarbon vapors produces CNTs. The synthetic method improves the level, amount, and type of nanotubes manufactured. Invariably, the inherent reaction conditions (Fu et al., 2004). This technique was first established in the 1960s and 1970s, and it has been effectively used in the development of carbon nanofibers for the last 20 years (Baker, 1989; Tibbetts, 1989). In this method, CNTs are obtained by decomposing carbon-containing materials (usually in gaseous form, such as CH4, C2H2) at high temperatures and flowing them through a transition metal catalyst. (typically Fe, Co or Ni) (José-Yacamán et al.,1993). This method can generate high-yield of carbon nanotubes, but they are structurally weaker compared to those caused by arc discharged or laser evaporation. This method can generate high-yield carbon nanotubes, but they are structurally more vulnerable than those generated by arc discharged or laser evaporation.

In contrast to other available synthesis methods, the CVD method has many advantages. Firstly, the product tends to be free from impurities (in the form of graphite or metal). Secondly, CNTs were produced at a lower temperature (550°C-1000°C), thus, significantly reducing the cost of the process and making it more available for lab usage (Ci et al., 2005; Elhissi et al., 2012). Finally, the metal catalyst can be mounted on a substrate, assisting the growth of aligned nanotubes in the desired direction relative to the substrate. While experimenting with the fullerene synthesis,

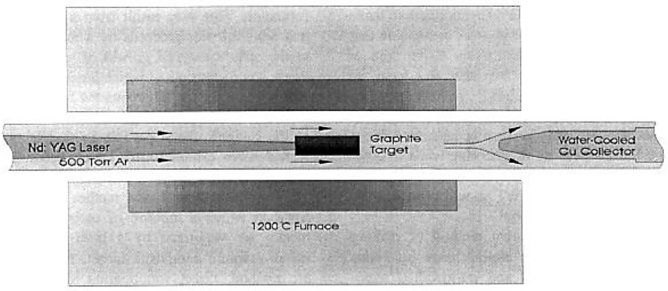
during the arc discharge evaporation of carbon in argon at a pressure of 100 Torr, the first needle-like carbon filaments were produced, which he named Carbon nanotubes. These filaments, which formed on the opposing end of the graphite electrode, were identified by Iijima as rolled graphite sheets inserted into each other.

In the same issue of nature 1993, two papers describing the same method for synthesizing single-walled carbon nanotubes were published. (Bethune et al., 1993; Iijima & Ichihashi, 1993). Two groups of researchers independently discovered that single shelled nanotubes could be produced by co-evaporating carbon and iron or cobalt. For the synthesis, the reaction vessel was filled with a mixture of argon and methane (40 Torr argon and 10 Torr methane). The iron carbide particles are formed with the carbon from the cathode or from methane under these conditions. On these nanoparticles, carbon nanotubes with only one shell were formed. Most miniature tubes had a diameter of 0.75 nm, while the largest had a diameter of 1.6 nm (Bethune et al., 1993; Iijima & Ichihashi, 1993).

Laser Ablation/Laser Vaporization

Laser ablation/laser vaporization of a graphite rod in an oven with Co and Ni as catalysts is the second most common method for synthesizing single-walled nanotubes (Thess et al., 1996). The soot produced by the laser was deposited on a cooled copper collector when argon flowed at a pressure of 500 Torr and a flow rate of 50 cm in a chamber heated to 1200°C. **Fig. 3** (Guo et al.,1995).

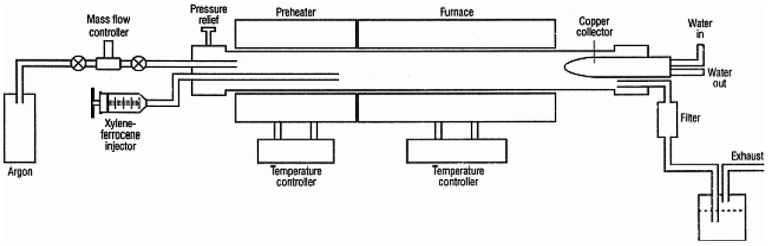
Figure 3. Instrument of laser vaporization



The process was later improved to produce more than 70% yield of nanotubes (Thess et al., 1996). The advantages of this method over arc discharge are that the nanotubes made are “pure,” with less amorphous carbon and no graphite particles on the outer walls.(Guo et al., 1995). The third most popular synthesis method is

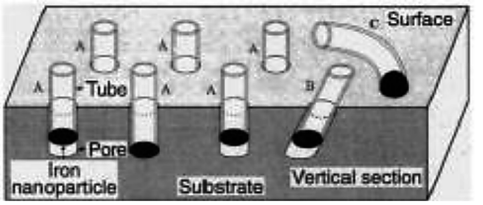
catalytic growth of carbon tubules by decomposition of hydrocarbons, which was introduced in 1992 (José-Yacamán et al., 1993). MWCNTs and SWCNTs were formed by this process, which later referred to as chemical vapor catalytic deposition (CCVD); as a catalyst, the iron particles (Fonseca et al., 1996; José-Yacamán et al., 1993), cobalt or iron on SiO2 (Fonseca et al., 1996; Hernadi et al., 1996; Kong et al., 1998; W. Li et al., 1996; Pan et al., 1998) iron or cobalt with zeolite support (Fonseca et al., 1996; Hernadi et al., 1996) iron on alumina substrate (Al_2O_3)(Qin et al., 1998) and cobalt di-silicide (CoSi2)(Mao et al., 1998) can be used. Acetylene (Fonseca et al., 1996; Mao et al., 1998), propylene, ethylene (Andrews et al., 2002; José-Yacamán et al., 1993) or methane (Baker, 1989; Kong et al., 1998) can be used as a carbon supplier at decomposition temperature of 650-900 °C. The pyrolysis of these compounds was carried out at 1100 °C with a mixture of methane or acetylene, producing SWNTs or MWNTs based on the process conditions (Hernadi et al., 1996; Kong et al., 1998). The use of the ferrocene-xylene combination can also produce Multi-walled carbon nanotubes. **Fig 4**.

Figure 4. Diagrammatic representation of reactor used for nanotubes synthesis from ferrocene-xylene mixture



The synthesis of carbon nanotubes (CNT) from carbon monoxide as a carbon source on molybdenum particles was documented (Dai et al., 1996) using a metal-catalyzed disproportion of carbon monoxide at 1200°C. Terrones et al. (Terrones et al., 1997) introduced the use of a silica substrate with laser etching templates. They initiated by depositing cobalt on a patterned substrate, then used an unusual chemical substance called 2-amino-4,6-dichloro-triazine to grow the CNTs. In particular, this was the first article on laser etching that developed a pattern for catalyst deposition on the substrate, resulting in aligned nanotubes. The proposed growth model is given in **Fig. 5**

Figure 5. Possible growth model of CNT on iron particles

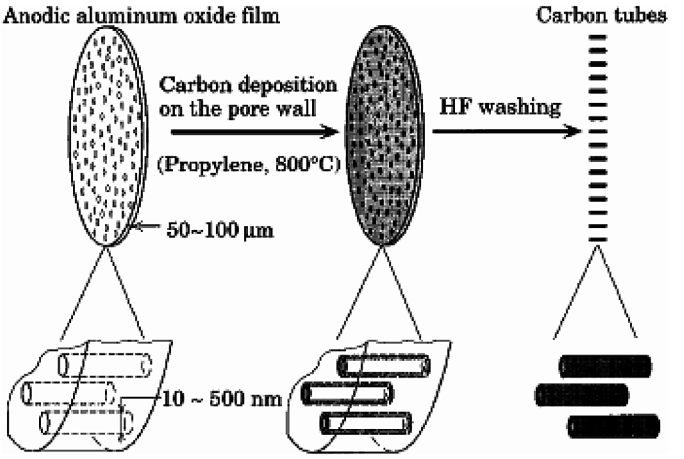


Catalytic Chemical Vapor Deposition

The technique of catalytic chemical vapor deposition (CCVD) has recently gained popularity since the reaction takes place at a far lower temperature, thus reducing the cost of producing carbon nanotubes (Baker, 1989). Another benefit of CCVD is that it allows you to control the thickness, diameter, and length of aligned multi-walled or single-walled nanotubes by varying the reaction conditions. In 1995, Japanese scientist Kyotani invented a non-catalytic chemical vapor deposition process to develop CNTs as a modification of this technique. (Kyotani, Tsai, & Tomita, 1995). The method of producing uniform, well-aligned multi-walled CNTs in the channels of alumina porous oxide films is called template synthesis (Keller et al., 1953).

Martin demonstrated in 1994 that porous alumina could be used as a base for various nanomaterials, ranging from polymers to metals (Martin, 1994; O'sullivan & Wood, 1970) Publications, especially those from Masuda's group, revealed that this method of using a highly ordered porous alumina template for the synthesis of ordered nanometal structures could be easily applied for a variety of applications (Masuda & Fukuda, 1995). Kyotani published a paper in August 1995 (Kyotani et al., 1995) explaining the preparation of carbon tubules in pores of the anodic alumina oxide film. This approach was also outlined by Itaya in a publication in 1984 (Itaya et al., 1984) The thickness and pore diameters of alumina films can be modified by altering the anodic oxidation process parameters (Jessensky et al., 1998; Masuda & Fukuda, 1995). The Kyotani group produces carbon tubules by thermally decomposing propylene gas (2.5 percent in N_2) in channels of porous alumina membrane at 800°C (Che et al., 1998; Kyotani et al., 1996). After carbon was deposited on the inner walls of the alumina membrane's pores, the alumina was dissolved in hydrofluoric acid, yielding multi-walled carbon nanotubes. The schematic of the process shown in **Fig. 6**

Figure 6. Schematic drawing of the formation of CNTs via chemical vapor deposition in alumina template pores



BIOMEDICAL APPLICATIONS OF FUNCTIONALIZED CNT

Purified carbon nanotubes are not soluble in water because of their hydrophobic surfaces; hence surface functionalization is needed to solubilize carbon nanotubes and to achieve better biocompatibility and low toxicity for medical applications (Digge et al, 2012; Zhuang et al., 2009). Depending on the type of the biomolecule attached to the carbon nanotube, the functionalization method for CNTs can be divided into two main approaches: covalent attachment (chemical bond formation) and noncovalent attachment (physio adsorption) (Yang et al., 2007; Zhang et al., 2010).

Oxidation of CNTs with strong acids like HNO3 is the way to obtain covalently functionalized CNTs. Carboxyl (–COOH) groups are formed on the open sides (tips) and defects on the sidewalls of SWCNT or MWCNT during the process, followed by further covalent conjugation with amino acid. Nitrene cycloaddition, arylation with diazonium salts, or 1,3-dipolar cycloadditions are widely used to create –COOH groups on the sidewalls of CNTs (Kateb et al., 2010; Zhuang Liu et al., 2007; Yang et al., 2007; Zhang et al., 2010).**Fig. 7**

Coating of CNTs with amphiphilic surfactant molecules or polymers may be used to achieve noncovalent functionalization (polyethylene glycol). Carbon nanotubes are perfect partners for noncovalent interactions with complementary molecules and macro biomolecules like (DNA), because of their aromatic (π electron) and large hydrophobic surface. These interactions can occur on the inside as well as the outside of CNTs; on the other hand, macromolecules cannot be attached on the inside of CNTs (Digge et al., 2012; Zhuang Liu et al., 2009; Y. Zhang et al., 2010).

Schematic noncovalent functionalization of CNTs is illustrated in F**ig. 8.** CNTs become soluble in water after functionalization and can be able to attach to the drugs or biomolecules (DNA, proteins, and enzymes etc.) in order to deliver them to the desired cells or organs (Digge et al., 2012; Kateb et al., 2010; Zhuang et al., 2007; Yang et al., 2007; Zhang et al., 2010).

Figure 7. Chemical modification of carbon nanotubes by nitric acid oxidation followed by carboxyl group esterification or amidation

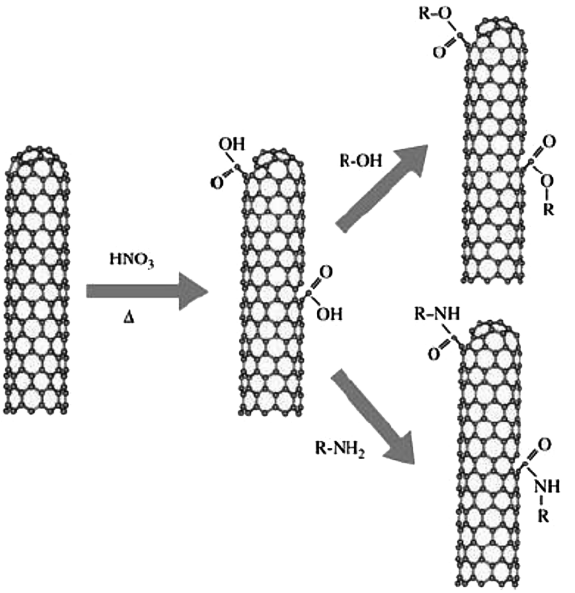
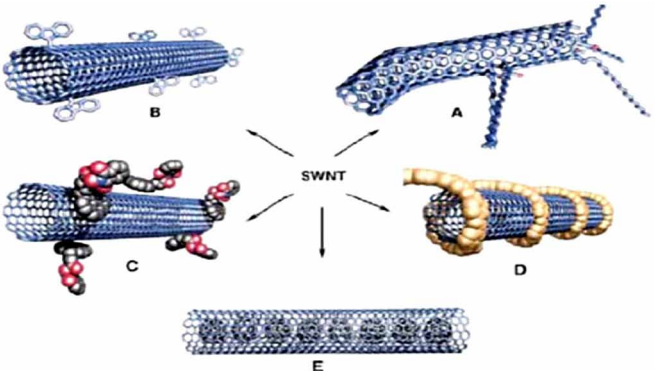


Figure 8. Functionalization possibilities for SWNTs: A) Functionalization at defect groups B) By covalent bond formation C) By surfactant-based noncovalent binding D) Exohedral functionalization with polymers, and E) endohedral functionalization



APPLICATION OF CNT IN PHARMACEUTICAL AND NANOMEDICINE

Some of the most common uses of CNTs in pharmacy and medicine are delivery of drug, biomolecule, and genes to the cells or organs. It can also be used for tissue regeneration, biosensor-based diagnosis, and assessment. **Fig 9** summarizes them. The general method for drug delivery by CNTs can be simply explained as follows. The drug is first attached to the surface or inside of functionalized carbon nanotubes. The nanocomposite is then introduced into the animal body in conventional ways (oral injection) or directly to the specified location using a magnetic conjugate, which is guided to the target organ, such as lymphatic nodes by an external magnet. Finally, the drug CNT capsule is ingested by the cell, and the nanotube then spills its contents into the cell, thus delivering the drug (Kateb et al., 2010; Zhuang et al., 2007; Singh et al., 2012; Usui et al., 2012; Zhang et al., 2010)

In general, functionalized carbon nanotubes can transport molecules of interest across the cytoplasmic and nuclear membranes without any toxicity; **Fig. 10** shows a schematic representation of the drug delivery process. Consequently, the drug CNT conjugate is safer and more effective than the drug alone in conventional preparation.

After approaching the target cell, the drug can be delivered in two ways: either the drug enters the cells without the CNT carrier or both the drug and the CNT carrier enter the cells. The latter form of internalization is more efficient than the first because the intracellular environment degrades the drug carrier conjugate after it reaches the cells, thus releasing drug molecules in situ, that is, within the cells. Although in the non-internalization process, the extracellular environment facilitates in the degradation of drug carrier conjugates, and the drug then passes through the lipid membrane by itself to reach the cells, so during this process, there is a chance of drug degradation. Briefly, the ability of CNTs to cross cell membranes for drug delivery is accompanied by their structure, which includes fundamental hydrophobic interactions, -π stacking interactions, and electrostatic adsorption.

Adsorption into the hollow cylinder, which helps in increasing the adsorptive potential (Yang et al., 2007). Furthermore, CNTs can enter cells not only to facilitate cellular reception of therapeutic molecules, but also to retain them unchanged during transport and cellular penetration.

Figure 9. Schematic representation for Application of CNT in pharmacy and medicine

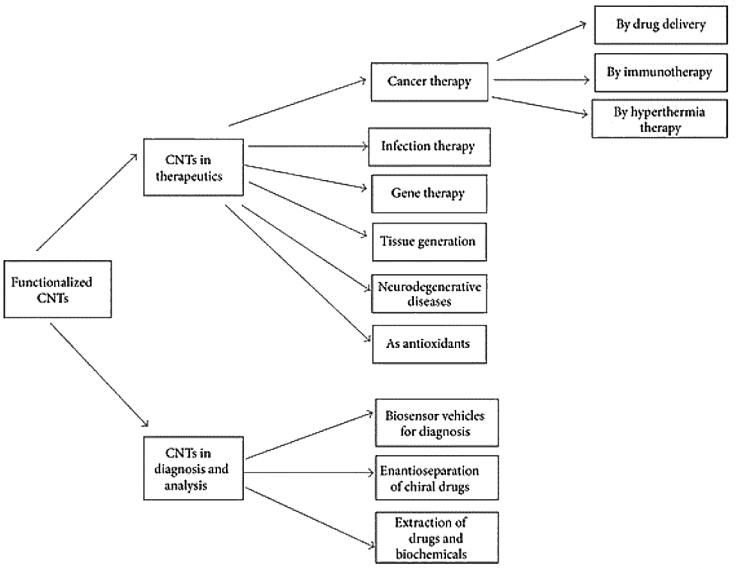
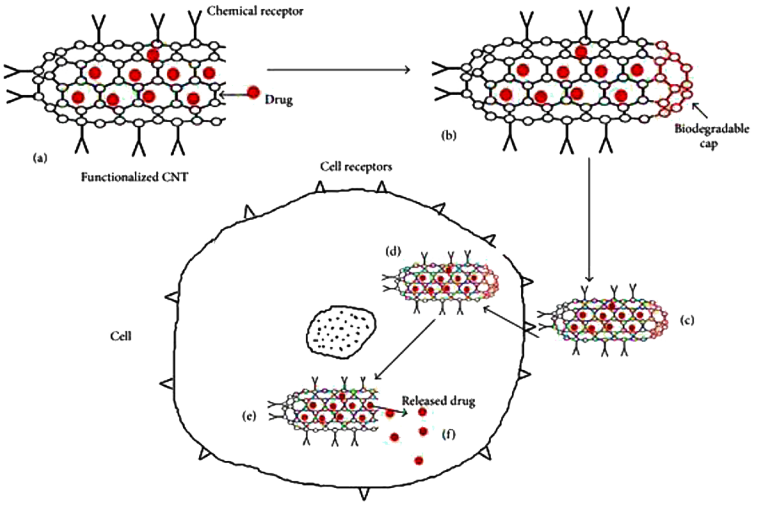


Figure 10. Schematic representation of drug delivery process



APPLICATION OF CNTS IN CANCER THERAPY

By Means of Drug Delivery

CNTs can be used as drug delivery systems in the treatment of tumors (Al-Jamal et al., 2011; Digge et al., 2012; Elhissi et al., 2012; Lay., 2011; Zhuang et al., 2009; Madani at al, 2011; Yang et al., 2007). Anticancer drug's potency is limited by their systemic toxicity and limited therapeutic window and drug resistance and cellular penetration. Since CNTs can easily cross the cytoplasmic and nuclear membranes, anticancer drugs transported by this vehicle would be liberated in situ with intact concentration, resulting in a higher effect in the tumor cell than conventional therapy alone. Hence, efficient delivery systems that can improve the cellular uptake of existing potent drugs are needed. In addition, CNTs have a high aspect ratio, which gives them a significant advantage over another delivery system because their large surface area allows multiple drug attachment sites. (Kateb et al., 2010; Liu & Sun, 2007; Usui et al., 2012; Zhang et al., 2010).

Epirubicin, doxorubicin, cisplatin, methotrexate, quercetin, and paclitaxel are anticancer drugs covalently linked with functionalized CNTs and successfully studied in vitro and in vivo. (Elhissi et al., 2012; Lay et al., 2011; Li et al., 2010; Madani et al., 2011). Researchers have linked anticancer drugs with magnetic CNTs and the complex obtained by fixing magnetite (Fe_3O_4) nanoparticles on the surface of nanotubes and the tips of shortened MWCNTs. This modification prevents the harmful effects of anticancer drugs on healthy organs and cells. In addition, other researchers have used the epirubicin magnetic CNTs complex to treat lymphatic tumors. An externally positioned magnet will direct such a device to the targeted tumor in the nodes (Zhang et al., 2011).

Anticancer drugs may also be attached to a complex formed by carbon nanotubes and antibodies against an antigen expressed on the cancer cell surface. To achieve targeted delivery, the antigen-antibody attraction causes CNTs to be taken up by tumor cells just before the anticancer drug is cleaved off CNTs (Elhissi et al., 2012; Lay et al., 2011; Madani et al., 2011). Multidrug resistance, driven by increased anticancer drug efflux by the overexpressed p-glycoprotein, which results in poor activity is a significant barrier to successful anticancer therapy (Elhissi et al., 2012). Li and coworkers (Li et al., 2010) researchers have found that SWCNT can be functionalized with p-glycoprotein antibodies and charged with the anticancer agent like doxorubicin, The cytotoxic activity of this formulation was higher than those of free doxorubicin. In vivo administration of SWCNT paclitaxel conjugate was found to have higher efficacy in controlling tumor growth in breast cancer model and having fewer toxic effects on normal organs (Madani et al., 2011; Zhang et al., 2011). Prolonged blood flow, higher tumor absorption, and slower drug release from

SWCNTs could explain the higher therapeutic efficacy and lower adverse effects of cancer drugs (Digge et al., 2012).

By Antitumor Immunotherapy

CNTs can be used as nano-carriers, making antitumor immunotherapy more efficient (Elhissi et al., 2012; Lay et al., 2011; Li et al., 2010; Pantarotto et al., 2004; Singh et al., 2012) The aim of this treatment is to activate the patient's immune system to target the malignant cancer cells. This can be done by delivering a cancer vaccine or a therapeutic antibody as a medicine. Some scientists have validated the use of CNTs as vaccine delivery tools (Pantarotto et al., 2004). In a clinical study, Yang's team discovered that coupling MWCNTs with tumor lysate protein (tumor cell vaccine) would significantly and precisely increase the effectiveness of antitumor immunotherapy. CNTs and their adjuvant effects can play a significant role in activating antitumor immunotherapy; but the mechanism is still unknown (Pantarotto et al., 2004; Yang et al., 2007).

Hyperthermia Therapy for Cancer Treatment

This CNT-based therapy has recently been proposed as an effective cancer treatment method. Since in the near-infrared region, SWCNTs have a high absorbance.(NIR;700–1100 nm). They produce large amounts of heat when excited with NIR light. Hence these nanomaterials are considered promising candidates for hyperthermia therapy (Elhissi et al., 2012; Lay et al., 2011; Madani et al., 2011). Excessive heating of SWCNTs shackled in tumor cells, as in the case of pancreatic cancer. It can induce local thermal ablation of tumor cells through the photothermal effect. In recent years, some progress has been made in the procedure, showing clinical viability.

OTHER APPLICATIONS

Treatment for Infections

CNTs have been examined to address the problems such as infectious agent resistance to a number of antiviral and antibacterial drugs, as well as vaccine ineffectiveness in the body. Some antimicrobial and antifungal drugs have been shown to be carried by functionalized carbon nanotubes (Rosen & Elman, 2009; Rosen, 2011).

CNTs can bind to amphotericin B covalently and transport it into mammalian cells. As compared to the free drug, this conjugate has a 40% lower antifungal toxicity (Pantarotto et al., 2004; Rosen et al., 2011).Pazufloxacin mesylate, an

antimicrobial agent with high adsorption, has been successfully combined with amino-MWCNT and will be used in infection treatment assays. Functionalized CNTs, when attached with B and T cell peptide receptors, can result in forming a multivalent system capable of inducing an effective immune response, making it a promising vaccine delivery system (Usui et al., 2012; Y. Zhang et al., 2010). Furthermore, the antibacterial effect of CNTs was due to carbon nanotube-induced oxidation of the intracellular antioxidant, resulting in higher oxidative stress and subsequent cell death in bacterial cells (Digge et al., 2012).

Gene Therapy by Using CNT

Gene therapy is a procedure that involves introducing a DNA molecule into the cell nucleus to correct a faulty gene that causes certain chronic or inherited diseases. Liposomes, cationic lipids, and nanomaterials such as carbon nanotubes (CNTs) are delivery tools for DNA transfer (Al-Jamal et al., 2011; Bekyarova et al., 2005; Yang et al., 2007). DNA probes, when attached to SWCNTs, are safe from enzymatic cleavage and interference from nucleic acid-binding proteins. As a result, the DNA-SWCNT complex has better biostability and improves its self-delivery ability compared to DNA alone (Bekyarova et al., 2005; He et al., 2020; Usui et al., 2012; Zhang et al., 2011). Stable complexes of plasmid DNA and cationic CNTs have been shown to strengthen therapeutic gene ability as compared to DNA alone. CNTs conjugated with DNA were discovered to release DNA before it was killed by the cell's defensive mechanism, resulting in a significant increase in transfection (Liu & Sun, 2007; Zhuang et al., 2009). The use of carbon nanotubes as gene therapy agents has demonstrated that these engineered structures can efficiently transport genes within mammalian cells while maintaining their integrity, as the CNT-gene complex has retained the ability to express proteins (He et al., 2020). Pantarotto and coworkers (Pantarotto et al., 2004) revealed that newly formed, novel functionalized SWCNT-DNA complexes have high DNA expression ability than DNA alone.

Tissue Regeneration and Artificial Implants

In recent years, innovations in the study of CNT synthesis and knowledge of cell and organ transplantation have led to the continued advancement of CNT-based tissue engineering and regenerative medicine. Among various other materials, such as natural and synthetic polymers, carbon nanotubes could be the best tissue engineering candidate. Since this nanomaterial is biocompatible, non-biodegradable, and can be functionalized with biomolecules, it can be used to facilitate organ regeneration. CNTs can be used as additives in this area to enhance the mechanical strength and

conductivity by incorporating them with the host's body (Bekyarova et al., 2005; Kateb et al., 2010; MacDonald et al., 2005; Usui et al., 2012; Zhang et al., 2010).

Indeed, MacDonald et al. (MacDonald et al., 2005) and the researchers have successfully merged carboxylated SWCNTs with a polymer or collagen to develop a nano composite that can be used as a tissue regeneration scaffold. CNTs, for example, have been shown to improve bone tissue regeneration in mice and cell differentiation arising from nerves by embryonic stem cells in vitro (Singh et al., 2012; Zhang et al., 2010). Normally, the body rejects the implants by inducing discomfort after they are implanted. However, nanotubes of a smaller size, bound to other proteins and amino acids, prevent this rejection. They can also be used as implants in the form of artificial joints that do not cause rejection from host. Carbon nanotubes filled with calcium and organized in the structure of bone can also serve as a bone replacement due to their high tensile strength.

For the Treatment of Neurodegenerative Disorders and Alzheimer's Disease

CNTs have been used in neuroscience as a potential biomedical material due to their small dimensions and accessible external modifications (Singh et al., 2012; Yang et al., 2010; Zhang et al., 2010). CNTs can cross the blood-brain barrier through different targeting mechanisms and serve as successful delivery carriers for the targeting brain. Yang et al. (Yang et al., 2010) have found that SWCNTs were successfully used to deliver acetylcholine with a high safety range in mice brains, which was affected by Alzheimer's disease. Most of the functionally modified SWCNTs or MWCNTs have been widely used to treat neurodegenerative diseases and brain tumors (Bekyarova et al., 2005; Digge et al., 2012; Zhuang Liu et al., 2009). These findings suggest that CNT-drug molecule complexes have a more significant effect on neuronal growth than the drug alone.

CNT as Antioxidants

Approximately fifty years ago, the principle of oxygen-free radicals was established. However, it was only in the last twenty years that their functions in the development of disease, as well as the protective effects of antioxidants, have been discovered (Pham-Huy et al., 2008). Despite these challenges, research into the potential role of carbon nanotubes as free-radical scavengers is still in its initial stages. CNTs, especially carboxylated SWCNTs, are antioxidants in nature,, and may have biomedical applications in the prevention of chronic illnesses, aging, and food preservation (Galano, 2008, 2010).

Francisco-Marquez et al. discovered that the existence of –COOH groups increases the free radical scavenging behavior of SWCNTs. That carboxylated SWCNTs are just as strong as their nonfunctionalized counterparts in scavenging free radicals (Francisco-Marquez, Galano, & Martínez, 2010). Antioxidant properties of carboxylated CNTs have been used in anti-aging cosmetics and sunscreen creams to prevent skin from free radicals produced by the body or UV light (Digge et al., 2012; B. Singh et al., 2012). More research into different CNT types is required in the future to improve their beneficial impact as a free radical scavenger for biomedical applications, as free radicals are well-known to be highly harmful (Galano, 2008; Pham-Huy et al., 2008).

CNTs as a Biosensor for Detection and Diagnosis

A biosensor is an analytical system that combines a biological component with a physicochemical detector. CNTs have been recently been used in biosensing nanotechnology, but it represents an exciting new field for therapeutic monitoring and in vitro and in vivo diagnostics. Many scientists, have combined carbon nanotubes with glucose-oxidase biosensors to enhance blood sugar monitoring in diabetic patients with greater precision and ease of manipulation than biosensors alone (Digge et al., 2012; Usui et al., 2012; Wang et al., 2004) . Other CNT-enzyme biosensors have been developed for therapeutic monitoring and diagnostics, such as CNT-based dehydrogenase biosensors or peroxidase and catalase biosensors (J. Wang, 2005; Zhu, Wang, & Xu, 2011). The sensitivity of the assay for electrical detection of DNA was greater with the alkaline phosphatase (ALP) enzyme linked to CNTs than with ALP alone. The assay using the SWCNT-DNA sensor, which was created by combining SWCNTs with single-strand DNA (ssDNA), had a much higher sensitivity than conventional fluorescent and hybridization assays. Antigen detection can also be done by using this CNT-biosensor-linked assay. As a result, it could provide a quick and easy method for molecular diagnosis in diseases that have molecular markers, such as DNA or protein. (Wang, 2005). Besides this, using acetylcholine esterase immobilized on the CNT surface, it can detect certain organophosphorus pesticides with electrochemical detection (Digge et al., 2012; J. Wang, 2005; Zhu et al., 2011). CNTs as biosensor vehicles are extremely important for establishing sensitive diagnostic and analysis techniques from the lab to the clinic due to their size and unique structure.

Separation of Chiral Drugs Using Carbon Nanotubes

In the drug industry, 56% of drugs are currently being used are chiral products, and 88% of drugs are distributed as racemic mixture (Nguyen et al., 2006). The US

Food and Drug Administration recently proposed that racemic medications should be tested for each enantiomer's action in the body and suggested the development of innovative chiral drugs as single enantiomers (Galano, 2008). Hence a number of new chiral drug separation technologies have been developed, which includes carbon nanotechnology (Silva et al., 2012) A microcolumn packed with SWCNT was recently used as a chiral selector for the separation of enantiomers with fluorescent detection. Yu et al. (Yu et al., 2011) have developed a chiral solid phase of MWCNT crosslinked with hydroxypropyl-β-cyclodextrin for enantio-separation of racemic clenbuterol, a bronchodilator, with a high-resolution factor. The helical winding of the graphitic rings around the tube axis also reveals that CNTs are chiral forms. Many racemic mixtures of drugs have been successfully separated as single enantiomers using chiral selector modified CNTs.

Solid Phase Extraction of Drugs Using CNTs

CNT surfaces provide excellent adsorption potential due to their strong interaction with other molecules, especially those containing benzene rings. Non-modified and modified carbon nanotubes have been identified as Solid Phase Extraction adsorbents for the extraction of drugs, pesticides, and natural compounds in various media, including biological fluids, drug formulations, the environment, plants, and so on (El-Sheikh, 2011). CNTs were reported to have equivalent or higher adsorption ability than silica-based adsorbent or microporous resins. Many uses of carbon nanotubes in SPE can be found in several recently published papers that deal with the topic in particular (El-Sheikh, 2011; Ravelo-Pérez et al., 2010). Many medications, such as benzodiazepines, sulfonamides, non-steroidal anti-inflammatory drugs (NSAIDs), barbiturates, antidepressants, propranolol, cinchonine, and quinine, have been isolated by SPE using either SWCNTs or MWCNTs as adsorbent materials in different samples, and then analyzed using various physicochemical techniques.(El-Sheikh, 2011). Many other applications of CNTs in SPE have been carried out for detection of pesticide (carbofuran, iprobenfos, parathion-methyl, etc.), natural products and phenolic compounds used as preservative. Furthermore, carbon nanotubes can be used to remove inorganic ions and organometallic compounds, and also to prepare stationary phases for GC, LC, and HPLC columns (El-Sheikh, 2011; Ravelo-Pérez et al., 2010).

ADME (Absorption, Distribution, Metabolism and Excretion) of CNTs

ADME of different types of CNTs has been studied, and many research articles on the subject have already been published in the literature (Hirlekar et al., 2009; Yang et

al., 2012; Zhang et al., 2011). The biodistribution and metabolism of these nanotubes are mainly influenced by physicochemical properties, size, surface modification, solubility, shape, diffusion, and chemical composition. Already a lot of research have been published in the literature, on the biodistribution of water soluble CNTs (SWCNT/ MWCNT) in animal model (Hirlekar et al., 2009; Wang et al., 2004; Yang et al., 2012). No toxic effects or deaths reported in any of these research. In both the studies, Iodine or Indium a radioactive isotope used as a tracer to observe their biodistribution in animals (Pantarotto et al., 2004; H. Wang et al., 2004).

The first study reveals that the administration route had no effect on CNT biodistribution and that the Iodine-SWCNT-OH complex spread rapidly across the body, with 94% of the nanotubes excreted unchanged in the urine and 6% in the feces (Hirlekar et al., 2009; Wang et al., 2004). Stomach, kidneys, and bone were the most common organs for its deposition, but there were no records of tissue injury or pain.

In the second study, animals were injected with two types of Indium-functionalized SWCNT or MWCNT through IV. Both forms of functionalized CNTs reported an affinity for kidneys, muscle, skin, bone, and blood 30 minutes after administration and with very similar biodistribution profiles. (Singh et al., 2006; Yang et al., 2012). It was observed that all types of CNTs, were efficiently removed from all tissues, with a maximum blood circulation half-life of 3.5 hours (Yang et al., 2012).

According to some researchers, CNTs can be broken down by myeloperoxidase (MPO), an enzyme found in mice neutrophils. But their findings counter the widely held view that carbon nanotubes are not broken down in the body.(Kagan et al., 2010). Since it clearly shows that endogenous MPO can break down CNTs into water and carbon dioxide, this action of how MPO transforms CNTs into water and carbon dioxide may be important in medicine. It also represents a breakthrough in nanotechnology and nanotoxicology.(Singh et al., 2012).

Peglyation of CNTs

Pristine carbon nanotubes are insoluble in the majority of solvents that have deterred their utility in biomedical applications despite their unique physicochemical characteristics like good penetrability, large surface area for imparting multifunctionality, photothermal/photoacoustic effects, and so on. All these advantages will be realized only if the nanotubes show sufficient dispersibility.

Due to the formation of large bundles held together by the van der Waals forces, pristine CNTs are difficult to disperse in solution. Various dispersion agents, such as peptides, biomolecules, surfactants, and polymers, were used to keep the nanotubes away from self- aggregating (Dalmasso et al, 2012; Filip et al, 2011; Han et al., 2012; Oleszczuk & Xing, 2011). To meet the optimum dispersion effect, other natural polymers such as gum Arabic, amylose, and some natural organic matter can

be used (Alpatova et al., 2010). Due to the existence of –COOH groups, oxidized carbon nanotubes have better dispersibility than pristine carbon nanotubes. However, despite of improved dispersibility, they have a low blood half-life due to rapid uptake by reticuloendothelial cells, so PEGylation can be used to increase the blood half-life (Pisal et al., 2010). Polyethylene glycol is a polymer made up of repeated units of ethylene glycol (HO-CH2–CH2-OH) with MW varying typically from 200 to 6000 amu. At low molecular weights (200 to 800 amu), it is a liquid, but at higher M.W(1000 amu), it becomes a waxy solid. The former PEGs are highly soluble in water, but as the molecular weight increases, the solubility decreases. PEG has a high degree of chemical stability in both oxidizing and reducing environments, and is resistant to acid and base-induced decomposition (Bhirde et al., 2010; Ravelli et al., 2013). Furthermore, when injected in small amounts as a protein conjugate in different species, high molecular weight PEGs are considered nontoxic (Pisal et al., 2010).

PEG has an excellent physico-chemical and biological properties, such as hydrophilicity, solubility in water and organic solvents, lack of toxicity, and lack of antigenicity and immunogenicity, which allowed it to be used in a wide range of biomedical and biotechnological applications (Ravelli et al., 2013; Tsubokawa et al., 1987). Terminal hydroxyl groups present on PEG can be covalently bound with a wide range of drug molecules. Carbon nanotubes can be PEGylated easily, and the presence of hydrophilic chains on the surface of CNTs avoids bundling of CNTs, thus increasing solubility and preventing carrier engulfment by the body's RES (Reticulo Endothelial System). SWCNT modified with branched PEG chains was shown to have a more extended circulation period, lower toxicity, and more efficient clearance from the body (Bhirde et al., 2010; Ravelli et al., 2013). PEGylated SWCNTs have a larger hydrodynamic scale and are less immunogenic (Mazzaglia et al., 2001; Tsubokawa et al., 1987).

PEGylation of CNT is performed in one of two ways: covalent or non-covalent functionalization (Tsubokawa et al., 1987). If a strong bond between the nanotubes and the drug biomolecules is required, covalent functionalization is the preferable method of modification. This covalent binding is highly dependent on the grafting of reactive species molecules onto the inert sp2 carbon structure of the -conjugated skeleton, which can only be accomplished by directly polymerizing pristine CNTs with hydrophilic polymers like polyethylene glycol (PEG), oligomers, or biomolecules with defect or sidewall functionalization. (Peretz and Regev, 2012). The most widely used surface defect-derived groups to bind CNTs with amine sites on biomolecules is carboxylic acid group. However, during the oxidation process, this method can result in loss of material as well as a partial loss of properties of the CNTs (Qi et al., 2012). Crosslinking agents such as carbodiimides (Hao et al., 2011), active esters (Darabi et al., 2014), thionyl, or oxalyl chloride activate the carboxylic acids first

(Ghini et al., 2013) to generate highly reactive intermediates that yield ester or amide linkages, which can then be covalently attached to a variety of biomolecules. Other methods for sidewall covalent functionalization of CNTs were found to be effective, including elemental fluorination, hydrogenation, radical additions, ozonolysis, electrophilic addition, and 1,3-dipolar cycloaddition of azomethine.

In comparison to covalent functionalization, noncovalent functionalization does not disrupt sp2 bonding and thus retaining the functional properties and native structure of CNTs more effectively. The use of sonication, mixing, centrifugation, or filtration are standard functionalization methods for noncovalent dispersion of CNTs (Fernando et al., 2004). Surface modifications by covalent and noncovalent methods for efficient CNT dispersion are reviewed in depth by Kim and the coworkers (Kim et al., 2012).

π-π Stacking of Aromatic Drug Molecules

Large surface areas exist for supramolecular chemistry on carbon nanotubes prefunctionalized noncovalently or covalently by a common surfactant or acid-oxidation routes. Water-soluble MWCNTs with poly(ethylene glycol) (PEG) functionalization *via* these routes allow for surprisingly high degrees of π-π stacking of aromatic molecules, including a cancer drug (doxorubicin) with ultrahigh loading capacity (Liu & Sun, 2007).

PEG–PLA Nanoparticles as Drug Carrier

Over the last two decades, another group of polymers has been widely studied to develop systems for sustained drug delivery-the aliphatic polyester-in particular bioresorbable poly(lactic acid) (PLA) (Rashkov et al., 1996). The ability of PLA to interact with other polymers such as PEG through hydrogen bonding is an essential factor for the controlled release of a drug from a delivery vehicle. This type of interaction is sensitive to pH and temperature, and thus, increasing the temperature or lowering the pH can lead to dissociation of hydrogen bonds, thus avoiding the drug's excess release.

The PEG–PLA nanoparticles have the advantages of both PEG and PLA. As a drug carrier, PEG–PLA nanoparticles have some benefits, eg, 1) reducing the first-pass effect and increasing bioavailability; 2) increasing drug loading and encapsulation efficiency; 3) reducing particle size and burst release while improving targeting; 4) avoiding recognition and removal by the reticuloendothelial system, thereby prolonging the circulation time of drugs in the blood and improving stability; and 5) good safety. In many studies, PEG–PLA nanoparticles were used as carriers for vaccine, protein, and gene, particularly in a sustained/controlled release drug

delivery system and targeted-drug delivery system that could enhance drug efficacy and reduce drug resistance (Xiao et al., 2010).

Controlled Release Drug Delivery System

PEG–PLA nanoparticles are mainly diffusion and degradation-controlled release systems. Hydrophobic drugs especially accumulate in the hydrophobic matrix. In diffusion-controlled systems, drugs are dissolved or dispersed in PLA based polymers, and the release rate is controlled by drug diffusion through a PLA matrix. In the controlled degradation system, drugs are dispersed in PLA, and the drug release rate is determined by degradation rate due to influences from PLA chain length, drug loading of nanoparticles, release medium, and other factors (Utreja et al., 2010).

Riboflavin-Conjugates for Targeted Drug Delivery

Nanotechnology offers a wide range of unique opportunities for the targeted delivery of various molecules to cancer cells through nanoparticles (NP) coupled with ligands for cancer cell membrane molecules. This approach can deliver anticancer drugs, therapeutic genes, and imaging molecules and aims to enhance the therapeutic index of a drug or improve the ability of an imaging agent to identify cancer. Recent studies have demonstrated the utility of this approach with anticancer drugs including methotrexate, doxorubicin, paclitaxel, and cisplatin as well as imaging agents for detection based on fluorescence, magnetic resonance imaging (MRI), and radioactive isotopes (Thomas et al., 2010).

The therapeutic or imaging molecules are carried either covalently attached to the particle or encapsulated within an NP. Riboflavin, more commonly known as Vitamin B_2, is a naturally occurring molecule with a vital role in the energy metabolism of cells. It is internalized via receptor-mediated endocytosis and is essential in synthesizing the redox cofactors FMN (flavin mononucleotide) and FAD (flavin adenine dinucleotide). Dendrimer conjugated ligands provide novel opportunities for the development of nanomedicines due to their unique ability to traverse biological barriers. Functionalized dendrimers can be used for imaging and receptor-mediated tumor targeting leading to enhanced efficacy of the drug while reducing toxic effect on healthy cells. Riboflavin receptors are over-expressed in breast and prostate cancer cells, and for this reason we studied active drug targeting using riboflavin as a ligand (Witte et al., 2012).

This concept is essential from a therapeutic point of view. In fact, it has been argued that the linkage of cytotoxic drug to selected vitamins, leading to vitamin-drug conjugates, would result in precisely delivering great amounts of the targeted drug at high doses to cancer cells, and thus, represents an attractive and valuable

approach for targeting tumor cells. Nowadays, biotin, folic acid, vitamin B12 and riboflavin, which are essential for the division of all cells and particularly for tumor cells have been recently experimented as targeting agents (Bareford et al., 2013).

TOXICOLOGY STUDIES OF CNTS

In the literature, the outcomes of CNT toxicological assays appear to be contrary. Some preliminary in vitro experiments have shown that CNTs are toxicologically benign to certain cells, whereas other studies have shown that CNTs, especially raw materials, are potentially harmful to a wide range of living systems (Chang et al., 2011; Digge et al., 2012; Ravelo-Pérez et al., 2010; Yang et al., 2007). It should be noted that the pharmacological effects of CNTs conjugated with drug molecules have yet to be examined in men, and therefore their clinical toxicity has not yet determined.

In Vitro Toxicological Studies

In vitro toxicity studies of water-dispersible nanotubes (SWCNT) on a human lung cell line reported that SWCNT had no intracellular localization and showed that SWCNT could trigger indirect cytotoxicity by changing the cell culture medium, resulting in an inaccurate toxic impact (Casey et al., 2008; Chang et al., 2011; Firme III & Bandaru, 2010; Yang et al., 2007). Dumortier et al. (Dumortier et al., 2006; Han et al., 2012) Water-soluble SWCNTs labeled with fluorescein were found to be nontoxic to cultures of rodent B- and T-lymphocytes as well as macrophages, thus retaining their feature. MWCNTs of smaller sizes proved to be more harmful than those of larger sizes. The increased oxidative stress caused by MWCNT induces cytotoxicity in rat glioma cells. However, numerous forms of cells, including human keratinocytes, rat brain neuronal cells, human embryonic kidney cells, and human lung cancer cells, have shown to be damaged by in vitro administration of pristine CNTs, which are water insoluble (Fisher et al., 2012; Shvedova et al., 2009; Ursini et al., 2012). For this reason, these insoluble pristine CNTs cannot be used as vehicles for drug and gene delivery in therapeutic applications.

In vivo Toxicological Studies

An important review article about CNT toxicity recently published has documented many in vivo toxicological studies performed in different animals using IV or SC injections and gastrointestinal exposure with functionalized or distributed SWCNTs or MWCNTs (Yang et al., 2012). Available safety data shows that CNTs have low toxicity through various exposure pathways for biomedical applications. CNTs can

cause significant toxicity in mice only when given at a very high dose (60 mg/kg) in the form of Polyethylene-Glycol-MWCNTs (PEG-MWCNTs) (Yang et al., 2012; D. Zhang et al., 2010). Despite the route of administration, SWCNT toxicity is closely linked to oxidative damage induced by them (Folkmann et al., 2009). CNTs, when used as tissue engineering products for cell growth by implanting subcutaneously, it has demonstrated an excellent biocompatibility and induced no significant toxicity, except mild inflammation (Fraczek et al., 2008). However, (Folkmann et al., 2009), some researchers have found that SWCNTs can cause oxidative stress to DNA in mice after oral administration, while others reported that implanted SWCNTs and MWCNTs can cause inflammation.(Fraczek et al., 2008). In contrary other studies on the toxicity of CNTs to skin, indicated that CNTs were nontoxic for skin and had strong biocompatibility after being implanted subcutaneously (Yang et al., 2012).

Toxicity of CNTs in Human Beings

As nanomedicine of functionalized CNTs attached to drug molecules have yet to be tested in humans for clinical trials, most publications in the literature indicated that pristine CNTs might be the source of lungs diseases in employees of CNT industries similar to workers of asbestos industries (Lacerda et al., 2006; Takanash et al., 2012). Authors concluded that CNTs were capable of causing inflammation, fibrosis, and biochemical changes in the lungs based upon many animal studies in which CNT specks of dust were administered directly to the trachea and pharyngeal cavity to determine the pulmonary toxicity of manufactured CNTs (Donaldson et al., 2006; Fisher et al., 2012; Lacerda et al., 2006; Shvedova et al., 2009; Takanashi et al., 2012; Ursini et al., 2012).

In a recent publication in 2013 (Ali-Boucetta et al., 2013; Poland et al., 2008), Ali-Boucetta et al. reported that the pathogenicity of long/ pristine CNTs could be reduced, and their effective length can dramatically decreased if the surface of CNTs are funtionalized by chemical treatment, with either TEG or PEG. However, there is still uncertainty about the potential risks by access to pristine CNTs and their residual impurities.

When various types of CNTs are evaluated in the clinic for short- and long-term therapy, the first critical concern is human toxicity. Some experimental toxicological tests *in vitro* and animals have recently found conflicting results; hence optimizing the physicochemical parameters to reduce CNT toxicity is exceptionally beneficial. Future CNT formulations, for example, should be attached with new sensitive markers so that they can directly enter target cells, or scientists should be able to instantly drive them from the outside to the target organ to prevent adverse effects on other normal tissue. More toxicological studies of various CNTs, from pristine

to functionalized CNTs and their conjugates, are strongly advised before being used in clinical trials and then sold internationally.

FUTURE RESEARCH DIRECTIONS

This chapter reveals recent applications of CNTs in various fields of drug and medicine. Since carbon nanotubes (CNTs) can move through cell membranes, they can transport drugs, genes, biomolecules, vaccines, and other materials deep into target cells. Carbon nanotubes have demonstrated a variety of impressive benefits such as invention of nanomedicine that opened up new options for drug delivery which are more successful than traditional methods. CNTs avoid biodegradation and are a powerful engineering option over other existing materials used to repair damaged organs; another innovative method is the use of collagen CNTs materials as scaffolds in tissue generation and artificial implants. CNTs, when combined with biosensors or other materials, have also proved to be practical tools for therapeutic monitoring and diagnosis. For general health, it's also a good idea to improve the free radical scavenger capacity of functionalized CNTs. Overall, nanotechnology can revolutionize future clinical ideas and provide opportunities for the treatment of many medical conditions.

CONCLUSION

A vast range of CNT applications can be found in the pharmacy and medicine domains. It focuses on the most promising approaches to using carbon nanotubes as a drug delivery system for pharmaceuticals and biomolecules in the treatment and diagnosis of a variety of diseases. Many synthetic approaches have been tweaked to increase CNT production and characteristics, and new techniques are being tested to obtain perfect CNTs. It's worth noting that the pharmacological effects of CNTs coupled with medication molecules have yet investigated in humans, therefore their clinical toxicity has yet to be determined. However, despite many surprising results of CNTs obtained during the beginning of this research field, there are still tremendous opportunities to be explored and significant challenges and risks to be solved. Therefore, more imagination and innovation are needed to elaborate on new CNTs and their conjugates with high efficacy and safety for medicinal use in the future. At the same time, several problems in this nanomedicine technology must be resolved or explained.

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Chapter 7
Role of Polyherbal Formulations of Medicinal Plants From Himalayan Regions in the Management of Diabetes

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ABSTRACT

Current research on phytochemicals is mainly focused on novel phenolic and polyphenolic compounds expressing their potential as therapeutic agents in various diseases like cancer, autoimmune diseases, cardiovascular disorders, diabetes, oxidative stress-related diseases, as well as their properties to inhibit the growth and proliferation of infectious agents. Among the human physiological disorders, one of the most severe endocrine metabolic diseases is Diabetes mellitus which is a clinical disease distinguished by a deficit in the production of insulin or resistance to the action of insulin. Globally, diabetes is an increasing health concern which is now emerging as an epidemic. About 700-800 plants are exhibiting anti-diabetic activity that has been studied. As far as nanotechnology in diabetes research is concerned, it has made possible the buildout of novel glucose measurement as well as insulin delivery modalities that possess the potential to excellently enhance the quality of life of the diabetic patient.

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INTRODUCTION

The term "medicinal plant" is given to broad classes of plants and herbs possessing medicinal properties. Such classes incorporate various types of plants used in herbalism ("herbology" or "herbal medicine"), which can be defined as the use of plants for medicinal purposes, and the study of such uses in context of animal physiology. The word "herb" is derived from the Latin word, "herba" and an old French word "herbe". Now-a-days the definition of herb has been extended to leafy green or flowering parts of a plant either fresh or dried. Earlier, the term "herb" was only applied to non-woody plants that die down to the ground after flowering. Medicinal plants are used as great sources of phenolic and polyphenolic compounds that are attributed to their medicinal properties. These benign compounds as part of phytochemical pool of different plant parts are the promising agents as antidiabetic, antimicrobial, anti-inflammatory, antifertility, antianxiety, antiaging, antiarthritic, antidepressant, analgesic, antispasmodic, etc. (Boy et al., 2018, Spinella, M. 2001). There are several plants that are reported for their anti-diabetes activity and the most potent and the most frequently studied for diabetes and its complications are *Allium cepa, Allium sativum, Zingiber officinale, Curcuma longa, Ginkgo biloba, Aloe Vera, Panax ginseng, Momordica charantia, Azadirachta indica, Phaseolus vulgaris,* etc. With continuously rising rates of prevalence and mortality, *Diabetes mellitus* is a severe health concern. It is characterized by excessive amounts of plasma glucose due to deficiency of insulin and insulin resistance, or both, leading to metabolic deformity in lipids, carbohydrates, and proteins. These lead to many secondary complications including ketosis, polyurea, retinopathy, polyphasia, and cardiovascular disorder (Nisha R et al., 2020, Bera TK et al., 2010). Despite the advent of hypoglycemic agents and their widespread use, diabetes and associated problems appear to be a global health concern, affecting almost 10% of the world's population and perceived to be a major source of high economic losses that can obstruct nations' growth in turn. Insulin and many oral hypoglycemic drugs, such as metformin, sulfonylureas, troglitazone, glucosidase inhibitors, etc., are commercially available treatment for diabetes. However, serious adverse side effects are reported to occur, such as lactic acidosis, diarrhea as well as hepatic and nephrotoxicity. By enhancing insulin sensitivity, rising the production of insulin, and reducing the amount of glucose in the blood, traditional medications are used to treat diabetes. In maintaining normal blood glucose levels, the adverse effect of drug therapy is not always satisfactory, and this observation has been granted to many medicinal and aromatic plants as a promising source of antidiabetic agents that is commonly used in different conventional medicine systems worldwide for the treatment of *Diabetes mellitus*, and many of them are considered to be successful against diabetes. In the last few decades, there has been an increasing interest in herbal medicine in

the management of diabetes both in developing and developed countries, due to their natural source and minimum side effect profiles (Mamun-or-Rashid ANM et al.,2014, Khan A et al., 2011). In this chapter we addressed the significance of some medicinal plants and novel herb-based formulations from Himalayan region of India that offers numerous possible advantages for synergistic activity in the medication of diabetes with or without structural modifications.

MEDICINAL PLANTS: A HISTORICAL PROSPECTIVE

Plants have been used as sources of food, perfume, and essential oils long before prehistoric period. Ancient Egyptian papyrus, Unani manuscripts, and Chinese writings described the use of herbs in management of various ailments. Various evidences exist that Indian Vadis, Unani Hakims, and European and Mediterranean cultures were involving herbs for their medical needs over 3000 years. Indigenous cultures such as Egypt, Rome, Iran, Africa, and America incorporated herbs in their healing rituals, while other developed traditional medical systems such as Unani, Ayurveda and Chinese medicine used herbal therapies systematically. Indian workers worked carefully to analyze and arrange the spices (Kabera et al., 2014). Charaka made 50 gatherings of 10 spices, every one of which would get the job done conventional doctors' necessities. Likewise, Sushruta orchestrated 760 spices in 7 particular sets dependent on a portion of their normal properties. The utilization of restorative plants isn't only a custom of the far-off past but 90% of the total populace depends totally on crude spices and crude concentrates as drugs (Kala, C. P.2005, Alamgir et al., 2017). A 1997 overview demonstrated that 23% of Canadians have utilized homegrown prescriptions. Also, it is assessed that around 75–80% of individuals of non-industrial nations and around 25% of individuals of created nations depend either straightforwardly or in a roundabout way on restorative plants for the primary line of treatment. Traditional medicinal systems continue to be widely practiced on many accounts. Rise in Population, prohibitive cost of treatments, inadequate supply of medicines, high side effect profiles of several synthetic drugs and development of antimicrobial resistance to currently used drugs for infectious diseases have led to enhanced emphasis on the use of plant derived bioactive compounds as the source of medicines for the innumerous kinds of human diseases and disorders. World Health Organization (WHO) recently estimated that more than 80% percent of people rely on herbal medicine formulations for some aspect of their primary health care needs worldwide. According to WHO, more than 21000 plant species have such phytochemical composition that express the potential for being used as therapeutic therapies. More than 35% of the entire plant species, at one time or other are used for medicinal purposes (Dubey et al., 2004, Alvin et al., 2014).

India is perched on a gold mine of very much recorded and generally all- around rehearsed information on natural medicine. This nation is considered as biggest maker of restorative spices and is appropriately called the greenhouse of the world. India authoritatively perceives more than 3000 plants for their therapeutic worth. It is by and large assessed that more than 6000 plants in India are being used in customary, society and homegrown medication, speaking to about 75% of the therapeutic requirements of the underdeveloped nations. WHO additionally has perceived the significance of customary medication and has been dynamic in making procedures, rules, and norms for the herbal medication (Kala, C. P. 2000).

PATHOPHYSIOLOGY OF *DIABETES MELLITUS*

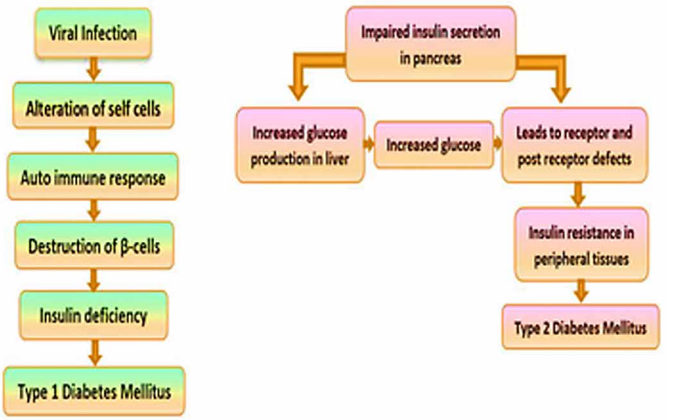
Diabetes is a metabolic disorder in which there is chronically increased blood glucose levels (BGLs) and an incapability to sustain BGL homeostasis. Individuals having type 1 diabetes are unable to produce insulin because of autoimmune mediated demolition of the insulin producing beta cells within the pancreas. In type 2 diabetes, there is insulin resistance, or unresponsive of cells to insulin in the bloodstream. In both cases, the inability of homeostasis-regulation can result in chronically high and low blood glucose levels known as hyperglycemia or hypoglycemia respectively. *Diabetes mellitus* is recognized as one of the world's five leading causes of death. According to the WHO, *Diabetes mellitus* is defined as a metabolic condition of multiple etiology characterized by chronic hyperglycemia with fat, carbohydrate, and protein metabolism disruptions arising from deficiencies in insulin release, insulin action, or both. The distinctive symptoms of *Diabetes mellitus* include polyuria, thirst, weight loss, blurred vision, Long-term impairment, dysfunction, and malfunction of multiple organs (Arumugam G et al 2013). There are four main types of *Diabetes mellitus* viz. type 1 diabetes, type 2 diabetes, other specific types of diabetes and gestational diabetes (Table 1).

Table 1. Different types of Diabetes mellitus with definition

S. No.	Types	Definition
1	Type 1 Diabetes	Type 1 diabetes is a disorder in which immune system abolishes insulin-making cells in pancreas. These are so- called beta cells. The disorder is usually spotted in children and youngsters, so it used to be termed as juvenile diabetes.
2	Type 2 Diabetes	Type 2 diabetes is a chronic disorder that prohibits insulin from being processed by the body the way it should. It is said that people with type 2 diabetes have insulin resistance.
3	Gestational *Diabetes Mellitus*	Gestational diabetes is a disease in which, during pregnancy, the blood sugar levels get elevated. Per year it affects up to 10% of women who are pregnant in the U.S. It effects pregnant women who are not diagnosed with diabetes ever.
4	Other types of Diabetes	Other types of diabetes comprise those caused by genetic abnormalities of the beta cells, the insulin-producing part of the pancreas such as neonatal diabetes

Insulin as a hormone plays a cardinal role in the absorption of blood glucose into most cells of the body, particularly in the muscle, liver, and adipose tissue. Thus, in the entire pathophysiology of *Diabetes mellitus*, lack of insulin or the inconsiderateness of its receptors reflects a critical task. Insulin into the blood is released by β-cells, which are located in the pancreatic islets of Langerhans, in response to increasing blood glucose levels, mainly after food intake. Insulin is used for absorption of blood glucose for the use of energy, for conversion to other molecules required, or for storage by approximately two-thirds of the body cells (Grover JK et al., 2002, Mutalik S et al., 2003). Lower glucose levels in the bold reduces insulin release from the beta cells and the breakdown of glycogen into glucose. The hormone glucagon, which works in the opposite manner to insulin, is regulating this whole process. If the quantity of insulin available is insufficient, if there is poor response to the effects of insulin (insulin insensitivity or insulin resistance) or if the insulin itself is nonfunctional or deficient, glucose will not be precisely absorbed and processed in the liver and muscles by the cells of body which require it. The net result is gradually increased blood glucose level, decreased synthesis of proteins, and other metabolic derangements, such as acidosis. Although, if the glucose content in the blood vestiges rises with time, the kidneys can reach a reabsorption portal, leading to urinary excretion, a condition called glycosuria (Salehi B et al., 2019, Gaonkar VP et al., 2020). (**Fig.**1)

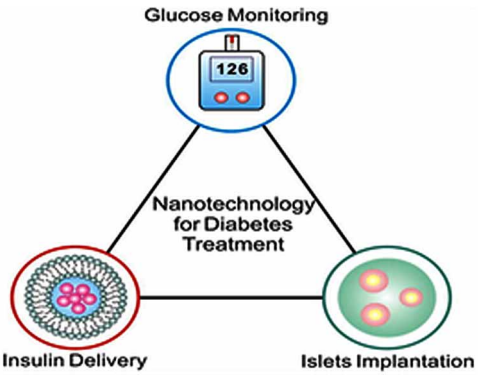
Figure 1. Pathophysiology of Type 1 & 2 Diabetes Mellitus



NANOTECHNOLOGY FOR DIABETES TREATMENT

The incorporation of nanotechnology in medicine revealed to have many possible benefits, for example, analysis of minute volumes of analytes as well as easy access to small and clinically relevant areas of tissues and cells. Diabetes management at its interface with nanotechnology seems to have revolutionized the treatment trend. Glucose sensors are examined with nanoscale components that include carbon nanostructures and metal nanoparticles. Their addition generally enhances the glucose sensor sensitivity, temporal response, and can result in generation of efficient sensors that are facilitated with continuous *in vivo* glucose monitoring. This enhanced glucose sensing technology seems to have an immediate and significant impact on the health of diabetic patients, as improved sensing results in more accurate insulin dosing and thus management. Additionally, strategies have been developed to deliver insulin on nanoscale level in which there is an automatic release of insulin in response to changing blood glucose levels. Nanomedicine has thus made possible the more robust insulin delivery strategy that can detect small changes in blood glucose levels and precisely regulate the rate of insulin release to maintain normal glucose levels (**Fig. 2**). Such strategies are tremendous developments over contemporary standards of care and when applied on clinical level, these technologies will allow improving the health and quality of life of diabetes more effectively (DiSanto et al., 2015).

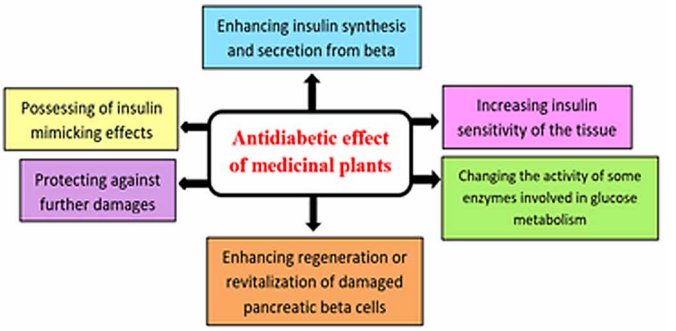
Figure 2. Nanotechnology approach for diabetes treatment



ANTIDIABETIC EFFECTS OF MEDICINAL PLANTS

Since the advent of human beings on this planet, natural herbal medicines have been used and are thus roughly as ancient as time itself. Phytochemical constituents mainly secondary metabolites are having disease modulating activities and are considered as rich resources of ingredients which can be used in drug development-pharmacopoeial, non-pharmacopoeial or synthetic drugs. Plant based medicines have better cultural acceptability, better compatibility and adaptability with the human body and pose minimum side effect profiles as compared to chemical allopathic drugs. The World Health Organization (WHO) has identified approximately 21,000 plants which are used around the world for medicinal purposes. Treatment with medicinal plants is considered very safe. The biggest benefit of using such remedies is that they are in synchronization with nature and independent of any age group or the sex of subject under treatment (Robertshawe, P. et al.,2007, Grabley, S., & Sattler, I. 2003). Health researchers are of the firm conviction that herbs are only solutions to cure a number of health-related problems and diseases. Thorough studies are being conducted on the novel compounds that form part of phytochemical pool of different plants and herbs to arrive at accurate conclusions about their use and efficacy as oral and topical drugs for management of different diseases and disorders. Related researches are showing promising results everywhere and this is the reason why herbal treatment is growing in popularity throughout the globe. In maintaining normal blood glucose levels, the adverse effect of drug therapy is not always satisfactory. While there are various chemical pharmaceutical treatments developed for patients, it is still the fact that such medications are not able to cure diabetes completely. Adversely, various side effects are produced by chemical hypoglycemic agents used currently (Chandra S. J et al., 2007, Wadkar KA et al., 2008). Therefore, the antidiabetic potentiality of medicinal foliage plus its herbal preparation in the treatment of disease has been highly considered in recent times (**Fig. 3**). Different medicinal plants with hypoglycemic assets are recognized as a substitute to synthetic agents. Natural herbs for the treatment of diabetes focus on lowering the level of blood sugar and reducing the adverse effects of the disease. In the last few decades, there has been an increasing interest in herbal medicine in the management of diabetes both in developing and developed countries, due to their natural source and minimum side effect profile (Modak M et al., 2007, Salehi B et al., 2019). In the Indian subcontinent, following are some polyherbal formulations derived from medicinal plants of Himalayan regions for the treatment of diabetes.

Figure 3. Antidiabetic effects of medicinal plants



POLYHERBAL FORMULATIONS AND THEIR POTENTIAL AS ANTIDIABETIC

- **Diabecon**

A polyherbal detailing fabricated by 'Himalaya' containing *Gymnema sylvestre, Pterocarpus marsupium, Glycyrrhiza glabra, Casearia esculenta, Syzygium cumini, Asparagus racemosus, Boerhavia diffusa, Sphaeranthus indicus, Tinospora cordifolia, Swertia chirata, Tribulus terrestris, Phyllanthus amarus, Gmelina arborea, Gossypium herbaceum, Berberis aristata, Aloe vera, Triphala, Commiphora wightii, shilajeet, Momordica charantia, Piper nigrum, Ocimum sanctum, Abutilon indicum, Curcuma longa,* and *Rumex maritimus* is recommended for bringing down the level of glucose, increment hepatic and muscle glucagon substance, advance B cells fix and recovery and increment c peptide level. It has cancer prevention agent properties and shields B cells from oxidative pressure. It possesses insulin like activity by decreasing the glycated hemoglobin levels, normalizing the microalbuminuria, and balancing the lipid profile (Bera TK, et al., 2006, Maroo J et al., 2002).

- **Dia-Care**

Fabricated by Admark Herbals Ltd., this formulation is professed to be compelling for both Type 1 and Type 2 diabetes. It contains Sanjeevan Mool; Himej, Jambu beej, Kadu, Namejav, and Neem Patients taking insulin will, at last, be freed from the reliance on it, when taken regularly. The entire treatment finishes in 6 stages, each stage being of 90 days. The flavor of the medication is exceptionally unpleasant. It is an unadulterated natural formulation that successfully and securely improves Sugar Metabolism (The Diabetes Prevention Program,DPP 2002).

- **Diabetes Daily Care**

Produced by Nature's Health Supply, it is a Unique natural formula, which successfully and securely improves sugar metabolism. It was planned for type 2 diabetes. It contains Alpha Lipoic Acid, Cinnamon 4% Extract, Chromax, Vanadium, Fenugreek half concentrate, Gymnema sylvestre 25% concentrate, Momordica 7% concentrate, Licorice Root 20% as essential ingredients (Thakkar NV & Jagruti AP 2010).

- **Epinsulin**

Advertised by Swastik plans, this formulation contains epicatechin, a benzopyran, as a functioning agent. Epicatechin expands the cAMP substance of the islet, which is related to expanded insulin discharge. It assumes a job in the change of proinsulin to insulin by expanding cathepsin movement. Furthermore, it has an insulin-mimetic impact on the osmotic delicacy of human erythrocytes, and it restrains Na/K ATPase movement from the patient's erythrocytes. It remedies neuropathy, retinopathy, and upset digestion of glucose and lipids. It keeps up the respectability of all organ frameworks influenced by the sickness. It is accounted for to be therapeutic for diabetes, Non-Insulin Dependent *Diabetes Mellitus* (NIDDM) and a decent adjuvant for Insulin Dependent *Diabetes Mellitus* (IDDM), to decrease the measure of required insulin (Smith Olsen, C., & Overgaard Larsen, H. 2003).

- **Diabeta**

A formulation of Ayurvedic Cure, accessible in the container structure is shown to have anti- diabetic potential. It is formulated with a blend of a demonstrated immunomodulators, antihyperlipidemic, and hepatoprotective compounds. Diabeta contains Gymnema *sylvestre*, *Vinca rosea* (Periwinkle), *Curcuma longa* (Turmeric), *Azadirachta indica* (Neem), *Pterocarpus marsupium* (Kino Tree), *Momordica charantia* (Bitter Gourd), Syzygiumcumini (Black Plum), Acacia arabica (Black Babhul), Tinospora cordifolia, and Zingiber officinale (Ginger) extracts. It assaults the different components, which accelerate the diabetic condition, and adjusts the degenerative difficulties. Diabeta conquers protection from oral hypoglycemic medications when utilized as adjuvant to instances of uncontrolled diabetes. Diabeta presents a feeling of well-being in patients and advances indicative help of objections like shortcoming energy, torment in legs, body hurt, polyuria, and pruritis (Babuji, S. S. H. et al., 2010, The Diabetes Prevention Program, DPP 2002).

- **Syndrex**

Fabricated by Plethico Laboratory, it contains concentrates of sprouted fenugreek seed. Fenugreek is utilized as an element of conventional definitions for more than 1000 years. It has profound effect on the stabilization of islet cells ((Joshi CS et al., 2007).

- **Dihar**

This polyherbal blend contains eight distinct spices *Syzygium cumini, Momordica charantia, Emblica officinalis, Gymnema sylvestre, Enicostemm, Azadirachta indiaca, Tinospora cordifolia,* and *Curcuma longa.* Literary works uncovered that blend of these eight spices shows successful anti-hyperglycemic activity in Strptozotocin (STZ,45 mg/kg iv single portion) instigated type 1 diabetic rodents. Treatment with Dihar (100 mg/kg) for about a month and a half-created decline in STZ incited serum glucose and lipid levels and builds insulin levels when contrasted with control. Dihar showed huge lessening in serum creatinine urea level and lipid peroxidation in diabetic rodents (Patel SS et al., 2009, The Diabetes Prevention Program, DPP 2002).

- **Diabet**

A polyherbal plan containing *Curcuma longa, Coscinium fenestratum, Strychnos potatorum, Phyllanthus reticulatus. Tamarindus indica,* and *Tribulus terrestris,* was researched for its glucose resilience and antidiabetic potential in alloxan prompted diabetic rodents. The glucose resilience test and hypoglycemic investigations was done in ordinary rodents at a portion of 500mg/kg. The item demonstrated its viability at that concentration (Lanjhiyana Sweety et al., 2011).

- **Diasol**

A polyherbal antidiabetic definition containing plant concentrates of *Eugenia jambolana, Foenum graceum, Terminalia chebula, Quercus, infectoria, Cuminum cyminum, Taraxacum officinale, Emblica officinalis, Gymnea sylvestre, Phyllanthus nerui* and *Enicostemma littorale*, indicated 63.4% decrease of blood glucose level in a portion of 125 and 250 mg/kg body weight and end up being compelling antidiabetic polyherbal formulation (Babuji, S. S. H. et al., 2010).

- **Dianex**

A polyherbal detailing was screened for antidiabetic action in rodents and it has been accounted for in written works that Dianex produce huge hypoglycemic movement in both typical and diabetic mice. It was directed orally in various dosages of 100, 250 and 500 mg/kg body weight as long as about a month and a half. Administrationof Dianex as long as about a month and a half demonstrated it to be compelling in long haul treatment (Ogbonnia SO et al., 2010).

- **DRF/AY/5001**

An indigenous polyherbal blend containing *Gymnema sylvestre, Syzygium cumini, Pterocarpus marsupium, Momordica charantia, Emblica officinalis, Terminalia belirica, Terminalia chebula* and *Shudh shilajit)* created by Dabur Research establishment Gaziabad, inspire hypoglycemic/antidiabetic impact in both typical and tentatively prompted hyperglycemic rats. DRF/AY/5001 hindered altogether the hyperglycemia actuated by epinephrine. It indicated critical decrease in blood glucose level at 1-3 hr. With single portion treatment in alloxan initiated diabetes rodents with 600 mg/kg of Drf/Ay/5001 was like that of Glibenclamide. DRF/AY/5001 gave almost comparable outcome with that of engineered drug Glibenclamide (Mandlik RV et al., 2008).

- **Diashis**

An investigation was directed on polyherbal formulation made out of eight restorative plants for the administration of streptozotocin (STZ)- initiated diabetes in rodents. The investigation uncovered that treatment with 'Diashis' in STZ-instigated diabetic rodents brought about a huge recuperation in the exercises of hepatic hexokinase, glucose-6-phosphate dehydrogenase, and glucose-6-phosphatase alongside revision in the degrees of fasting blood glucose, glycated hemoglobin, and liver and skeletal muscle glycogen. The oxidative pressure status in the liver was revised by 'Diashis' which was featured by the recuperation in the exercises of catalase, peroxidase, and glutathione-S-transferase (Bera TK, et al., 2006).

- **Diabrid**

A homegrown based antidiabetic formulation was clinically assessed in 60 diabetic patients for a half year. The clinical examinations uncovered that Diabrid was all around endured in high dosages and was discovered to be a potential antidiabetic drug in mellow and moderate diabetic cases (180-280 mg/dl). The glucose level

was controlled inside 2-multi week relying on the introductory glucose level. The hypoglycemic action was portion reliant and slow. No harmful impact was seen on the kidney and liver (Quadri NM et al., 2006).

- **Diakyur**

A polyherbal detailing made out of *Cassia javanica, Cassia auriculata, Salacia reticulate, Gymnema sylvestre, Mucuna pruriens, Syzygium jambolaum, and Terminalia arjuna,* experimentally end up being a potential antidiabetic. The report demonstrated that Diakyur has huge hypoglycemic action just as anti-lipid peroxidative action. Literature investigations inferred that Diakyur is beneficial for long haul treatment in diabetic condition (Joshi CS et al., 2007).

- **Diasulin**

This polyherbal formulation contains extracts of Cassia *auriculata, Coccinia indica, Curcuma longa, Emblica officinalis, Gymnema sylvestre, Momordica charantia, Scoparia dulcis, Syzygium cumini, Tinospora cordifolia,* and *Trigonella foenum* . Investigation revealed that it controls the blood glucose level by expanding glycolysis and diminishing gluconeogenesis with a lower interest of pancreatic insulin than in untreated rodents. This is conceivable, in light of the fact that it manages the exercises of hepatic glucose metabolic catalysts. Diasulin additionally brought about huge lessening in tissue lipids and lipid peroxide development (Pari, L., & Saravanan, R. 2004).

- **ESF/AY/500**

A polyherbal detailing expected to be utilized for diabetic patients has been screened for cancer prevention initially. It is made out of eight restorative plants, namely *Aerva lanata, Aegle marmelos, Ficus benghalensis, Catharanthus roseus, Bambusa arundinaceae, Salacia reticulata, and Szygium cumini and 'Eruca sativa'.* Tthe ethanolic concentrate of ESF/AY/500 displayed critical cell reinforcement action indicating expanded degrees of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and diminished degree of lipid peroxidation. It has been revealed that EFPTT/09 evokes hypoglycemic and antidiabetic impact in both typical and alloxan actuated diabetes rodents. It likewise inspired a huge cancer prevention agent impact in diabetic rodents by its capacity to repress lipid peroxidation and raise the enzymatic cell reinforcement in pancreatic tissue. It has been discovered that at a portion of 600 mg/kg, the hypoglycemic impact of EFPTT/09 almost equivalent to that of Glibenclamide (5 mg/kg.). Exploration demonstrated that treatment with

5EPHF at portion 200 mg/kg to diabetic rodents brought about huge decrease of serum glucose, glycosylated hemoglobin, complete cholesterol, fatty oil, low thickness lipoprotein, creatinine, and urea though huge, expanded degree of insulin and high thickness lipoprotein was noticed (Sajeeth CI et al., 2010).

- **Glyoherb**

A polyherbal detailing was assessed for its antihyperglycemic, antihyperlipidemic, and cancer prevention agent impacts against ordinary and streptozotocin-prompted diabetic rodents. 'Glyoherb' sugar control granules have potential antidiabetic function as it brings down serum glucose levels and expands glucose resistance in STZ-actuated diabetic rodents. This polyherbal formulation also possess huge antihyperlipidemic activity as it brings down serum cholesterol and fatty oil levels. It was fairly discovered to be improving kidney and liver capacities. Also, 'Glyoherb' has potential cell reinforcement action as it diminishes lipid peroxidation. The antidiabetic action of 'Glyoherb' might be ascribed to its cell reinforcement properties too. Consequently, past exploration presumed that 'Glyoherb' might be viewed as a promising common and safe solution for the avoidance or deferral of diabetic intricacies (Thakkar NV & Jagruti AP 2010).

- **Karmin Plus**

An indigenous polyherbal definition containing *Momordica charantia, Azadirachta indica, Picrorrhiza kurroa, Ocimum sanctum,* and *Zinziber officinale* was assessed for antidiabetic movement by Banger et al and it was discovered that item demonstrated viability at two portion levels at 200 mg/kg and 400 mg/kg body weight for antidiabetic activity. Studies demonstrated that polyherbal detailing was compelling in diminishing plasma glucose levels in the diabetic rodents and demonstrated a beneficial impact on cardiovascular system. The high LD 50 worth (16.5g/kg) demonstrates that definition could be safe for use (Om PB et al., 2009).

- **SMK001**

Literature uncovered that SMK001 is a potential antidiabetic polyherbal detailing. Researches explored the anti-diabetic impact of SMK001 by assessing in the streptozotocin (STZ; 60 mg/kg, single intraperitoneal infusion) prompted diabetic rodents. Results demonstrated that SMK001 altogether decreases the blood and pee glucose level, and it shows more favorable impact at a portion of 100mg/kg contrasted with that of Glibenclamide 5mg/kg (Kim JD et al., 2006).

- **PM021**

Herbal equation comprises of two homegrown segments, *Mori Folium* and *Aurantii Fructus*, which is regularly used to treat diabetes in Korea. Antidiabetic impact of PM021 on the sort II diabetic Otsuka Long–Evans Tokushima Fatty (OLETF) rodents was tested. The outcomes demonstrated that PM021 fundamentally forestalled increments in body weight, blood glucose, and food consumption that came about because of the enlistment of corpulence and diabetes. PM021 likewise improved glucose resistance in OLETO rodents (Maroo J et al., 2002, The Diabetes Prevention Program, DPP 2002).

FUTURE RESEARCH DIRECTIONS

Medicinal plants and herbs have remained the greatest sources of essential medicines and oils since times immemorial. Even today researches are much more focused on them to trace out novel compounds for the management of diseases and disorders that have wreaked havoc on human health. In the quest for new medicines, ethnobotany and ethnopharmacology have emerged as important sources of information. Studies on structure-activity relationships and their effects on the design of novel drugs have made pharmacochemistry an advanced constituent in the category of pharmaceutical sciences- one of the most valuable and therefore significant consummations. Phytomedicines are being recognized by researchers, physicians, and patients for their better therapeutic value as they possess fewer adverse effects as compared with modern chemical medicines. The need of the hour is to develop scientific approaches via which phototherapeutic compounds could be delivered in a sustained manner to increase patient compliance and avoid repeated administration. By designing novel drug delivery systems (NDDS) for drug delivery such strategies can be achieved. Nanotechnology is one such novel approach. Nano-sized drug delivery systems of herbal drugs have a potential future for increasing the bioactivity as well as overcoming problems associated with toxic phytoconstituents. Hence, integration of the nanocarriers as NDDSs in the traditional medicine system is the need of hour to conflict more chronic diseases like cancer asthma, diabetes, cardiovascular diseases, and others.

CONCLUSION

Innumerous types of medicinal plants have been considered for their conceivable hypoglycemic activities and the specialists have done some starter examinations.

Their extracts containing thousands of phenolic, and polyphenolic has demonstrated the viability of the botanicals in reducing the sugar level. Now-a-days, there is an extraordinary premium towards plant-based drugs for diabetes as well as for other fatal conditions like autoimmune disorders, cancer, ageing, cardiovascular complications. One of the serious issues with this natural definition is that the dynamic fixings are not very much characterized. It is critical to know the dynamic segment and their sub-atomic communication, which will assist with examining the remedial viability of the target compounds.

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KEY TERMS AND DEFINITIONS

Antioxidants: Compounds that inhibit oxidation, a chemical reaction that give rise to free radicals and chain reactions that may damage the cells of organisms.

Diabetes: A chronic (long-lasting) health condition metabolic disease that causes high blood sugar.

Hormone: Hormones are organic substances secreted by complex multicellular organisms that functions in the regulation of physiological activities and in maintaining homeostasis.

Insulin: Insulin is a hormone in our body that is responsible for allowing glucose in the blood to enter cells, providing them with the energy to function.

Nanotechnology: Nanotechnology is science, engineering, and technology conducted at the nanoscale, which is about 1 to 100 nanometers.

Phytochemicals: Chemicals that occur naturally in Plants and their parts

Polyphenolic Compounds: Polyphenolic compounds are a diverse group of naturally occurring compounds that contain multiple phenolic functionalities.

Chapter 8
Bionanotechnology Approaches to Combat Biofilms and Drug Resistance

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ABSTRACT

This chapter deals with the formation of biofilms, their resistance to antibacterial agents, the importance and risk of biofilms, and nanotechnology methods for biofilm control in the food industry. Biofilm is a multi-layer cell cluster embedded in an organic polymer matrix, which protects microbial cells from environmental stress, antibiotics, and disinfectants. Microorganisms that live in contact points and the environment in food processing are mostly harmful because the microbial community in the wrong location can lead to contamination of the surfaces and products produced during the processing. When new nanomaterials (for example, silver or copper

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are incorporated) are used, the growth of surface biofilms can also be reduced. In recent years, new nanotechnology-based antimicrobials have been designed to kill planktonic, antibiotic-resistant bacteria, but additional requirements rather than the mere killing of suspended bacteria must be met to combat biofilm-infections.

INTRODUCTION

Biofilm is a microbial community of extracellular matrix rich in polysaccharides. Microbial biofilm was first discovered in 1936. When a glass rod was added to the microbial solution, the adhesion of the microbial cell layer to the bottle wall and the biological activity of the suspension culture were significantly increased; subsequent research introduced the ubiquity of biofilm and planktonic microorganisms (Probert & Gibson, 2002). Various non-biological and biological surfaces, such as minerals, metals, animal or plant surfaces, lungs and intestines, as well as all types of medical implants are prone to bacterial colonization and biofilm formation. On the one hand, the advantages of biofilms have been applied in industrial processes. The microbial biofilmspose a huge risk, including chronic infections caused by these biofilms (R. M. Donlan & Costerton, 2002). Most importantly, biofilms are characterized by their resistance to biocides, antibiotics, and clearance caused by humoral or cellular host defense mechanisms (J. W. Costerton, Stewart, & Greenberg, 1999). Therefore, the use of traditional concentrations of bactericides or antibiotics is not effective in eliminating biofilms.

To control the risk caused by the formation of undesirable biofilms in the medical industry, it is necessary to formulate corresponding strategies to prevent and control the formation of biofilms. So, in this regard we need to fully understand the initial formation mechanism of biofilms, including attachment, development, maturation and detachment, and molecular level related regulatory process (Simoes, Borges, & Simoes, 2020). In fact, the microbes in the planktonic state hardly form biofilms, but the formation of biofilms occurs only in the presence of microbial groups (Berlanga & Guerrero, 2016). The strange thing is that the number of microorganisms that grow in planktonic growth is less than 0.1% of the total microorganisms (J. W. Costerton, Lewandowski, Caldwell, Korber, & Lappin-Scott, 1995). In general, the biofilm can be defined as an aggregated microbial community surrounded by an extracellular polymer (EPS) matrix, which develops on various inert or organic surfaces. Certainly, these biofilms are regulated by various physiological, environmental, and genetic factors. Admittedly, it is a very complex phenomenon, ranging from the structural characteristics of biofilms to various biofilm-related resistance mechanisms. Therefore, due to the complexity of biofilm formation and

the antimicrobial resistance associated with biofilms, medical and industrial impacts are still difficult to control. Consequently, more research on biofilms is still needed in order to fully understand this phenomenon and to develop more effective methods for the prevention and eradication of these biofilms (Simoes et al., 2020).

Nevertheless, several speculations come about regarding the resistance of biofilm cells, including slow growth pattern of sessile cells, interaction of exopolymer with the antimicrobials, mutation, certain resistance genes expression, and the presence of a diffusion barrier to the chemicals posed by the glycocalyx, (Pace, Rupp, & Finch, 2005). In the natural ecological environment and pathogenic systems, bacterial biofilms are ubiquitous. The formation of biofilms can be beneficial or harmful. Many factors that affect the development of biofilms have been extensively studied, including the types of microorganisms, cell surface composition, surface, nutrition, fluid dynamics, and cell-to-cell communication.

Recently, by means of further understanding, the cell-to-cell communication in microorganisms, quorum sensing has become one of the most important mechanisms for controlling the development of highly structured biofilms on biological and non-biological surfaces. The resistance of biofilms to antibiotics often leads to the failure of chemotherapy and further refractory infections. In fact, biofilms are associated with more than 65% of all medical infections (Pace et al., 2005).

Nonetheless, it is believed that the use of biosynthesized NPs facilitate electrostatic interactions that result in the structural rupture of the biofilm matrix. Their reduced size allows penetration into microbial cell walls leading to loss of cell viability and alteration in the biofilm cell physiology. The use of NPs also ensures controlled release of the antimicrobial agent, presenting reduced toxicity and greater stability, thus also providing greater antimicrobial effects on the biofilm (Fig. 1) (Banerjee et al., 2020; Habimana et al., 2018; Nayan, Onteru, Singh, & Energy, 2018; Souza, de Oliveira Vieira, Naldi, Pereira, & Winkelstroter, 2021). The possibility of using medicinal plants and phytochemicals with antimicrobial effects for the synthesis of NPs contributes to the biofilm eradication. Many phytochemicals can alter the cell membrane and compromise the respiratory activity of cells, in addition to cause lipid peroxidation and the production of free radicals that cause deleterious effects on biofilms (Rodríguez-Serrano et al., 2020; Ruddaraju, Pammi, sankar Guntuku, Padavala, & Kolapalli, 2020).

In a previous reported study, dextrin was used for biological synthesis of silver particles, demonstrating a remarkable reduction of approximately 70% in the formation of biofilms by the pathogens *K. pneumoniae*, *P. aeruginosa*, *C. albicans,* and *S. aureus MRSA* (Rajkumari, Busi, Vasu, & Reddy, 2017). The study also evaluated the positive effect on the inhibition of EPS secretion, guaranteeing an important role of biosynthesized NPs in controlling the infections by multi-resistant microorganisms that form biofilms. In another investigation the *Avicennia marina* was used for

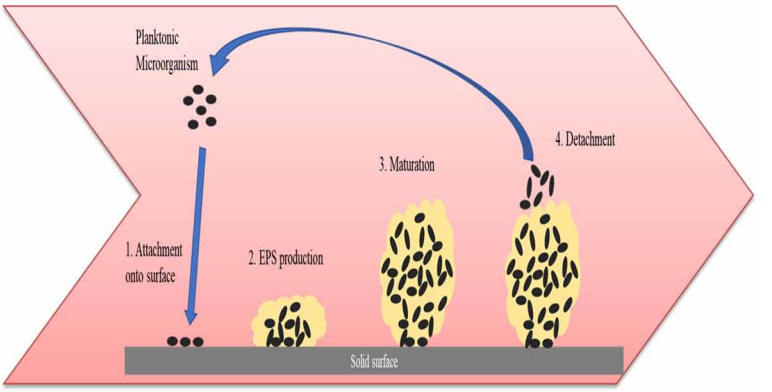
biosynthesis of Fe_2O_3NPs, thus obtaining a percentage of 65% inhibition of biofilm formation at a very low concentration of 2 ppm for species of *P. aeruginosa* and 5 ppm for the pathogenic *S. aureus*, while complete anti-biofilm activity was achieved with the doses of 28 µg/mL for *E. coli* and 52 µg/mL for *P. aeruginosa* (Ramalingam, Dhinesh, Sundaramahalingam, Rajaram, & Interfaces, 2019).

BIOFILM FORMATION

The first scientific research about the biofilm appeared in 1943. However, it was not clearly understood until the 1970s, when the researchers realized that biofilms are widespread (J. W. Costerton et al., 1987). Bacteria exist in two basic states, floating or fixed cells. Microorganisms in planktonic state are very important for their rapid proliferation and spread, while fixed or slow-growing microbial populations are more conducive to their persistence. Studies have shown that adherent microorganisms in the form of colonies, called biofilms, exist in almost all natural and pathogenic ecosystems (Bjarnsholt, Jensen, Moser, & Høiby, 2011; J. W. Costerton et al., 1995).

Moreover, the process of biofilm formation is complex and is usually divided into five stages: 1) The development of surface conditioning film 2) The movement of microorganisms to the surface 3) Adhesion 4) Growth and division of organisms and surface colonization, formation of microcolony and biofilm; phenotype and genotype changes 5) Biofilm cell detachment/dispersion (Palmer & White, 1997; Percival, Knottenbelt, & Cochrane, 2011). There are also reported documents that divide the formation and reproduction of biofilms into the following four steps: (1) Transport (2) Initial adhesion, (3) Substrate adhesion, (4) The formation of microcolonies, leading to the formation of mature biofilms to form cells and surrounding extracellular

Figure 1. Schematic illustration of different stages of biofilm formation



polymer matrix, the last step is the scattering or destruction of biofilms (**Fig. 1**) (Pometto III & Demirci, 2015).

Furthermore, regarding the properties of biofilms, microbes have different growth rates and physiology relative to the floating state, and can show different physiological responses to different nutritional conditions (Hodgson, Nelson, Brown, & Gilbert, 1995). Although gas and liquid nutrients are diffused and transported through the biofilm matrix, studies have shown that bacteria that form biofilms require less oxygen and nutrients than bacteria in a planktonic state. Surprisingly, compared with its floating form, it is more conducive to growth, changes in physiology, and increases tolerance to various stresses (Fox, Leonard, Jordan, & Microbiology, 2011). Although gas and liquid nutrients are diffused and transported through the biofilm matrix, studies have shown that bacteria that form biofilms require less oxygen and nutrients than bacteria in a planktonic state. Surprisingly, compared with its floating form, it is more conducive to growth, changes in physiology, and increases tolerance to various stresses (Bolton, Dodd, Mead, & Waites, 1988; Pometto III & Demirci, 2015).

Certainly, the formation of biofilms is an important physiological phenomenon for microbial pathogens to survive in the environment or mammalian hosts. The microbial cells in the floating state are first attached briefly, and then permanently attached as a single layer on the surface or tissues of the inert material. This monolayer produces larger clusters of cells, which eventually develop into a highly structured biofilm consisting of mushroom-shaped bacterial microcolonies separated by fluid-filled channels. These channels can transport nutrients to various parts of the biofilm, while toxic waste diffuses out. Endogenous oxidative stress produces diversity and adaptability in biofilm communities (Boles & Singh, 2008).

RESISTANCE TO ANTIMICROBIALS

Biofilm is a microbial community composed of bacteria encased in an autogenous polymer matrix attached to the surface of various inert and active substances (Steenackers, Hermans, Vanderleyden, & De Keersmaecker, 2012). The biofilm on the food contact surface is the source of pathogenic bacteria and spoilage bacteria, which increases the risk of microbial contamination in food processing plants, and leads to serious public health problems and potentially significant economic impacts (Shi, Zhu, & Technology, 2009). However, it should be noted that the resistance of a biofilm to antibiotics is not the same as its antibiotic resistance, because when the bacteria are wrapped in a biofilm, they can withstand antibiotic treatment, but if the biofilm is destroyed, the bacteria will become easy to treat (Bayles, 2007).

Obviously, the microorganisms in biofilms grow in a protected microenvironment mainly by producing biofilm substrates composed of extracellular polysaccharides, proteins and nucleic acids (Davey, O'toole, & reviews, 2000). The structure of the biofilm and the physiological characteristics of the microorganisms in the biofilm also provide intrinsic resistance to antibiotics. Indeed, the resistance of biofilms to antibiotics is thousand times that of equivalent to planktonic bacteria (Hoyle & Costerton, 1991). The ability of microorganisms acting on the biofilm matrix by antibiotics is reduced, which is an important factor in the resistance of a certain biofilm. This may be caused by chemical interaction with extracellular biofilm components or adsorption to anionic polysaccharides (Percival et al., 2011). Once microorganisms attach to a certain surface, they may express a biofilm phenotype that is more virulent than that in a planktonic state (Mah & O'Toole, 2001). It is suggested that cells with specific phenotype of biofilm may be induced. These phenotypes may express active mechanisms, such as the expression of bacterial extracellular glucans combined with them, and physical sequester of antibiotics to reduce the efficacy of antibiotics (Gilbert, Das, & Foley, 1997).

Biofilms as usual are highly resistant to most antimicrobial agents and disinfectants. The attached bacteria in the biofilm can acquire resistance through the transfer of resistance plasmids. The acquisition of this resistance is particularly important for patients with urinary catheters and orthopedic patients in the medical environment. Studies have shown that plasmids carried by many organisms encode multiple antimicrobial resistances, especially in the medical field. Microorganisms can grow in free form (plankton) or biofilms attached to solid surfaces (Kumamoto & Vinces, 2005). Surfaces that support the growth of biofilms include inanimate environmental materials, biological materials in contact with host tissues and systems or host tissues themselves. It is known that there are significant differences in the behavior and phenotype of microbes in the state of plankton and biofilm. Perhaps the best example is the study of antibacterial effects at different growth stages (Hill et al., 2003).

Furthermore, compared with planktonic cells, bacteria in biofilms are difficult to eliminate because they are well protected from antibiotics, disinfectants, host immune system and environmental stress. The use of standard National Committee on Clinical Laboratory Standards (NCCLS) broth microdilution methods for susceptibility testing cannot accurately determine the activity of antibiotics against biofilm microorganisms because these techniques are based on exposing plankton to antimicrobial agents. Instead, the biofilm is exposed to antimicrobial agents, removed from the attached matrix, homogenized and quantified as a viable cell counting (R. M. Donlan & Costerton, 2002). In the development of a model biofilm system, in addition to the culture medium and inoculum, the matrix and fluid dynamics also need to be considered.

Above all various studies have shown that the inherent resistance of biofilm bacteria to antimicrobials is a common phenomenon. The resistance of biofilms to bacteria may be three or more orders of magnitude higher than that of the same strain in a planktonic state, depending on the species-drug combination (Ceri et al., 1999). After exposure to high concentrations of antibiotics, a small number of surviving persistent bacteria will immediately reproduce on the surface and become more resistant to antimicrobial treatment. Paradoxically, once these bacterial cells escape from the biofilm, they usually return to a form that is sensitive to antimicrobials (J. W. Costerton et al., 1987). The general mechanism of biofilm resistance to antibiotics is as follows: 1) The polymer outside the biofilm slowly penetrates the antibiotic; 2) The growth rate of the biofilm cell is slow; 3) The rate of genetic transfer in the biofilm increases; 4) The resistance gene in the biofilm 5) Hypermutation of biofilms; 6) Multicellular nature of biofilm communities (Pace et al., 2005). However, some studies have shown the opposite view that the biofilm and planktonic cells of *Pseudomonas aeruginosa* have similar resistance to the killing effect of antibiotics. They concluded that, at least for *Pseudomonas aeruginosa* (a model organism for biofilm research), the idea that biofilms are more resistant than planktonic cells is groundless (Spoering & Lewis, 2001).

Identically in order to survive, microorganisms have evolved cell protection mechanisms or resistance mechanisms to combat harsh environmental conditions. As plankton cells transform into an attached form, biofilm resistance becomes more complicated. Therefore, biofilms have unique characteristics that make cell membranes thousand times more resistant than planktonic cells. Due to this fact, it is often difficult or impossible to eradicate disease infections related to biofilms and become serious chronic diseases. A group of bacteria consisting of *Pseudomonas aeruginosa*, *Enterococcus faecalis*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Enterobacter*, which are characterized by resistance and in particular resistance to antibacterial agents, Known as the "ESKAPE pathogen" (Santajit & Indrawattana, 2016).

In addition to medical and health care, drug resistance produced by cell attachment on surfaces is also a huge hazard in the petroleum industry, drinking water distribution systems, paper industry, metal processing industry, and food processing industry. Since the health problems associated with biofilms will generate huge global health and economic costs, the link between biofilms and antibiotic resistance deserves deep attention. Several studies have shown that certain antibiotics can induce biofilm formation. Other researchers focused on the relationship between biofilm formation and multidrug resistance (MDR), and proved that microorganisms with biofilm formation ability are more resistant to antibiotics than microorganisms without biofilm formation ability (Gurung et al., 2013).

The underlying mechanisms of antibiotic resistance in biofilms can be divided into the following five categories: 1) Restriction of the penetration of antibiotics; 2) Different physiological activities; 3) Persistence and phenotypic variation; 4) Specifics related to the growth pattern of biofilms tolerance mechanism; 5) Specific tolerance mechanism that has nothing to do with the growth pattern of biofilm (Bjarnsholt et al., 2011).

IMPORTANCE AND RISK OF BIOFILMS

Biofilms can be formed on a variety of surfaces, including natural aquatic systems, living tissues, residential medical equipment, and industrial/or drinking water system pipes. Most microorganisms grow in the form of biofilm in water environment (Percival et al., 2011). These biofilms may be benign or pathogenic, releasing harmful products and toxins, and these harmful products and toxins are encapsulated in the biofilm matrix. Biofilm formation is a phenomenon that occurs under a variety of conditions both in natural and man-made environments, and appears on most wet surfaces, plant roots and almost every living animal. Biofilms may exist as beneficial epithelial communities in rivers and streams, trickling filter beds in wastewater treatment plants, or mammalian digestive tracts (J. Costerton, Irvin, & Cheng, 1981). However, biofilms are not limited to the solid/or liquid interface but can also be found at the solid/or gas or liquid/or liquid interface (for example, airborne pathogens and pathogenic bacteria) have been shown to be important factors in the biodegradation of surface coatings; The biofilm/or liquid interface at the liquid is related to the degradation of hydrocarbons, including fuels, engine oils and industrial coolants. In humans, it is estimated that 65% of all nosocomial infections are of biofilm origin. Once biofilms are formed, their infections are difficult to eradicate because they have the flexibility to be cleared by host defense mechanisms and antibacterial agents (Percival et al., 2011).

Additionally, studies have shown that biofilm microorganisms initiate initial attachment to the surface, forming a community structure and ecosystem, and a specific mechanism for detachment. In addition, biofilm is becoming one of the buzzwords in the food industry (Merino, Procura, Trejo, Bueno, & Golowczyc, 2019). There are various definitions of biofilms, where biofilms are collections of microbial cells that are irreversibly attached (not removed by gentle washing) to the surface and are surrounded by a matrix mainly made of polysaccharide materials. Non-biological materials such as mineral crystals, corrosion particles, clay or silt particles or blood components, depending on the environment in which the biofilm is formed, can also be found in the biofilm matrix. Organisms related to biofilms are also different from microorganisms in their planktonic state in transcribing genes.

Biofilms in nature usually continue to adhere to certain surfaces, rather than pure unattached cultures. In this case, the bacterial cells in the biofilm have the ability to exchange genetic components at a higher rate, which may help to acquire new genes to improve virulence and environmental survival (R. Donlan, 2002). Bacteria generally seem to be more resistant to physical and chemical agents in biofilms. The cleaning process affects the food source, remaining on the surface, which in turn affects the bacterial population on the surface. In addition, it is suspected that the bacteria in the biofilm will communicate with each other by releasing specific chemicals. As the number of bacteria increases, the concentration of these chemicals in their microenvironment increases at a certain concentration.

Since Costerton et al. defined the term biofilm in 1978 (J. W. Costerton, Geesey, & Cheng, 1978), due to the importance of biofilms in many fields (such as clinical microbiology, environmental microbiology and food microbiology), research has continued to increase over the years. As we all know, most of the microorganisms found in nature live in structured groups, which are encapsulated in different kinds of polymer substances, such as carbohydrates and proteins. Surprisingly several pathogens, such as *Listeria monocytogenes*, methicillin-resistant *Staphylococcus aureus* (MRSA), *Enterobacter sakazakii*, Enterohemorrhagic *Escherichia coli*, *Salmonella typhi*, *Campylobacter jejuni*, *Yersinia acidophilus*, *Sclerococcus*, *Legionella*, *Actinobacillus pleuropneumoniae*, *Mycoplasma* and *Candida albicans* can produce biofilms on food surfaces and pipes (J. Costerton et al., 1981; Juvonen et al., 2001; Wirtanen & Salo, 2016). It is proven fact that the treatment of biofilm infections is difficult. Antibiotics can effectively fight the planktonic microorganisms released from the biofilm, but they cannot eliminate the biofilm (Marrie, Nelligan, & Costerton, 1982).

The spread of various microorganisms through food is related to human infections. Among these microorganisms, *Campylobacter* and *Salmonella* are the two main food-borne pathogens in the world. *Salmonella* and *Campylobacter* can continue to exist throughout the food supply chain due to their ability to form biofilms (Lamas et al., 2018). *Campylobacter jejuni* forms biofilms on various non-biological surfaces. Interestingly, *Campylobacter* is often isolated from biofilms in various natural environments, which suggests that the formation of biofilms may help this bacteria to survive in the given environment (Bae, Oh, Jeon, & chemotherapy, 2014).

In addition, the biofilm of *Campylobacter jejuni* is involved in enhanced fluoroquinolone resistance. Under aerobic or stress conditions, *Campylobacter jejuni* adapts to the biofilm lifestyle, allowing it to survive under harmful conditions, and this biofilm can act as a reservoir for living planktonic microorganisms. The increased ability of biofilm formation under aerobic conditions is likely to be an adaptation to the zoonotic lifestyle of *Campylobacter jejuni* (Reuter, Mallett, Pearson, van Vliet, & microbiology, 2010).

Biofilm bacteria show several characteristics different from planktonic bacteria, one of which is increased resistance to antibacterial agents, this process is considered to be the main contributor to the etiology of infectious diseases (J. W. Costerton et al., 1999). The human gastric pathogen *Helicobacter pylori* forms biofilm *in vitro.* The formation of *Helicobacter pylori* biofilm reduces the sensitivity to clarithromycin (CLR), and it is easier to produce *Helicobacter pylori* CLR resistance mutations in the biofilm than planktonic bacteria (Yonezawa et al., 2013). This may indicate that the evaluation of the biofilm formation ability of *Helicobacter pylori* may play an important role in the prevention and control of antibiotic resistance. Likewise, biofilms represent a rich source of mutational resistance of *Staphylococci* to antibiotics (Ryder, Chopra, & O'Neill, 2012).

During various acute and chronic infections, the human microbiome and bacterial pathogens also adopt the growth state of biofilms (Hall-Stoodley, Costerton, & Stoodley, 2004; Macfarlane, 2008). Due to the refractory nature of organisms in this growth state, they can resist most antibiotics and the killing effect of the immune system, so the infections associated with biofilms are difficult to eradicate (Izano, Shah, & Kaplan, 2009; Jensen, Givskov, Bjarnsholt, Moser, & Microbiology, 2010; Stewart & Costerton, 2001; Vuong et al., 2004). In addition, there is limited but growing evidence that biofilms may promote the emergence of antibiotic resistance. It is reported that the binding rate in biofilms of *Enterococcus* and *Pseudomonas* has increased and mutation frequency of antibiotic resistance has been found in the biofilms of *Pseudomonas aeruginosa* and *Streptococcus pneumoniae* to be increased (Ehlers, Bouwer, & Technology, 1999).

As a result, infections based on biofilms are extremely difficult to cure. Biofilms are important in medicine because they are related to the pathogenesis of many bacterial infections, which are difficult to successfully eradicate with antimicrobials (J. W. Costerton et al., 1999). Non-healing wounds due to chronic biofilms are also a problem. Complex non-healing wounds are usually related to the presence of biofilms containing multiple bacteria, and at least *Staphylococcus aureus* (Wolcott, Gontcharova, Sun, Zischakau, & Dowd, 2009). For example, in patients with diabetic neuropathy, small incisions often become life-threatening wounds due to the common underlying condition of immunocompromised hosts. These conditions often lead to severely infected diabetic foot ulcers, which often become chronic and difficult to treat. These chronic wounds usually have no effect on commercially available drugs such as appropriate antibiotics, selective biocides, and advanced dressings. The use of anti-biofilm agents to remove bacterial biofilms from these types of chronically infected wounds is the key to their healing (Wolcott & Rhoads, 2008). Otherwise, the limb is usually amputated, or the infection may spread, posing a high risk of death. Using conventional treatment methods, this infection now causes more than 100,000 limb amputations and kills thousands of people in the United States in one

year alone (Ziegler-Graham et al., 2008). Therefore, there is an urgent need for a new therapeutic agent specifically for staphylococcal biofilms. The National Institutes of Health estimates that as many as 80% of human infectious diseases are based on biofilms (J. W. Costerton et al., 1999). However, infection management based on biofilms is very new to the medical community and is subject to frequent review. Despite this, a series of treatments that can successfully eliminate biofilm bacteria have saved many limbs and lives. According to new standards of care, including anti-biofilm strategies, as many as 91% of wounds have now been healed. These wounds are considered incurable and can lead to amputation of large limbs. In addition, through the use of anti-biofilm strategies, the use of conventional antibiotics has been reduced by 85%, which indicates that the key to improving the recovery rate is to implement anti-biofilm treatment (Wolcott & Rhoads, 2008).

The formation of biofilms by microorganisms has been considered a serious problem in the food industry. Due to the diversity of bacteria in nature and different biofilm formation mechanisms, it is difficult to develop a perfect strategy to control biofilms. The design of appropriate biofilm control strategies depends to a large extent on our understanding of the mechanism of biofilm formation in the wild environment. Cooperation between researchers from different disciplines is a trend in biofilm research. Large-scale and high-resolution characterization of biofilms in the wild will require the introduction of systems biology methods for biofilm research, which in turn will generate biomarkers to better detection of biofilms. The mechanism of biofilm diffusion also needs further study, especially under field conditions. The combination of biofilm dispersants and conventional biofilm control agents may greatly enhance current biofilm control methods (den Besten, Ding, Abee, & Yang, 2015).

The unique phenotype of microbial biofilms makes them resistant to antibiotics. The increasing use of indwelling medical devices has increased the incidence of persistent infections with implants, which are closely related to biofilms and are usually persistent, multi-drug resistant microorganisms. The chronic nature of biofilm infections increases the risk of sequelae of their promotion of immune complexes (Pace et al., 2005).

ROLE OF NANOMATERIALS IN BIOFILM CONTROL

Considering the aforementioned problems caused by the biofilms, there is great need for the development of effective remedies for control and eradication of resistant microorganisms. The main problem of eliminating this complicated biofilm structure is resistance to present clinically used drugs used. Therefore, it is necessary to find new compounds with efficient anti-biofilm activity. Nanotechnology-based

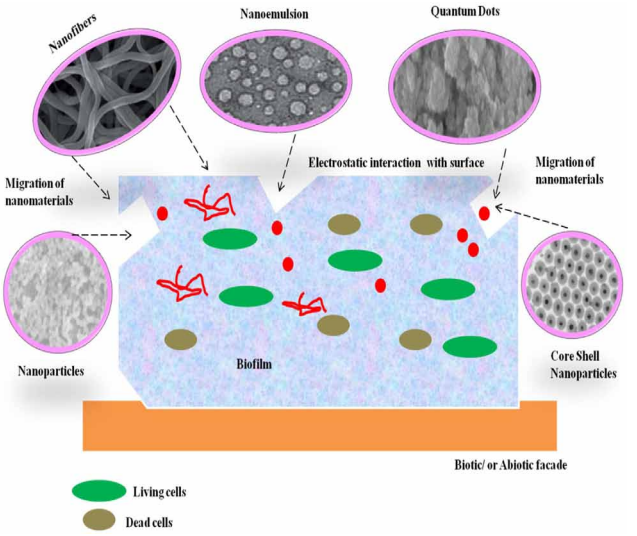
antibacterial agents and delivery systems can be used to control microbial biofilms (Liu et al., 2019; Ramos et al., 2018).

Unquestionably, nanotechnology has played an important role in all fields of science and has contributed to the advancement of physics, chemistry, engineering, medicine, and pharmaceutical industries. In medicine, nanotechnology is becoming more and more important due to its applications in the prevention, diagnosis and treatment of various diseases (Lin et al., 2015). Currently, the main types of nanosystems used to deliver biologically active substances are liposomes, microemulsions, nanoemulsions, cyclodextrins, solid lipid nanoparticles, polymer nanoparticles and metal nanoparticles. Nanostructured systems have become a promising tool for the treatment of infectious diseases that are resistant or durable to conventional treatments and can improve the quality and life expectancy of patients suffering from such diseases (Bharali et al., 2011). Due to the resistance mechanism and biofilm formation of these microorganisms, the effectiveness of conventional antimicrobial agents is gradually declining. One promising strategy to overcome bacterial resistance is nanotechnology, which uses nanocarriers to deliver drugs and biomolecules to prevent and treat bacterial biofilms (Pelgrift & Friedman, 2013). The applicability of these systems in biofilm processing is variable. However, nanotechnology-based drug delivery systems can promote direct interaction between drugs and the complex structure of biofilms and play a role in different stages of biofilm formation.

The nanoparticles can be synthesized by a wide variety of methods, including mechanical stretching, soft lithography, microfluidics or self-assembly using different materials like inorganic, small molecules, macromolecules, and polymers. Size and shape, surface and interior properties of the resulting nanoparticles are important to consider with respect to the control of biofilm-infection. Nanotechnology-based new antimicrobials include metal-based nanocomposites (such as metal oxide, Ag, Au etc nanoparticles), carbon-based nanomaterials (such as graphene materials, carbon quantum dots), polymer-based nanoparticles (such as natural and synthetic polymeric nanoparticles) (Liu et al., 2019).

Nanoparticles not only possess antimicrobial properties of their own, but can also be applied as antimicrobial delivery systems, particularly with core structure. There are different types of antimicrobial nanocarriers including mesoporous silica nanocarriers, liposomes, polymeric nanocarriers, and dendrimeric nanocarriers (Liu et al., 2019).

Figure 2. Schematic representation of interaction between different kinds of nanomaterials and biofilm



FUTURE RESEARCH DIRECTIONS

This chapter deals with the formation of biofilms, its resistance to antibacterial agents, the importance and risks of biofilms, and nanotechnology methods for biofilm control. All in all, the regulation of biofilms by a variety of physiological, environmental, and genetic factors is not yet fully understood. The promise of nanotechnology-based antimicrobial agents and delivery systems in infection control is promising. The application of nanotechnology in drug delivery systems has great potential and can be considered as an effective alternative method for the treatment of microbial biofilms soon. The ability of nanoparticles to synergize with active molecules to inhibit biofilms is a promising feature because it allows drugs available in clinical practice to be used in a more effective manner, thereby ensuring that the limitations related to the bioavailability of antimicrobial agents are overcome. To fully understand this phenomenon and develop more effective methods to prevent and eradicate biofilms, more research on biofilms is still needed.

CONCLUSION

Medical biofilms still pose as a critical issue for the clinical community, as most of the traditional therapies are not effective, due to the recalcitrant cells within these

communities and the emergence of new highly resistant strains. New nanotechnological strategies are being developed in order to overcome the problems associated with bacterial or /and fungi biofilm formation. At this point of time, few of these therapies although are being applied systematically by the medical community. Even so, the nanotechnology approaches seem to be now the most promising field of research to control/eradicate biomedical biofilms, most especially for the multi-resistant microorganisms. Nanotechnology, as a novel biofilm control strategy may have potential for public health, environmental and economic benefits by effectively limiting the levels of biocides used in cleaning and disinfection practices. Nanoscience and its applications are very recent fields and fundamental properties of nanoparticles are being discovered every day. Further studies and investigation are still needed but the ability of nanoparticles to penetrate the biofilm, enter the cells and affect their biochemical functions makes them potential tools in biofilm control. The exploration of novel approaches toward the improvement of human life is everlasting, and it is evident that the search for alternatives for the treatment and control of microbial diseases associated with biofilms is a complex path. It may be concluded that the application of nanotechnology has enormous potential and can be considered as an effective alternative for the treatment of microbial biofilms soon. The ability of the nanoparticles to synergize the active molecules for the inhibition of biofilms is a promising characteristic as it allows the use of drugs available in clinical practice in more efficient manner that guarantees overcoming of the constraints related to the bioavailability of the antimicrobials.

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Chapter 9
Phytochemicals and Novel Nanotherapeutic Approaches in the Management of Rheumatic Diseases

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ABSTRACT

Over 100 types of arthritis have been recognized in which the dominating forms are osteoarthritis and rheumatoid arthritis. Joint stiffness, pain, swelling, lowered range of motion of joints affected, redness around joints are the main complications of almost all types of arthritis. Medications like non-steroidal anti-inflammatory drugs (NSAIDs), opioids, corticosteroids, and immunosuppressants are only used to control the symptoms of the disease but are not able to alleviate them properly. However, with the incorporation of disease-modifying antirheumatic drugs (DMARDs) as well as tumor necrosis factor inhibitors (TNFi) in treatment, there are now promising therapeutic options to select from for the management of rheumatoid diseases. Nanotherapeutic approach has enabled us to deliver the disease-modifying agents directly to the inflammation site, thus eschewing off-target and unwanted systemic effects. Therefore, it provides an opportunity to reconsider the therapeutic compounds that were considered too toxic to be administrated via oral or parenteral route.

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INTRODUCTION

The benign immune system in our body plays a cardinal role in defending different types of infectious diseases as well as eliminates the altered cells that may prove fatal. But if any type of exaggeration occurs in the elements of this system, it leads to several fatal disorders. Such disorders range from hypersensitive or allergic reactions to numerous derangements like loss of normal ability to differentiate non-self from self, resulting in immune actions against bodies own tissues and cells called auto-immune disorders (Choudhary *et al.,* 2015). Among some such common disorders like pernicious anemia, myasthenia gravis, serum sickness, etc. rheumatic diseases are also common with almost of unknown etiology (Hajja *et al.,* 2018). Rheumatic diseases mainly affect joints, but some types of arthritis also involve organs. Rheumatic diseases are chronic systemic inflammatory disorders with primary symptoms of pain, swelling, Joint stiffness, lowered range of motion of joints affected, redness around joints, destruction of cartilages and bones which sometimes may lead to permeant disabilities as well as secondary health issues like muscle weakness, fatigue, malaise, tenderness, loss of flexibility, poor sleep, and decreased aerobic fitness. Despite the presence of much more knowledge in the field of immunopathology, the exact etiology of Rheumatic diseases remained a far cry. Rheumatic diseases have become a common reason that people miss work and experience a decreased life quality (Tripathy *et al.,* 2010). These disorders make it difficult for affected individuals to be active physically. More than 100 types of arthritis are known today in which osteoarthritis dominates by affecting more than 3.8% of people followed by Rheumatoid arthritis. According to WHO, rheumatoid arthritis (RA) affects 1-2% of the world population, and females are 3-4 times more susceptible to these disorders than males (Chunxia *et al.,* 2011). Main pathological alterations in rheumatoid arthritis are synovial membrane hyperplasia, inflammation, cell infiltration, and neovascularization which eventually may lead to articular destruction and cartilage erosion. This attack is principally targeted at flexible synovial joints. In this whole pathology, capsule inflammation around the joints and secondary swelling of the synovial cells is triggered which may lead to deformity (Babushetty *et al.,* 2012). Occasionally rheumatoid arthritis can incorporate other internal organs like nerves, lungs, eyes, or heart. Initial symptoms of rheumatoid arthritis can be non-specific like feeling unwell, tired soreness in joints, complications in handling and walking. Gradually it involves more and more joints of the body. Although the precise etiology of this disorder is not known fully, several hypotheses put forth by some immunologists suggest that it is prompted by a combination of immuno-genetic and environmental factors. Some viruses have been also found to trigger rheumatic disorders (Mazumder *et al.,* 2012).

The main goal of the management of rheumatic diseases is to eliminate symptoms of pain, inflammation, and functional maintenance. Clinically, the initial management of rheumatoid diseases involves the use of non-steroidal anti-inflammatory drugs (NSAIDs) and disease-modifying anti-rheumatic drugs (DMARDs) followed by glucocorticoids to reduce the pain and inflammation as well as slow down the disease progression. This treatment strategy approach has now changed to the use of novel biological agents or so-called biologics such as tumor necrosis factor inhibitors (TNFi), monoclonal antibodies, TNF-α antagonists such as infliximab, etanercept, etc. IL-1 antagonists like anakinra and the agents that disturb T- cell activation like abatacept, immunosuppressive and cytotoxic medications like azathioprine, cyclophosphamide, and cyclosporin are now thoroughly used in chronic cases (Singh *et al.,* 2012, Jeoung *et al., 2013)*. Novel treatment strategies are significantly lessening the disease progression and improving the quality of afflicted ones. Yet in many cases, the patients either do not respond to or shortly develop tolerance to such therapies. Moreover, such therapies inversely alter the functioning of the immune system, digestive system, kidneys, liver, and nervous system. All these therapeutic agents minimize the symptoms of pain, inflammation, and joint destruction but are not without deadly side effects. Their long-term use risks include serious infections, gastric ulcers, hepatotoxicity, nephrotoxicity, hematologic toxicity, cardiovascular diseases, immune system malfunctioning, etc. The high risk of malignancies and infections associated with the use of such agents needs to be monitored continuously (Shen *et al.,* 2011, Mishra *et al.,* 2011). Also, TNF antagonists have been revealed to be linked with Leukocytoclastic vasculitis (LCV) (Suha *et al*., 2011). Considering all these complications caused due to use of such medications, an urge has been raised to search for alternative therapeutic agents and their targeted delivery into specific tissues. Nanotechnological approaches are promising when such issues are taken into consideration. This approach incorporates novel tools and techniques that are aimed at disease diagnosis and delivery of therapeutic agents at sites of interest using carriers of sub-micrometer size termed nanocarriers. Through these nanocarriers, targeted delivery of disease-modifying agents is feasible. It allows adjusted drug delivery directly to inflammation sites keeping in view the alterations in disease expression. Bioactive disease-modifying compounds are encapsulated into the nano carriers and selectively delivered to joints under inflammation to accomplish effectual drug concentration locally. Treatment options involving direct drug delivery through intra-articular injections are available, but such strategies are invasive and pose a threat of injection site infections. Hence, nanocarrier delivery is preferable. Other benefits associated with nanocarrier delivery system is that target drug solubility is enhanced, drug depredation is avoided as circulation is skipped and site-specific bioavailability of drug can be increased to effectual level. With

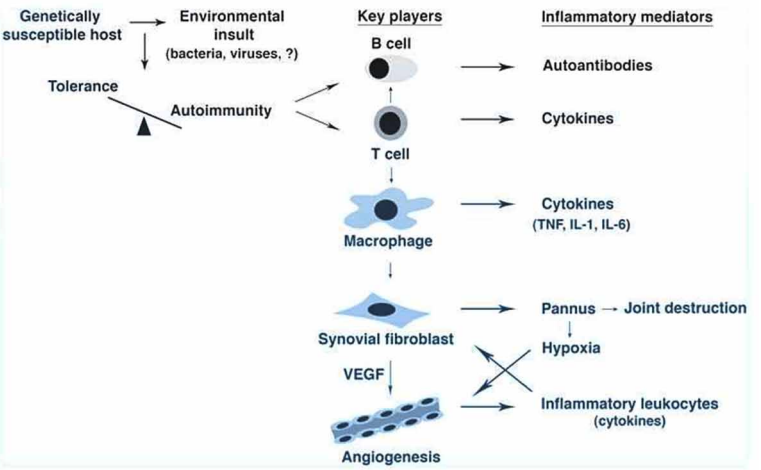
this off-target unwanted systemic effects like toxicity to delicate tissues and organs are skipped (Pham C. T. 2011).

Alternative therapeutic agents that pose less threat when administrated orally to treat rheumatic disorders have been revealed to occur naturally as bioactive compounds in phytochemicals. Infect vast research exists that reveal the potential use of phytochemicals as anti-rheumatic agents. This gave an added impulse to current research to be mainly focused on the use of plant-based phenolic and polyphenolic compounds like flavonoids, alkaloids, terpenoids, phenolic acids, etc.as anti-rheumatic agents (Subramoniam *et al., 2013).*

RHEUMATOID ARTHRITIS: A PATHOPHYSIOLOGICAL INSIGHT

Rheumatoid arthritis (RA) is an autoimmune disorder that leads to progressive cartilage erosion resulting in chronic polyarthritis and distortion of mainly diarthrodial joints (Surjeet *et al.,* 2011). This disorder is almost of unknown etiology as its precise pathogenesis mechanism has not been elucidated properly. The joint change in RA seems to be directly linked to the synovial cell malign growth as a pannus that overlays and erodes bone and cartilage (Mohammed *et al.,* 2015). Joint space-maintaining synovial membrane becomes highly cellular because of immunological hyperactivity as a large number of CD4 T cells especially CD17 cells infiltrate inside (Sachin *et al.,* 2013). This whole action that is fiery immunological hyperactivity gives an intense stimulus to the cells lining the synovium which in turn undergo Dr. Jekyll and Mr. Hyde transformation into the invasive Pannus, bringing about bone damage and joint erosion via the production of destructive mediators like pro-inflammatory cytokines. (**Fig. 1)** (Sanmugapriya *et al.,* 2012). Reports now-a-days are also supporting the role of reactive free radicles associated with its pathogenesis (Dimitra *et al*., 2018). Researchers are putting forth their forceful efforts to trace out the molecular basis for its pathogenesis. It has been revealed that certain proinflammatory cytokines such as IL-1β and TNF-α and IL-6 are important players in disease perpetuation (Marri *et al.,* 2013). CD4 T-cells were said to play a cardinal role in the pathogenesis of Rheumatoid arthritis as they heavily infiltrate the synovial membranes during RA synovitis. However, in recent years this 'T-cell centric hypothesis' in RA pathogenesis has now been challenged because therapies that would deplete CD4 T-cell population failed to alleviate RA in clinical trials. As a result, it is now being proposed that proinflammatory cytokines secreted by macrophages, fibroblast-like synoviocytes such as IL-1, IL-6, TNF-α are key mediators of Rheumatoid arthritis because application of 'anti-cytokine therapy' against such cytokines showed promising results and thus revolutionized current RA treatment (Jeoung *et al., 2013).*

Figure 1. Pathogenesis of RA



As of the latest reports from research, Th17 cells which are linage of CD4 T-cells but different from Th1 and Th2 cells, play a paramount role in inflammatory and autoimmune disorders. These cells produce the cytokine IL-17 in the rheumatoid arthritis synovium. This 'Th17 cell-centric theory' adds an impulsive insight into how T- cells participate in the perpetuation of Rheumatoid arthritis. It is now being proposed that Th17 cells are potent mediators of rheumatoid arthritis, coordinating cartilage damage, bone erosion, and joint inflammation (Dimitra *et al*., 2018). Central to the pathophysiology of RA is inflammation of the synovium with synovial thickening and erythema. Patients afflicted with Rheumatoid arthritis are having synovial tissues characterized by neovascularization, mononuclear cell infiltration, and synovial fibroblast proliferation. Formation of invasive tissue 'Pannus' due to synovial vessel endothelial cell transformation into high endothelial venules take place and is considered a marked feature of rheumatoid arthritis. The pannus contains fibroblasts, mononuclear cells along matrix metalloproteinases (MMPs) which are later converted into fibrous type Pannus with vascularized layer. Inflammation progression around the joints is mainly due to pro-inflammatory cytokines which also synergically lead to the production of more Matrix metalloproteinases (MMPs) from chondrocytes and synovial cells (Shyama *et al.,* 2015). The presence of high titer of rheumatoid factor (RF) as well as anticitrullinated peptide antibodies (ACPAs) is taken as a serological hallmarks of RA (Rathore *et al.,* 2007).

Current reports are associating reactive oxygen species (ROS) and reactive nitrogen species (RNS) which are regarded as reactive free radicles, with the pathogenesis of Rheumatic arthritis. These highly reactive species are generated in the biological systems having aerobic metabolism. Their production seems to increase at the sites

under chronic inflammation (Patil *et al.,* 2011). Reactive species like Hydroxyl radicles, hypochlorous acid, and superoxide radicles have been found to contribute to tissue erosion in Rheumatoid arthritis. The generation of reactive oxygen species in the joints of rheumatoid arthritis patients is directly linked to enhanced metabolism rate in synovial tissue, enhanced pressure in the synovium cavity reduced capillary density, as well as by the action of overactive WBCs. Reactive oxygen species have the potential to erode basic articular elements and thus contribute to the symptoms of inflammation. Elevation in plasma conjugated dines, malondialdehyde, and deviation of free radical scavenging vitamins like vitamin A, E as well as catalases are directly correlated with increased oxidative stress and tissue damage (Baranwal *et al.,* 2012*).* Alterations of such kind also inversely affect glutathione reductase activities in synovial fluid of Rheumatoid arthritis. A Higher level of thioredoxin which acts as a marker of oxidative stress is also seen in the synovial fluid of afflicted patients (Sahu *et al.,* 2014).

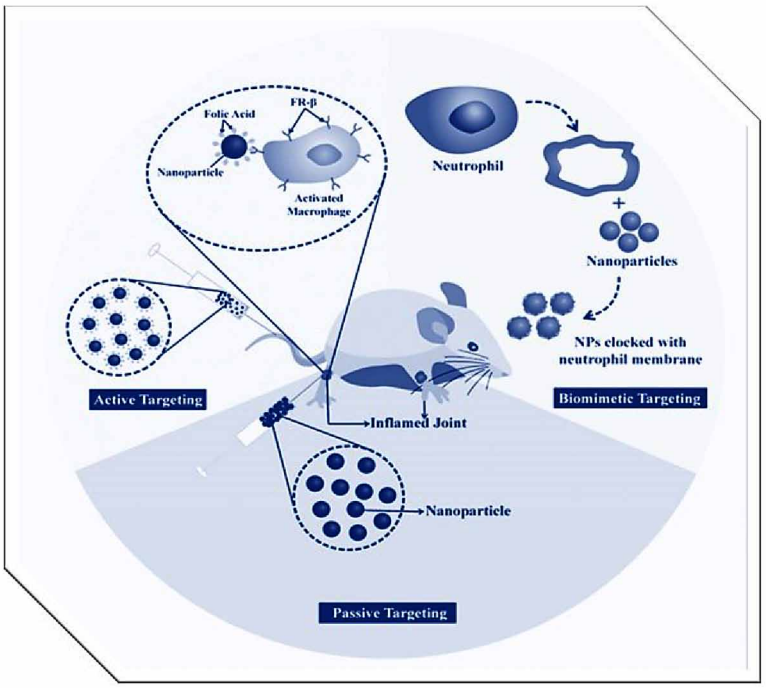
NANOTHERAPEUTIC APPROACHES IN THE MANAGEMENT OF RHEUMATIC DISEASES

In current Rheumatic disease management strategies in which the therapeutic agents used range from Nonsteroidal anti-inflammatory drugs (NSAIDs) to novel biologics, nonselective activities of such drugs often limit dose escalation as well as pose a threat to the normal physiological functioning of other tissues and organs. By packing bioactive disease-modifying agents into nanocarriers and delivered locally to the afflicted sites under inflammation, effectual drug concentration can be achieved locally. Due to nanocarrier delivery, drug stability and solubility are enhanced and there are fewer risks of drug degradation. Using nanocarrier system, a macrophage targeting approach was investigated (Pham C. T. 2011). Macrophages are the main players in the pathophysiology of RA as they produce pro-inflammatory cytokines, and their number is increased in the joints under inflammation. By targeting these macrophages via nanocarriers, their pro-inflammatory cytokine release was attempted to modulate. This approach known as passive targeting involves delivering anti-macrophage nanocarriers directly into the specific sites in a controlled manner which are then efficiently phagocytosed by macrophages so as to modulate their inflammation mediating activity. In the first study, the compound encapsulated in nanocarrier was clodronate, a bisphosphonate that was able to trigger apoptosis in macrophages. Targeting of phagocytic cells that release pro-inflammatory cytokines at the sites of inflammation through parenteral delivery of nanotherapeutics has also been pursued actively however through this route, nanocarriers are quickly cleared by Reticuloendothelial macrophages, thus minimizing the availability of drug

reaching the inflammation site. Therefore, attempts are being made to encapsulate bioactive compounds in nanocarriers with surface modifications for selective targeting of immune cells (Ceponis *et al.,* 2001). Similar approaches have been incorporated in the delivery of Nonsteroidal anti-inflammatory drugs (NSAIDs) and Glucocorticoids (GCs).

For achieving the analgesic effect, NSAIDs are widely involved in rheumatoid diseases. These drugs inhibit the activity of enzyme cyclooxygenase (COX) that possess the main pathophysiological role in many pathways like pain, inflammation, angiogenesis, cartilage and bone erosion etc. However there use in RA management is often overlooked due to higher side effect profiles especially in pediatric and elderly people (Amer *et al.,* 2010) Selective cyclooxygenase-2 (COX-2) inhibitors proved more promising in pain management in rheumatoid diseases with lower gastrointestinal side effects as compared to COX-1 inhibitors, but it was soon revealed that their long-term use lad to increase in cardiovascular disorders like stroke and cardiovascular infraction. For this reason, several COX-2 inhibitors were suspended and withdrawn from the market (Khan *et al.,* 2011). It has also been revealed that NSAIDs apart from having analgesic and anti-inflammatory effects also have immunomodulatory and anti-angiogenic actions recently explored for cancer therapy. Coupled with the nanocarrier delivery system, researchers are prompted to reconsider the benefits of NSAIDs in the management of rheumatoid diseases. Nanocarrier delivery enables controlled release and site-specific delivery of potent NSAIDs thus skip the off-target unwanted effects. Studies showed that lipid microsphere (LM) preparations encapsulating indomethacin- a potent NSAID, improved its anti-inflammatory effects while minimizing gastrointestinal distress. LM being rapidly cleared by Reticuloendothelial system addition of polyethylene glycol (PEG) delayed this quick degradation thereby prolonging their bioavailability and circulation time in the body. With filled with NSAIDs like indomethacin, these nanocapsules showed potent anti-inflammatory action via an adjuvant-induced model. This is evidenced by the decrease in serum levels of proinflammatory cytokines like IL-6 and TNF-α and an enhanced level of anti-inflammatory cytokine IL-10 (Srinath *et al.,* 2000, Bernardi *et al.,* 2009). This model is thought to function through the accumulation of the NSAID- nanocapsules at inflammation sites via enhanced permeability and retention (EPR) effect. NSAIDs being hydrophobic drugs have been also covalently attached to another emerging nanoparticle class called Dendrimers. Their branching configuration entraps the drug molecules through their end functional groups to enhance their solubility and retention time (Fahmy *et al.,* 2007).

Figure 2. Active and passive targeting via nanoparticles



Similarly, glucocorticoids (GCs) are considered fast-acting anti-inflammatory drugs whose prolonged use is also discouraged. Systemic administration of GCs makes them susceptible to quicker degradation, so high and frequent administration is often needed to accomplish desired anti-inflammatory effects. Nanocarrier preparations of GCs are also aimed at site-specific delivery in a sustained release manner. By encapsulating prednisolone in a mini-PEG-liposomes of 100 nm size, Metselaar *et al.* in 2003 revealed that these nanocarriers sustained in circulation with a greater half-life of more than 50hrs, with the effect lasting for more than two weeks. Extravasation of these PEG-liposomes into inflamed joints enhanced the retention and bioavailability of the drug with better solubility. Recently, glucocorticoid conjugated polymers have attained much interest in application in rheumatoid diseases. Here polymer bond drugs are released more slowly and thus necessitates less frequent administration (Ishihara *et al.,* 2010). In summary, polymeric, and liposomal glucocorticoid and NSAID preparations have enhanced their safety profile by minimizing the dosage and frequency of administration. Such recent advancements in therapeutic nanotechnology have revolutionized the treatment strategies for various diseases especially rheumatoid disorders.

The use of nanotechnology-based gene therapy has also revolutionized rheumatoid arthritis treatment. The intentional delivery of interference producing nucleic acids in the cell to repress or silence the expression of the protein is termed gene therapy and now-a-days is considered a promising approach in the treatment of many human diseases and disorders. In rheumatic diseases, this approach can be incorporated to either suppress the expression of proinflammatory cytokines (IL-6, IL-1β, TNF-α) or trigger an overexpression of anti-inflammatory cytokines (IFN-β, IL-10, IL-4). The incorporation of viral vectors like adenovirus (Adv), retrovirus (Rv), etc. for gene therapy in Rheumatic arthritis has been explored in animal models well as in clinical trials. Main concerns arising due to the use of such viral vectors include humoral immune response to viral antigens, spreading of vector, off-target transgene expression, and oncogenic effects. In the search for non-viral vector delivery of nucleic acids to modulate gene expression, nanotechnology has provided the best tools. Nanotechnology-based vectors have many advantages over viral vectors like minimal immunogenicity, infection less delivery, and less risk of mutagenesis. Nanocarriers termed Lipoplexes have proved much more beneficial in the delivery of small interference RNA (siRNA) designed to suppress TNF-α expression to reduce inflammation in rheumatoid diseases (Pham C. T. 2011).

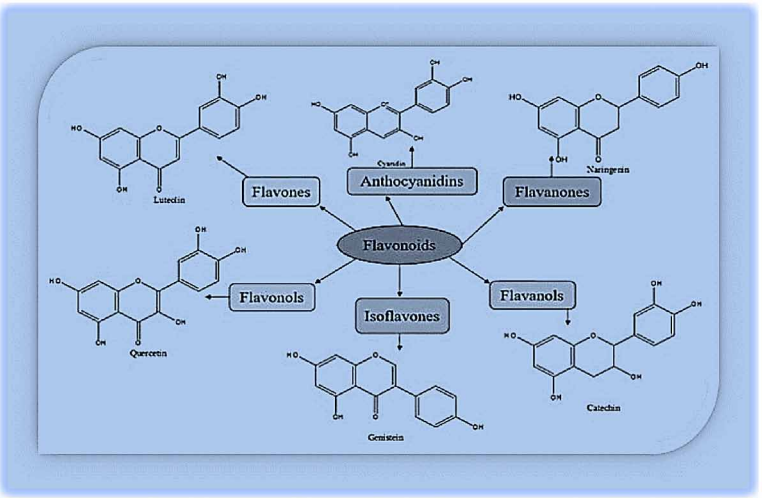
FLAVONOIDS AND RHEUMATIC DISEASES: HERBAL THERAPY FOR THE MANAGEMENT OF RHEUMATIC DISEASES

In developing nations of the world where resources are meager, traditional plants with medicinal properties are used for the treatment of innumerous diseases including rheumatic diseases and it would not be an exaggeration to put forth that the use of herbal medicines in the management of different diseases is an old as mankind (Panche *et al.,* 2016). Continuing this practice, researchers today are also much more focused on the benign compounds that are part of phytochemicals and have beneficial effects on human health. This is because currently available medicines that are used in the treatment of rheumatic diseases are having high side effect profiles or are much more expansive. Nature has bestowed us with the wealth of medicinal plants widely distributed on this planet earth as great sources of therapeutic compounds. Such compounds have the potential to alleviate different kinds of diseases and disorders without having harsh side effects on the normal physiological functions of our bodies (Corradini *et al.,* 2011). WHO has revealed that more than 78% of

the world's population incorporate herbal supplements for their basic health care needs. More than 2550 plant species in India are used as herbal medicaments either directly as folk medicines or indirectly in the production of pharmaceuticals. Since times immemorial, Indian people have used herbal formulations under the officially alternative health systems like Ayurveda, Unani, Homeopathy, Sidha, and Naturopathy. Much more is still unrevealed about the natural compounds in phytochemicals that have the potential to cure various diseases and disorders. From the existing knowledge of Pharmacognosy, it is thus possible to trace out novel compounds that may be used in the management of rheumatic diseases (Patwardhan *et al.,* 2010, Agrawal *et al.,* 2011). Innumerous numbers of herbal formulations like polyherbal formulations have been made from plant extracts to minimize the symptoms and progression of rheumatic diseases. Anti-arthritic activities of various phytochemical formulations have been confirmed on Freud's complete adjuvant (CFA)- induced arthritis model in Wister rats. Their results were promising as they revealed the significant minimization in arthritis index as well as, the reduction in the markers of inflammation like C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and serum rheumatoid factor (SRF) as compared to corticosteroids (Mishra *et al.,* 2011).

Plants are the main sources of majority of foods, drugs, and dietary supplements. Plant chemicals called phytochemicals can be classified as primary and secondary metabolites. Primary metabolites are central to sustain plant life as they are the main players of the functions like cell division, growth, reproduction, respiration, metabolism, and storage. Secondary metabolites are not merely the plant waste products of primary metabolism but have profound effects on plant defensive mechanisms, ecology, and evolution. Among the major plant secondary metabolites are flavonoids. The term 'Flavonoid' includes the compounds that are defined by pigment. This term is derived from the Latin word *flavus* meaning yellow. Chemically these compounds are polyphenols conjugated to sugars in glycosylated forms. However, some exist in free form as aglycones (Morales *et al.,* 2012). Flavonoids include the class of more than 6000 compounds having 15 carbon skeletons with the core structure of 2- phenyl- benzopyrone in which the three-carbon bridge is cyclized with oxygen. Such structure makes them important variable phenolic compounds with marked antioxidant and anti-inflammatory potentials. Flavonoids are ubiquitous in vegetables and fruits that are regularly eaten by humans. These compounds occur as secondary metabolites in plants (fruits, vegetables, roots, stems, flowers, bark, leaves) and are reported to have propitious effects on human health for the reason of which they are incorporated in the constituents of various nutraceuticals, medicines, cosmetic products (Gonzalez *et al.,* 2011).

Figure 3. Flavonoid sub-classes



Flavonoids have been reported to possess anti-viral, anti-allergic, anti-mutagenic, anti-tumor, anti-inflammatory, anti-oxidative, anti- carcinogenic, and anti-aging effects along with the ability to modulate cellular enzyme functions, induce apoptosis, inhibit cell proliferation, among others. Investigations are focusing mainly on antioxidant activities, particularly their role in cancer control. They have been reported to be efficient singlet oxygen quenchers and thus could reduce the load of ROS in systems under stress by acting as antioxidants. Based on their chemical structure flavonoids have been categorized into six major sub-groups; Flavones, Flavanones, Isoflavonoids, Chalcones, Anthocyanins, and Anthoxanthins (**Fig. 3**). The research process on flavonoids gained an added impulse since the discovery of the French paradox in which a low mortality rate was observed in populations due to consumption of red wine which is the richest source of flavonoids and high saturated fat intake (Kumar *et al*., 2103). Current trends of research on these phenolic compounds relate to their identification, isolation, characterization, and functioning in biological systems as well as their effects on the growth and proliferation of plant pathogenic microorganisms. Knowledge of bioinformatics and molecular docking is being employed to predict the potential application of flavonoids related to human health and disease (Soo *et al.,* 2013*)*. Rheumatic diseases being especially inflammation and oxidative stress-related disorders may be alleviated safely through the use of bioactive flavonoids that have been revealed to have powerful anti-inflammatory and antioxidant potential. Being powerful anti-inflammatory agents through their immunomodulatory potential; their use in the management of inflammatory and autoimmune diseases has started to emerge. In

both human rheumatic diseases and animal models of arthritis, dietary flavonoids from different medicinal plants have been reported to minimize the symptoms of joint inflammation and gradually alleviate rheumatic disorders. Due to diversity in the sub-classes of flavonoids and indecipherable problems related to their purity as well as dosage, an established immunomodulatory potential of flavonoids in clinical trials had remained controversial so far. Also, their exact mechanism of action in alleviating rheumatic diseases remains elusive. However, it has been reported that direct or indirect antagonism of pro-inflammatory cytokines via immunomodulation of key inflammatory signaling cascades, reduced recruitment of proinflammatory cell types, enhanced free radical scavenging potential are primary mechanisms that different classes of flavonoids exert to alleviate rheumatic diseases (Izzi *et al.,* 2012, Hughes *et al.,* 2017). Flavonoids like apigenin, quercetin, kaempferol, and luteolin have been reported to diminish cytokine expression and secretion. Regarding this therapeutic potential, they can be termed as cytokine modulators and thus modulators of both innate and adaptive immune responses. Research is much focused on their potential effect to elevate the regulatory T cells (tregs) and their potential to induce overproduction of anti-inflammatory cytokines especially IL-10. Receptor-ligand actions like, PI3K/Akt inhibition, mTORC1 inhibition, TLR suppression, IKK/MAPK inhibition, NFκB, and JAK/STAT inhibition have been attributed as key targets of flavonoids to mediate anti-inflammatory effects (Grover *et al.,* 2010, Indra *et al.,* 2013).

FUTURE RESEARCH DIRECTIONS

The objective of the present chapter is to evaluate the potential of plant bioactive compounds in the management of rheumatoid diseases, which are disorders of chronic joint inflammation along with swelling and pain. Such compounds are able to control inflammatory responses, proinflammatory cytokines, osteoclast differentiation and prevent bone erosion in the joints. In this chapter, we reviewed anti-arthritic potential of phytochemicals via gathering data from various research articles. Till date clinical trials carried out on anti-arthritic activity of phytoactive compounds are very less. Hence, more research and clinical trials are desired to bring novel phytoactive compounds as safe and effective anti-arthritic agents in the market, either alone or in combination with other anti-arthritic agents that are currently in use.

CONCLUSION

At least 100 types of arthritis are known today in which osteoarthritis dominates by affecting more than 3.8% of people followed by RA, which is one of the prototypes of chronic inflammatory polyarthritis characterized by infiltration of B-cells, T- cells, fibroblasts, and macrophages inside the synovial membranes, leading to inflammation and function loss. Treatment of rheumatic diseases has been revolutionized through the development of novel biologics, but off-target side effects and development of tolerance are the main concerns associated with them when administrated via oral and systemic routes. Nanosystems have enabled site-specific and localized delivery of NSAIDs, GCs, interference-producing nucleic acids like siRNA, and other disease-modifying agents, while decreasing the frequency and quantity of drugs used, thus skipping potential unwanted off-target effects to some extent. Because drugs used to treat rheumatic diseases like non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying anti-rheumatic drugs (DMARDs), glucocorticoids and new generation immunosuppressants have wreaked havoc on the normal physiological functions of the body, there a dire need to trace out potent novel compounds that may somehow interfere with the signaling pathways of pro-inflammatory cytokines and recruitment of inflammation mediating cell types. Currently innumerous kinds of medicinal plant phytochemical are under clinical trials to target the rheumatic disease progression. It is being hypothesized that phytochemicals act through producing interference in chemical messenger signaling responsible for triggering inflammation. Flavonoids being anti-oxidative and anti-inflammatory in nature have been specially found to exert such a role in inflammatory and auto-immune disorders. So in-depth research on these benign compounds is the need of the hour.

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KEY TERMS AND DEFINITIONS

Arthritis: Arthritis is a term that describes around 200 conditions that cause pain in the joints and the tissues surrounding the joints.

Cytokines: Cytokines are small messenger proteins that are crucial in controlling the growth, differentiation and activity of immune system cells.

Flavonoids: Flavonoids are a group of plant secondary metabolites which are supposed to provide health benefits through cell signaling pathways and antioxidant effects.

Nanodelivery: Delivery of drugs via nano-drug delivery systems (NDDSs) which are different classes of nanomaterials.

Nanotechnology: Nanotechnology is science, engineering, and technology conducted at the nanoscale, which is about 1 to 100 nanometers.

Chapter 10
Encapsulation of Flavonoids in Nanocarriers:
A Novel Strategy to Enhance Their Bioefficacy and Oral Bioavailability

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ABSTRACT

The term "flavonoid" is a broad term given to the collection of natural polyphenolic compounds which occur in plants (fruits, vegetables, roots, flowers, stems, bark, leaves) as their secondary metabolites. Subsequent research reveals that flavonoids possess anti-inflammatory, anti-mutagenic, anti-oxidative, anti-ageing, and anti-carcinogenic effects along with their capacity to modulate enzymatic activities, inhibit cell proliferation, and inhibit bacterial growth, among others. The main shortcomings of oral administration of flavonoids as therapeutic that various studies have revealed are related to their stability, bioefficacy, and bioavailability. Novel nanotechnological strategies involving nanocarrier systems are proving promising to overcome the delivery challenge of flavonoids as therapeutics. Nanocapsules, nanospheres, solid lipid nanoparticles, nanoemulsions, micelles are examples of novel nanocarrier systems that are currently being explored for targeted and efficient bio functioning of flavonoids after their oral administration.

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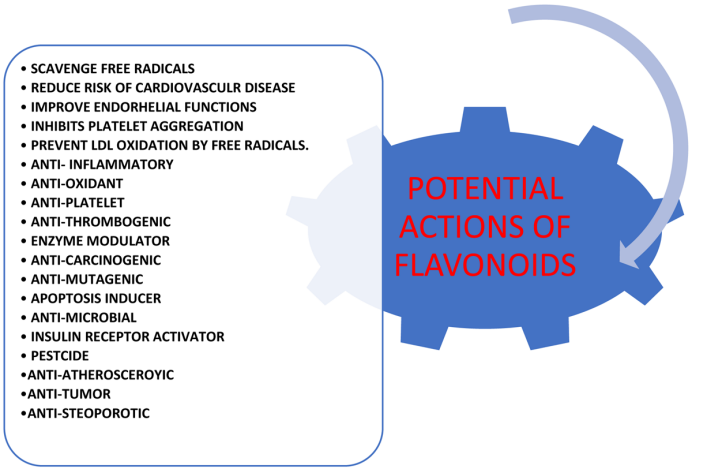
INTRODUCTION

Plants are main sources of majority of foods, drugs, and dietary supplements. All the plant chemicals known as phytochemicals can be classified as primary and secondary metabolites. Primary metabolites are central to sustain plant life as they are main players of the functions like cell division, growth, reproduction, respiration, metabolism, and storage. Secondary metabolites are not merely the plant waste products of primary metabolism but have profound effects on plant defensive mechanisms, ecology, and evolution (Udomsuk *et al.,* 2011, Corradini *et al.,* 2011). Among the major plant secondary metabolites are flavonoids. Flavonoid is the name given to class of more than 6000 compounds having fifteen- carbon skeleton with the core structure of 2- phenyl- benzopyrone with three-carbon bridge cyclized with oxygen. Such structure makes them important variable phenolic compounds with marked antioxidant activities (Morales *et al.,* 2012). Flavonoids are abundantly found in vegetables and fruits that are regularly eaten by humans. Such compounds occur as secondary metabolites in plants (fruits, vegetables, roots, stems, flowers, bark, leaves) and are reported to have propitious effects on human health for the reason of which they are incorporated in the constituents of various nutraceuticals, medicines, cosmetic products (Winkel *et al.,* 2011). Flavonoids have been reported to have anti-viral, anti-allergic, anti-mutagenic, anti-tumor, anti-inflammatory, anti-oxidative, anti- carcinogenic and anti-ageing capacities along with the ability to modulate cellular enzyme functions, induce apoptosis, and inhibit cell proliferation, among others. (**Fig. 1**). They have been reported to be efficient singlet oxygen quenchers and thus could reduce the lode of ROS in systems under stress by acting as antioxidants (Panche *et al.,* 2016). Investigations are focusing mainly on the antioxidant activities, particularly their role in cancer control. Almost all plant parts including fruits and vegetables pack a big flavonoid punch. Compounds like procyanidin, catechin, epicatechin, chlorogenic acid, Phloridzin and quercetin are main flavonoids occurring in edible plant parts. They are actively incorporated in the plant life processes like UV filtration, symbiotic nitrogen fixation and play an important role as chemical messengers, regulators of physiology, and inhibitors of pathogens that are involved in plant diseases. Data from literature have also revealed that flavonoids get incorporated in the response against pathogens, both when they are enhanced following infection of plants tissues, as well as when they are applied externally. A plethora of evidence supports that after a plant is challenged by a pathogen or other abiotic stressors like physical, chemical, or biological stressors, various biochemical changes in the plant tissue take place inwardly which trigger down- or upregulation of specific phenolic compounds. Such alterations which mainly lead to the over expression of phytoalexins in turn may play a cardinal role in resistance/susceptibility of that plant to that invader. An added

impulse on the process of research on flavonoids is gained since the discovery of French paradox in which low mortality rate was observed in populations because of consumption of red wine which is considered as richest source of flavonoids. Current trends of research on Flavonoids and other phenolic compounds relate to their identification, isolation, characterization, and particularly in the prevention of degenerative conditions including cancers, cardiovascular and neurodegenerative diseases. Knowledge of bioinformatics and molecular docking is being employed to predict potential application of flavonoids related to human health and disease. Current trends of research relate to their identification, isolation, characterization, and disease modulating capabilities as well as their impact on defending the growth and proliferation of plant pathogenic microorganisms by acting as phytoalexins (Kumar *et al.,* 2013, Kay *et al.,* 2012*).*

Despite the beneficial effects of flavonoids on human health, their main concerns to be used as therapeutic are related to their stability, bioavailability, and absorption after oral administration. Even in the form of glycosides, they show limited water solubility and poor bioavailability. Their delicate configurations are easily susceptible to modifications after being exposed to light, temperature, and pH. In their natural form, flavonoids have poor gastrointestinal absorption, poor permeability, and instability towards gastric and colonic pH. C Certain studies have shown that flavonoids are subjected to active efflux mechanisms on their absorption across the intestinal wall. Moreover, these compounds are extensively disintegrated to different metabolites by intestinal microbiota and/or enzymes which have varied bioactivity as expected from original compounds (Manach *et al.,* 2005, Bilia *et al.,* 2014). To overcome the shortcomings of flavonoid post administration stability, bioavailability, and absorption, nanosystems involving nanocarrier delivery are being designed. Upon encapsulating the potent flavonoids in nanocarriers and administrated orally, their bioefficacy and bioavailability have been shown to enhance to the effectual degree. Nanocarrier mediated delivery have enhanced their solubilization potential, altered absorption pathways and prevented their metabolic disintegration by the gut microorganisms and enzymes. Through nanocarrier encapsulation, they have efficiently withstood the gastric pH and other factors that were rendering them instable. Thus, their therapeutic outcome depends on the improvement of their pharmacokinetic profile after administration (Roger *et al.,* 2010).

Figure 1. Biological functions of flavonoids



CHEMICAL STRUCTURE OF FLAVONOIDS

Flavonoids are group of polyphenolic plant and fungus low molecular weight secondary metabolites. They possess a general structure of 15- carbon skeleton possessing two phenyl rings A & B and a heterocyclic ring C. Rings A and B are joined by mediation of the oxygen having heterocyclic ring C. This chemical structure is denoted as C6-C3-C6 (Soo *et al.,* 2013). Subclasses of flavonoids are generated because of variations occurring in the heterocyclic ring (**Fig 2**). Multiple hydroxyl groups in polyphenol bases are variably conjugated which gives rise such a huge number of specific compounds. Flavonoids possess a characteristic flavone nucleus derived biosynthetically from malonate and phenylalanine (Gonzalez et al., 2011*)*. Plant flavonoids take the form of glycosides because of conjugation with sugars and organic acids. Conjugation with sugars mostly at position 3 in the heterocyclic C ring of flavonols and anthocyanins is common and sometimes conjugation with position 5 and 7 of A ring have also been reported. Rhamnose, rutinose, acetate, malonate, galactose, glucose and caffeic acid conjugate with flavonoid skeleton rings which results in the increase in their molecular weight. For example, in food plants like tea, onion, apple the most naturally occurring glycosides of quercetin appear to be the 3- rhamnoside-glactoside (bio quercetin), 3- rutinoside (rutin), & 3- glucoside (iso quercetin) (Manach *et al.,* 2004). Antioxidant properties of flavonoids are attributed to multiple phenolic groups (3' & 4' hydroxyl groups), C2-C3 double bound, and C5 hydroxyl groups (Panche *et al.,* 2016).

DIFFERENT SUB CLASSES OF FLAVONOIDS

Based on their chemical structure flavonoids have been categorized into six major sub-groups including Flavones, Flavanones, Isoflavonoids, chalcones, anthocyanins and Anthoxanthins [4]. Keeping in view the carbon atom of the C ring with which B ring is fused along with the degree of unsaturation and oxidation of the C ring, flavonoids have been grouped into various sub-categories like flavonols, flavones, flavanones, flavonols (catechins), Isoflavonoids, neoflavanoids, anthocyanins, and chalcones **(Fig. 2 and 3)** (Panche *et al.,* 2016, Hussain *et al.,* 2012).

- **Flavonols:** This subgroup possesses a ketone group in their core structure and at position 3 of C ring contain hydroxyl group. These groups are glycosylated as well. This class is very diverse in hydroxylation patterns. Best examples of this class include Kaempferol, Quercetin, Myricetin and Fisetin. Proanthocyanins are mainly composed of flavonols (Dillard *et al.,* 2000). Main sources of Flavonols include tomatoes, apples, oranges, berries, grapes along with tea and red wine. This class is considered to be largest flavonoid subgroup to be present in vegetables and fruits. This class of flavonoids are considered as potent antioxidants and have been reported to confer health benefits by reducing risk of cardiovascular diseases (Galeotti *et al.,* 2008).
- **Flavones***:* Flavonoids that between positions 2 & 3 possess double bond and a ketone group at position 4 of the C ring are categorized under flavones. These flavonoids mainly occur in the form of glycosides in flowers, leaves, herbs, and fruits. Best examples of this class include tangeritin, luteolin, and apigenin. In most fruits, these flavonoids possess at position 5 of ring A, a hydroxyl group. Main sources of flavones include Ginkgo, Mint, Celery, red Peppers, and Chamomile (de *et al.,* 2010*).*
- **Flavanones:** These are also called as dihydroflavones and are subclass of flavonoids having saturated C ring which means double bond is saturated between positions 2and 3. These flavonoids are characteristic feature of almost all citrus fruits and vegetables like lemon, oranges, grapes, and tomatoes. In fact, bitterness of all these fruit juices is because of these flavonoids Examples of this class include Eriodyctiol, Naringenin, and Hesperitin. These flavonoids are considered as elegant free radical scavengers (Seelinger *et al.,* 2008, Panche *et al.,* 2016).
- **Isoflavonoids**: Isoflavonoids form a large sub-group of flavonoids and occur mainly in leguminous plants and soya beans. Some have also been reported to occur in microbes (Dixon *et al.,* 2010). Genistein and Daidzein are best studied Isoflavonoids which have been reported to have oestrogenic properties. For this reason, they are sometimes known as phyto-oestrogens.

Effect of genistein induced metabolic and hormonal changes through which various disease pathways can be influenced is reviewed by Szkudelska & Nogowski. These flavonoids are also effective ROS scavengers (Szkudelska *et al.,* 2007).

- **Neoflavanoids***:* These polyphenolic compounds differ from rest of flavonoids in having a 4- phenylchromen backbone and no hydroxyl group at position 2. Calophyllolide is best studied neoflavanoid that was isolated from seeds of *Calophyllum inophyllum* (Garazd *et al.,* 2003).

Figure 2. Sub classes of flavonoids based on variations in the heterocyclic ring

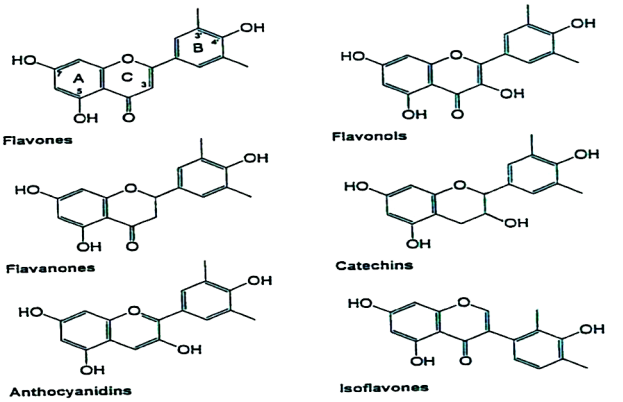
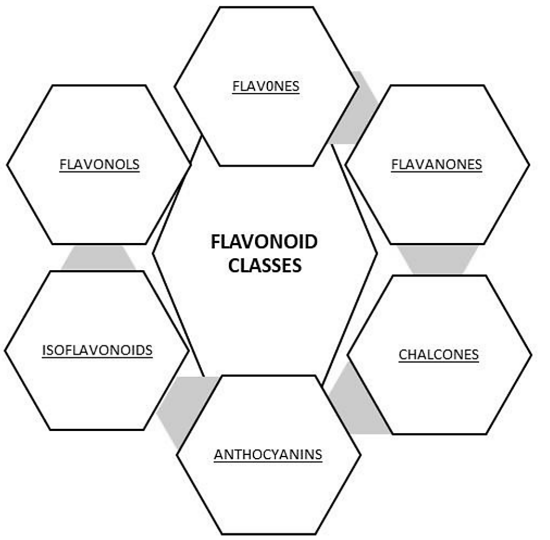


Figure 3.



- **Anthocyanins***:* This subclass of flavonoids impart pigmentation to vegetables, fruits, and flowers in which they naturally occur. Pigment colorations depend upon acylation of hydroxyl groups associated with A and B rings and on pH. Best examples of anthocyanins include Malvidin, Cyanidin, Peonidin and delphinidin ((Kumar *et al.,* 2013).
- **Flavanols**: These are also known as Catechins. These compounds are 3-hydroxy flavanone derivatives. In their core structure hydroxyl group is always linked with C ring at position 3 and hence they are also called as flavan- 3- ols. These compounds are not saturated as double bond between positions 2 & 3 do not exist at all. These compounds are highly multi-substituted and act as free radical scavenging and anti-inflammatory agents in biological systems. Apples, Bananas, Pears, Peaches, Mangoes, and cherries are main dietary sources of flavanols (Annadurai *et al.,* 2012).
- **Chalcones***:* These are only flavonoids that lack the 'ring C' from their basic skeleton frame unlike rest of flavonoid sub-groups. For this reason, they are sometimes known as 'open chain flavonoids and best examples of this subgroup include phloretin, phloridzin, and arbutin that occur most abundantly in Berries, Pears, wheat, Maize and Tomatoes. These compounds are reported to have numerous health benefits and have thus gained much more attention in research (Buer *et al.,* 2010).

Figure 4. Different sub classes of flavonoids

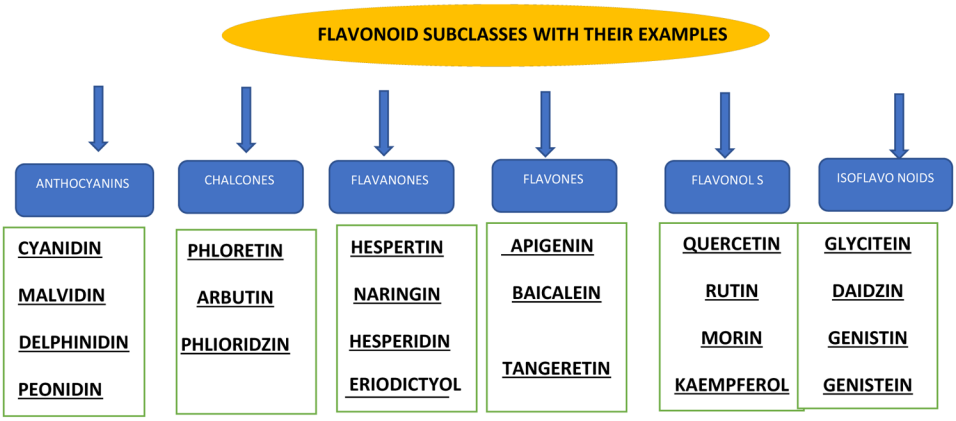
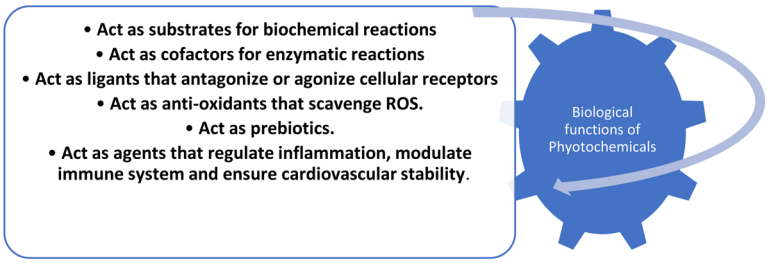


Figure 5. Biological functions of phytochemicals



BIOLOGICAL FUNCTIONS OF FLAVONOIDS

Flavonoids are among important phytochemicals as secondary metabolites. Phytochemicals are reported to have human health benefits when consumed via pant-based foods and supplements. Important biological functions of phytochemicals are summed up in **Table 1**.

Table 1. Recently revealed biological activities of flavonoids

Study	Reference
A potent antioxidant flavonoid namely Rutin has been shown to block apoptosis in umbilical vein endothelial cells by augmenting glutathione production (master antioxidant), quenching reactive oxygen species that protect DNA damage.	Gong *et al*., 2010
Luteolin was shown to decrease vascular permeability by acting as anti-inflammatory agent after parenteral and oral administration in animal models. It also displayed cytoprotective properties when used in combination with vitamins	Seelinger *et al*., 2008
Myocardial oxidative injury induced due to isoproterenol was shown much restored by quercetin, a potent antioxidant flavonoid.	Liu *et al*., 2012
Consumption of plant foods containing Flavonoid Kaempferol was found to reduce the risk of cancer development, cardiovascular diseases, and auto-immune disorders.	De Pascual- Teresa *et al*., 2010
Anthocyanins and Flavonols have been shown to reduce the cholesterol content in erythrocyte membranes.	Duchnowicz *et al*., 2012
Baicalin have been reported to decrease oxidative stress induced due to hyperglycemia by enhancing the expression of antioxidant enzymes.	Waisundara *et al*., 2011
Myricetin displayed the properties of enhancing expression of cellular antioxidant enzymes like Superoxide dismutase (SOD), Catalase (CAT) and Glutathione peroxidase (GPx), that were retarded via hydrogen peroxide treatment.	Wang *et al*., 2010
Naringenin displayed antioxidant as well as anti-hyperglycemic effects in diabetic rats under experiment.	Annadural et al., 2012
Isoquercetin (IQ) being one of the most important flavonoids has been reported to have hydroxyl radical, superoxide anion, and nitrate scavenging abilities.	Li et al., 2011
Quercetin, catechin, taxifolin and kaempferol diminished the superoxide ion and hydrogen peroxide cytotoxicity.	Park *et al*., 2010

The main biological functions of flavonoids as phytochemicals are discussed as under:

- **Plant physiology:** Flavonoids are secondary metabolites that are widely distributed in pant kingdom, serving many biological functions. They act as most important pigments in plants that impart color to fruits and flowers to attract pollinators. Important functions in higher plants where flavonoids are incorporated include, symbiotic nitrogen fixation, UV filtration, floral pigmentation, among others. They also play a role as chemical messengers, modulate function of certain cellular enzymes, inhibit cell cycle at certain points and regulate metabolism (Benavente *et al., 2008,* Udomsuk *et al.,* 2011).
- **Antioxidant activity-** To some extent, fruits and vegetables resist oxidative damage due to their natural flavonoids and in this sense, they become dietary source of antioxidants when consumed (Morales *et al.,* 2012). Antioxidant properties of flavonoids are attributed to the phenolic hydroxyl groups on the A & B rings. Due to their hydroxyl substitutes in hydrogen atoms, they are efficient free radical scavengers. They have been reported to be singlet oxygen quenchers and thus can reduce their load in systems under oxidative stress. They can also inhibit free radical generating enzymes like xanthine oxidase which is liable for superoxide production (Mira *et al.,* 2002, Park *et al.,* 2010).

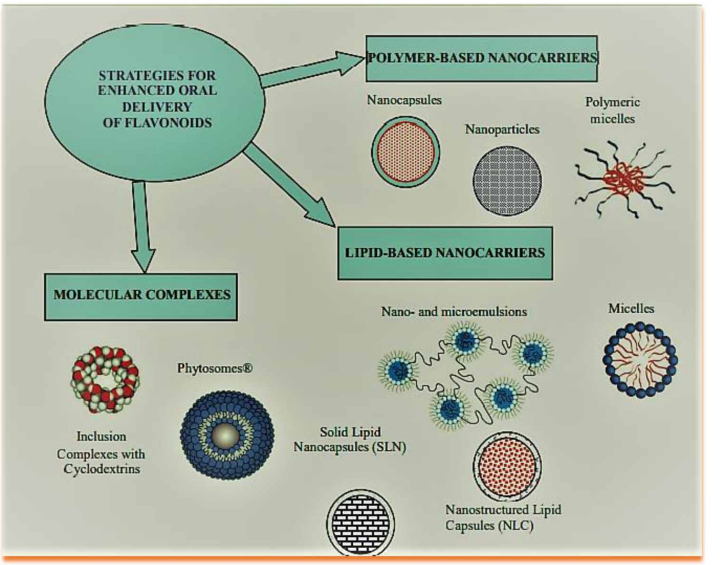
FI (OH) + R· ~ FI(O) + RH FI(OH) + 02·· ~ FI(O) + HOO·

It has also been reported that antioxidant potential of flavonoids is enhanced with increasing the number of hydroxyl groups in ring B.

- **Metal chelating ability of flavonoids-** Flavonoids are efficient metal ion chelators at the 3-hydroxy-4 keto group mostly when the ring A is hydroxylated at position. if there is O-quinol group at ring B, metal chelating activity is also enhanced (Mira *et al.,* 2002*).* Flavonoids are good at iron and copper chelation. For example, iron chelating ability of rutin in fat peroxidation can be evaluated by the formation of iron-rutin complexes. Flavonoids with 2, 3- double bond and have catechol group in the B ring have efficient Fe3+ chelating activity. On the other hand, number of hydroxyl groups present in a flavonoid is directly proportional to its copper reducing activity. In this sense, flavonoids may play a paramount role in metal overload diseases and conditions of oxidative stress incorporating transition metal ions (Lurdes *et al.,* 2002).

Other biological actions of flavonoids include their ability of inhibition of cell proliferation, inducing apoptosis, modulating cellular enzymes, reducing the risk of cancer and cardiovascular diseases. Moreover, some findings report that flavonoids also have numerous clinical properties such as, anti-inflammatory, antitumor, antithrombogenic, antiosteoporotic, antiatherosclerotic, and anti-microbial effects (Grassi *et al.,* 2010), Izzi *et al.,* 2012). Flavonoids possess the ability of reducing coronary heart diseases via three actions: enhancing coronary vasodilation, decrease blood platelet aggregation, and preventing oxidation of low-density lipoproteins (LDPs). Flavonoids have been reported to interact with ABC drug transporters that are incorporated in drug absorption, drug resistance, drug distribution and drug excretion. This ABC transporter- Flavonoid interaction could enhance the absorption of poorly absorbed drugs but may increase the risk of drug toxicity (Iwashina, T. 2013). Recently revealed biological activities of flavonoids are reviewed in the table 1.

Figure 6. Nanosized delivery systems for oral route



NANOCARRIER DELIVERY SYSTEMS TO INCREASE ORAL BIOAVAILABILITY OF FLAVONOIDS

Inspite of being propitious to human health, the main issues associated with flavonoids is their post administration instability. in gastrointestinal tract they have low bioavailability, water solubility and permeability. These compounds are

susceptible to gastric enzyme and pH degradation. Several studies have shown that flavonoids are subjected to active efflux mechanisms on their absorption across the intestinal wall. Moreover, these compounds are extensively disintegrated to different metabolites by intestinal microbiota and/or enzymes which have varied bioactivity as expected from original compounds (Plapied *et al.,* 2011). Development of nanosized carriers in the size range of 10- 100 nm represent a promising approach to overcome the delivery challenge of flavonoids as therapeutics after oral administration. Such strategies for enhanced oral delivery of flavonoids that are currently being explored for targeted and efficient bio functioning of flavonoids include the polymer-based nanocarriers (Nanocapsules, Nanoparticles, polymeric micelles), molecular complexes (Inclusion Complexes with Cyclodextrins, Phytosomes), and lipid-based nanocarriers (lipid nanospheres, solid lipid nanocapsules (SLN), nano- and microemulsions, Nanostructured Lipid Capsules (NLC), micelles). (Fig 2). Surface properties, particle size and shape of nanoparticles play a cardinal role in the uptake of loaded molecules across the gastrointestinal mucosa. Therefore, encapsulating, and administrating flavonoids in nanocarriers significantly enhances their absorption and permeability. Positive zeta potential and hydrophobicity of nanoparticles enhances their uptake from gastrointestinal tract. Other mechanisms that have been shown to support enhanced absorption of flavonoid-nanocarriers are electrostatic interaction between positive nanocarrier surfaces and negatively charged mucin, modulation of tight junctions by nanoparticles via interaction with junction proteins, enhanced transcytosis and receptor mediated endocytosis, targeted phagocytosis of nanoparticles by specialized microfold cells (M-cells), chylomicron based absorption by enterocytes mediated by lipases for lipid based nanocarriers. This all enhances solubilization and dissolution of loaded flavonoids in GI tract (Gaucher *et al.,* 2010).

Polymer-based nanocarriers being structurally efficient can accommodate a wide variety a drug molecules due to hydrophobicity and hydrophilicity within the polymeric system. The carrier material of polymer-based nanocarriers is generally natural or synthetic biodegradable polymers. Poly-α-cyanoacrylate alkyl esters, polylactic acid, polyglycolic acid, Polyvinyl alcohol and polylactic-glycolic acid are examples of synthetic polymers. Natural ones are more preferred because of less toxicity associated with them. They are either polysaccharides or proteins. Pectin, alginate, gum arabic, starch and its derivatives, cellulose and its derivatives represent the natural plant-based polysaccharides while as chitosan, xanthan gum are examples of animal-based polysaccharides from which polymeric nanoparticles are designed. Polysaccharide nanoparticles have unique properties that make them promising carriers to deliver the hydrophilic drugs. Being natural biomaterials, polysaccharide nanoparticles are safe, stable, non-toxic, and biodegradable. Polysaccharides have abundant natural resources and demand a low cost in their

processing. Flavonoids and other disease-modifying agents are embedded or dissolved in polymeric nanoparticles. They can also be adsorbed or coupled on their surfaces. Then accordingly these nanocarrier systems are named. For example, in core-shell nanocapsules therapeutic agents are encapsulated in the core surrounded by polymeric wall whereas in matrix carrier systems bioactive compounds are embedded in the polymeric matrix (Dube *et al.,*2010*).* There is a sustained release of drug molecules from these nanocarriers to ensure that no molecules are released till they are reached to systemic circulation thereby skipping various physiological barriers that could interfere with drug metabolism. Most of the loaded nanoparticles enter in enterocytes through transcellular transport after they reach the pical membrane of intestinal epithelial cells. Via clathrin and caveolae mediated endocytosis, small particles (100-400nm) are internalized by enterocytes. Specialized Peyer's patches (M cells) as well as follicles of the GALT present in the gastrointestinal tract uptake the loaded carrier molecules. By coating nanoparticles with cationic chitosan, they are protected from endolysosomal degradation. Nanocarrier micelles alter the membrane permeability, inhibit the efflux transport proteins and mucoadhesion inside the GI tract to ensure the enhanced drug absorption. There are several mechanisms via which the protected and functional bioactive ingredients are released from these nanosystems. These include desorption of the adsorbed/surface bound ingredients, dissolution, diffusion via matrix, matrix erosion through enzymatic degradation or through the combination of these processes (Konecsni *et al., 2012).*

FUTURE RESEARCH DIRECTIONS

The present chapter summarizes recent developments in Nanodelivery of Flavonoids as well as other phytoactive compounds and its application to combat diseases and disorders associated with oxidative stress, inflammation etc. Nanobiotechnology is fast growing area of applied biological sciences. It has opened the routes for novel drug delivery systems that has prominently subsided the unwanted and off-target effects of drugs and other bioactive molecules. Amalgamating the nanobiotechnology and phytochemical therapeutics had proved promising in bringing the novel bioactive compounds in use against various pathological conditions. Thus, it is the need of the hour to conduct more research and clinical trials with phytoactive compounds and their encapsulation in nanocarriers to deliver them site specifically. This review on biological potential of flavonoids and their encapsulation in nanocarriers has been done by gathering data from different researches and is a humble attempt to encourage the researchers to perform their research in this field.

CONCLUSION

Flavonoids are natural phenolic compounds that occur in plants as secondary metabolites. These compounds play an important role in human health and disease. Their Propitious effects on human health gained an added impulse in their research. Their role as regulators of cellular activity and potent antioxidants makes them best supplements to fight off free radicals and reduce oxidative stress in biological systems. Fruits, vegetables, tea, red wine, and nuts are best dietary source of flavonoids. Gastric instability and low water solubility in their natural forms are the main limiting factors for flavonoids to be absorbed systematically after oral administration. As a result, various potent bioactivities shown by flavonoids in vitro demonstrate less or no in vivo activities. When same flavonoids are encapsulated and administered through nanocarrier delivery systems, their stability is enhanced as well as they show much better absorption profile in the gastrointestinal tract. As a result, their biological activities are enhanced and prolonged. Finally, encapsulated flavonoids are released from these nanocarriers in a controlled manner to ensure their maximum bioefficacy.

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KEY TERMS AND DEFINITIONS

Antioxidants: Compounds that inhibit oxidation, a chemical reaction that give rise to free radicals and chain reactions that may damage the cells of organisms.

Carcinogens: Cancer causing compounds are said to be carcinogenic.

Free Radicals: A molecule having one or more unpaired electron in its outer shell is called a free radical.

Inflammation: Inflammation is part of the process characterized by swelling, pain and redness by which the immune system defends the body from harmful agents, such as bacteria and viruses.

Mutagenesis: Occurrence of mutations in the genome of an organism is termed mutagenesis.

Nanodelivery: Delivery of drugs via Nano-drug delivery systems (NDDSs) which are different classes of nanomaterials.

Nanotechnology: Nanotechnology is science, engineering, and technology conducted at the nanoscale, which is about 1 to 100 nanometers.

Phytochemicals: Chemicals that occur naturally in plants and their parts.

Secondary Metabolites: Secondary metabolites are compounds of living organisms that are not incorporated directly in growth or reproduction of an organism but are produced to confer value-added advantages.

Chapter 11
Electrospun Nanofibers for Scheming Water Pollution: Pioneer Strategies

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ABSTRACT

Water pollution is one of the key global problems which require immediate attention. Worldwide, it is predicted that more than 50% of countries will encounter water scarcities by 2025 which will increase to 75% by 2075. Each year more than 5 million people die due to water-borne diseases. The threat due to pollution by industries, exponential population growth, urbanization, by pathogenic microorganisms from human and animal waste, etc. The rise in water pollution and its subsequent effects on human health and environment is a matter of great concern. The water pollutants ought to be removed to improve water quality for human use. Nanoparticles or zero dimensional materials have been extensively studied since long, whereas one dimensional material (nanorods, nanotubes, nanowires, or nanofibers) have recently grabbed a lot of interest from global researchers. Nanofibers having large aspect ratio are grabbing incredible attention owing to dependency of physical property on directionality having high porosity and surface area as compared to normal fibers.

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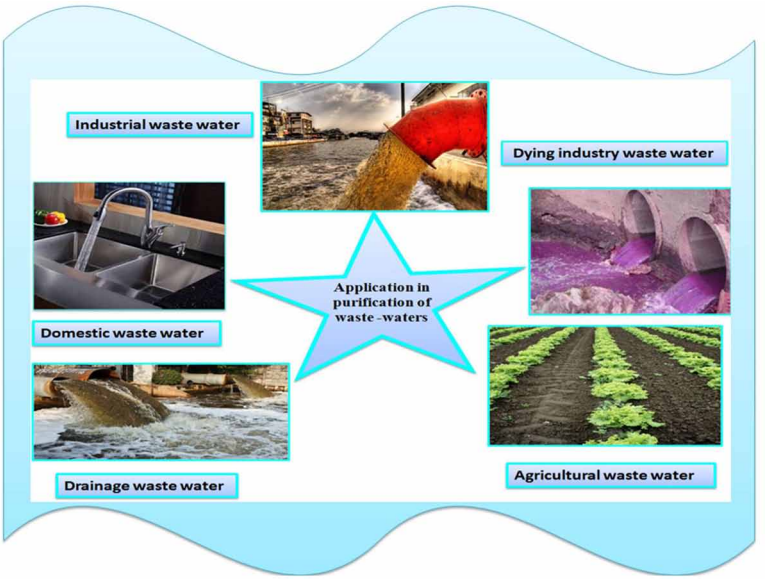
INTRODUCTION

Wastewater comes from various industrial resources (**Fig. 1**); for instance; aluminum, fabric, steel, petroleum, foodstuff, metal refinement as well as petrochemical and leather manufacturing, (Xue, Cao, Liu, Feng, & Jiang, 2014). On one hand we have several oil/waters partition methodologies (centrifugation, air flotation, coalescence, gravity separation, etc.); however; on the other hand, these techniques have scores of drawbacks, such as low separation effectiveness, prolonged duration, and elevated energy usage. Conversely, membrane separation method is believed to be outstanding method for oil/water separation process. This method has scores of usefulness such as steady quality of permeation, relatively low operating cost, and low energy costs. Therefore, membrane tools are widely being utilized for purification of wastewater. Although, this is energy-efficient process for removal of contaminations for water purification, however, the key challenge of this technology is selection of materials that can improve membrane characteristics as well as efficiency. Principally, there are two major kinds of membrane supplies such as polymeric and inorganic, (ceramic and composite), that are mostly utilized in membrane development for wastewater treatment. Environmental remediation imposes execution of innovative materials and techniques, which should be cost effective as well as energy proficient. In this direction the nanomaterials with distinctive physicochemical characterization are most favorable resolution. Consequently, there is urgent requirement for designing of novel nanomaterials for attenuation of ecological problems in economic approach. Nevertheless, the electrospun nanofibers are desirable possessions owing to high aspect ratio and excellent porosity which impart amazing selection and permeability to filter membranes. The functional properties and applications of these fibers are enhanced through nanocomposite approach. The nanofibers can be blend with metal oxides, carbon nanotubes, worthy metals as well as novel biomolecules all through the electrospinning and post-electrospinning to impart fascinating and practical properties. Furthermore, to meet operational necessities such as to improve mechanical firmness, lessen of pressure drop, *etc.*, nanofibers are blended by non-woven microfibers to form a crossbreed crust. These unique nanofibrous composites can accomplish amazing goal of environmental remediation.

Similarly encapsulating inorganic nanomaterials, e.g., ZnO, Ag, Au nanoparticles (NPs) etc, as well as graphene within polymeric matrices significantly advances permeation, antifouling, photocatalytic, and antibacterial characteristics of nanofibers. Interesting aforementioned nanocomposites offer excellent mechanical strength and thermal stability. Furthermore, these electrospun nanofibers having excellent antimicrobial features can reject biological contaminants (viz.; bacteria, fungi, mycoplasms and viruses etc.) in wastewater and therefore will conduct excellent

disinfection and microbial control. Conclusively, well organized nanofibrous filters with aforementioned characteristics are required for pertinent future water purification industries (Mousa, Alfadhel, & Abouel Nasr, 2020). An extensive estimation has been offered on existing research and development of electrospun nanofibers containing various antimicrobial compounds. The impact of encapsulation of antimicrobial compounds (organic or/ and inorganic) on properties of precursor solutions with different polymers and characteristics of resultant electrospun nanofibers are recapitulated in this chapter.

Figure 1. Possible sources of wastewaters and role of novel Electrospun nanofibers for purification

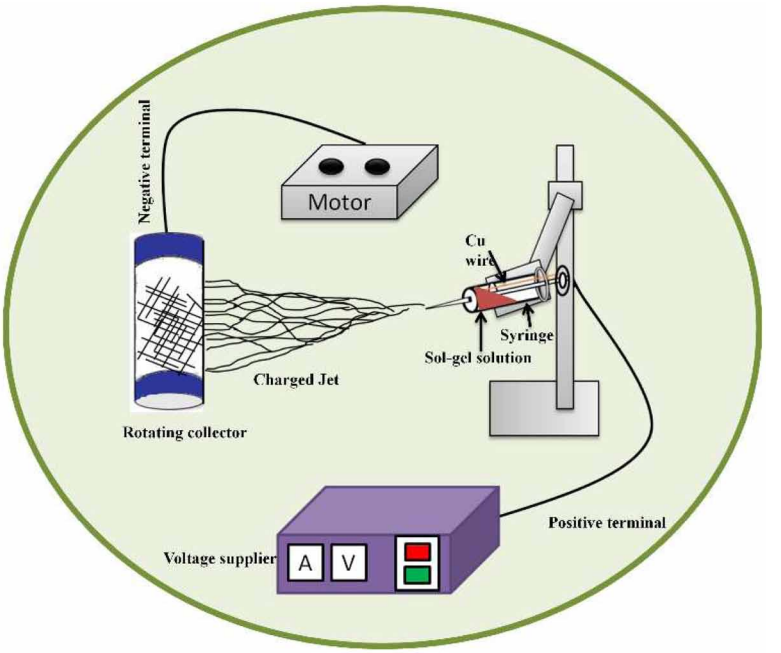


Electrospinning Process

Electrospinning is an established technique to fabricate nanofibers. The extraordinary characteristics displayed by electrospun materials are utilized for various applications. The high surface area and controlled grain size attained by electrospinning enhances materials with certain interesting properties which make them very suitable for certain applications. Electrospinning is also one of the fastest growing techniques for nanofibers synthesis. In this technique, we use electrostatic forces to generate fine fibers utilizing high molecular weight polymer solutions.

Conventionally, an electrospinning typically comprises of three main parts: a high-power provider, a spinneret (i.e. syringe tip) as well as a collector (a revolving cylindrical axle) (**Fig. 2**). Prior to electrospinning, polymers are completely dissolved in solvent and then it is fed into the syringe or pipette tip to electrospin. The thickness of synthesized fibers and their morphology depend on various parameters, like conductivity or viscosity of solution, strength of electric field, space between spinneret and grounded collector, operating temperature, and moisture etc.

Figure 2. Schematic Diagram of Electrospinning Set-up



Ceramic Nanofibers

In last few years, there has been a lot of advancement in ceramic nanofibers preparation. Ceramic oxide nanofibers are stable at high temperature, so, used in wide range of applications because of their high surface ratio. Ceramic oxide nanofibers show better properties compare to their bulk counterparts. During last decade, there has been remarkable progress in synthesis of ceramic nanofibers.

Ceramic nanofibers show exceptional characteristics like increased surface area, easy to tune composition and exceptional stability (Dai, Liu, Formo, Sun, & Xia, 2011; Nazari, Kashanian, Moradipour, & Maleki, 2018). Moreover, porous

ceramic nanofibers are considered as good support for nanoparticles for enhanced catalytic reactions due to its elevated plane and lofty permeable morphology. Ceramic nanofibers are getting more beneficial and functional materials in numerous applications due to their surface dependent and size dependent properties. Ceramic oxides nanostructures are known for their stability and green chemistry contrary to several polymers which are toxic. Ceramic nanofibers are usually prepared by electrospinning of ceramic precursors in addition to polymer solution then after calcination at high temperatures.

APPLICATIONS

Scientists have started to investigate numerous applications of nanofibers which have special characteristics like high aspect ratio, porous morphology, and superior physico-mechanical features as in this procedure, exploitation of solution and progression factors can easily be completed to acquire preferred fiber morphology and mechanical strength. The applications of electrospun nanofibers have been discussed in the below section of this chapter.

Nanofibers in Photocatalytic Applications

Using nanofibers as photocatalyst has many benefits in photocatalytic reactions owing to their higher surface to volume ratio. Nanofibers having high surface areas and sufficient porosity exhibit higher influence on organic pollutant degradation. Degradation efficiency increases if surface contacts between catalyst and pollutant are more, so, nanofibers play an important role here. Among the photocatalysts, titania is most exploited as photocatalyst owing to its excellent chemical and physical properties. It has been reported that the electrospun TiO_2 nanofibers demonstrated better photodegradation of methyl orange dye compared to TiO_2 nanoparticles or TiO_2 thin film (Hamadanian, Akbari, & Jabbari, 2011; Zhang, Xu, & Han, 2009). The reaction in photocatalysis includes production of excited electrons and holes and photocatalytic efficiency is dependent upon separation of charge, transport of charge to surface and charge recombination. Higher photo-efficiency of nanofibers was due to some features like high surface area, fast charge separation and fast diffusion rates between excited electrons and holes. Very recently, TiO_2/g-C_3N_4 hierarchical nanofibers were synthesized with high absorption in visible light and efficient photocatalytic activity for hydrogen evolution of 1202 $\mu molg^{-1}$ in 7 hours (Zou *et al*., 2021). Similarly, in another study titania nanofibers decorated with Au-Ag NPs photocatalyst exhibited intense light absorption property which covered all visible light wavelength having strong stability (Chattopadhyay, Bysakh, Mishra,

& De, 2019). Nowadays, carbon nanomaterials are also getting a lot of attentions for their applications in various fields. The unique property of carbon nanofibers shows higher degree of graphitization as compared to conventional activated carbons (Figueiredo *et al.*, 2006; Serp, Corrias, & Kalck, 2003). Carbon nanofibers generally used as support for photocatalytic materials. CNFs hydrophilic properties are due to oxygenated functional groups positioned on its surface which assist in allowed facile bonding of TiO_2 particles using sol–gel synthesis method (Keller, Rebmann, Barraud, Zahraa, & Keller, 2005). Recently, CNF doped ZnO were prepared and applied for photodegradation of methylene blue (MB) under sunlight. Total degradation of dye was attained within 10 minutes at low ultra-violet (UV) intensity in natural sunlight (Dehghani *et al.*, 2020). Additionally, in very recent report CdO-ZnO core-shell nanofibers were synthesized by electrospinning method and demonstrated outstanding photocatalytic efficiency of 98.4% for MB degradation under sunlight (Maafa *et al.*, 2021). Similarly, $MnWO_4/WO_3$ composite nanofibers showed photocatalytic breakdown of methyl orange (85%) in visible light irradiation and stable photocatalytic cyclability (Li *et al.*, 2018).

Nonetheless, the Graphene (Gr) incorporated composite nanofibers synthesized by a sol-gel nozzle-less electrospinning method having band gap of 2.5 eV can efficiently turn on organic dyes under visible light and UV-light irradiation. Titanium dioxide-Zinc Oxide-Bismuth oxide-Graphene (TZB-Gr) displayed superior degeneration rate of 0.0371 min^{-1} as compared to P25 and TZB ($k = 0.0008\ min^{-1}, 0.008\ min^{-1}$) in presence of visible light degradation of MB and higher degradation rate (k) of (0.1557 min^{-1}) than P25 and TZB ($k = 0.0162\ min^{-1}, 0.0482\ min^{-1}$) under UV degradation of MB (Kanjwal, Lo, & Leung, 2019). Liu *et al.* reported synthesis of mesoporous $BiVO_4$ nanofibers having surface area four times than that of normal solid counterparts. It's photocatalytic degradation of Rhodamine B (RhB) demonstrated an intensely better photocatalytic activity in visible light irradiation, which is three times to that of conventional solid counterparts (Liu, Hou, Gao, Yao, & Yang, 2016). Asif *et al.* reported Co_3O_4/Fe_2O_3 composite nanofibers having band gap energy of 2.12 eV, exhibited photodegradation efficiency (97%) of acridine orange (AO) dye under sunlight at pH~10 (Asif, Khan, & Asiri, 2014). $Bi_2Fe_4O_9$ nanofibers were prepared by sol-gel electrospinning method at 700 °C with band gap energy of 2.1 eV shows 70% degradation efficiency for methyl orange (MO) (Qi, Zuo, Wang, & Chan, 2013). Sharma *et al.* reported the preparation of graphene-oxide-based hydrophobic PAN/GO nanofibers by electrospinning method for photocatalytic degradation of Rhodamine 6G (R6G) dye in sunlight (Sharma, Sokhi, Balomajumder, & Satapathi, 2017). In another study heterostructured $Co_{0.5}Mn_{0.5}Fe_2O_4$-polyaniline macroporous hollow core shell nanofibers were prepared by electrospinning and chemical polymerization method which shows high photocatalytic efficiency for breakdown of MO in visible light (Jung, Kim, & Lee, 2019). Conclusively, aforementioned studies clearly show

that the novel electrospun nanofibers possess great potential for photocatalytic activity. **Table 1** summarized some of the interesting reports which demonstrated the use on nanofibers photocatalyst for degradation of water pollutants.

Table 1. Recent report on nanofibers photocatalyst for degradation of pollutants

Photocatalysts	Pollutants	Efficiency (time)	Reference
CdO/ZnO	Methylene blue (UV light)	98.4% (210 min.)	(Maafa et al., 2021)
g-C_3N_4/TiO_2/Ag	Methylene blue (Sunlight)	98% (40 min.)	(Ghafoor et al., 2019)
$MnWO_4$/WO_3	methyl orange (Visible light)	85% (120 min.)	(Li et al., 2018)
Graphene-TiO_2/ZnO/Bi_2O_3	methyl orange (Visible light)	99.86%(70 min.)	(Kanjwal et al., 2019)
g-C_3N_4/Ag_3PO_4/PAN	Rhodamine B (Visible light)	96% (120 min.)	(Tao et al., 2019)
$BiVO_4$	Rhodamine B (Visible light)	87.1% (180 min.)	(Liu et al., 2016)
Ce-doped β-Ga_2O_3	Methylene blue (UV light)	80% (125 min.)	(Kim, Heo, Koh, Shin, & Choi, 2021)
Co3O4/Fe_2O_3	Acridine orange (Sunlight)	97% (180 min.)	(Asif et al., 2014)
$Bi_2Fe_4O_9$	Methyl orange (Visible light)	70% (180 min.)	(Qi et al., 2013)
PAN/GO	Rhodamine 6G	65% (12 hours)	(Sharma et al., 2017)
g-C_3N_4@CdS	Methylene blue (Visible light)	98% (40 min.)	(Jiang et al., 2014)
$Co_{0.5}Mn_{0.5}Fe_2O_4$-PANI	Methyl orange (Visible light)	92% (120 min.)	(Jung et al., 2019)
WO_3/Fe(III)	Methyl orange (Visible light)	94.6% (180 min.)	(Ma et al., 2017)
$CuWO_4$	Methyl orange (Visible light)	90% (180 min.)	(Chen et al., 2019)
Zn-doped Ga_2O_3	Rhodamine B (UV light)	92% (60 min.)	(Du et al., 2021)

Electrospun Polymer Nanofibers (EPNFs) for Water Remediation

Water pollution associated with heavy metal and dye contaminated wastewater is the most serious problem that has resulted from rapid industrialization and urbanization. The release of huge amount of toxic heavy metals such as copper Cu(II), cadmium Cd(II), lead Pb(II), mercury Hg(II), chromium Cr(IV), nickel Ni(II)) and colored dyes to aquatic systems cause many problems such as human body diseases and their ability to reduce sunlight transmission (Ayoub Abdullah Alqadami, Naushad, ALOthman, Alsuhybani, & Algamdi, 2020; Alsuhybani, Alshahrani, Algamdi, Al-Kahtani, & Alqadami, 2020). In recent years, many processes were employed to eliminate heavy metals and dyes from wastewater such as chemical precipitation (J. Zhu et al., 2018), photodegradation (Ayodhya & Veerabhadram, 2018), coagulation (Harrelkas, Azizi, Yaacoubi, Benhammou, & Pons, 2009), biodegradation (Varjani, Rakholiya, Ng, You, & Teixeira, 2020), membrane separation (Gao, Sun, Zhu, & Chung, 2014), ultrasonic degradation (Rehorek, Tauber, & Gübitz, 2004), chemical oxidation (Lin & Chen, 1997), and adsorption (A.A. Alqadami, Khan, Siddiqui, & Alothman, 2018). Among them, adsorption of heavy metals and dyes is considered a preferable and successful method due to its advantages such as easy operation, low cost, and high efficiency (A.A. Alqadami, Khan, Siddiqui, Alothman, & Sumbul, 2020; M.A. Khan, Wabaidur, Siddiqui, Alqadami, & Khan, 2020; Naushad, Alqadami, & Ahamad, 2020). Recently, researchers have made great efforts in producing highly efficient and low-cost adsorbents. With the advent of nanotechnology, various nanomaterials have been used as an effective and alternative to conventional adsorbent materials. In the last two decades, scientists have paid much attention to using electrospun polymer nanofibers (EPNFs) in water treatment. These EPNFs showed valuable adsorption for different water pollutants for example heavy metal and dyes because of their unique properties as aforementioned as well as possessing adsorption sites, and high adsorption capacity (Xue, Wu, Dai, & Xia, 2019).

Heavy Metal Adsorption by EPNFs

Nanofibrous materials are excellent adsorbents for heavy metals due to many advantages such as high porosity, large specific surface area, ease to be prepared, functionalized and separated, high adsorption capacity, and fast adsorption rate (F. Zhu, Zheng, Zhang, & Dai, 2021), (Du & Zhang, 2020). The presence of some functional groups on the surface of nanofibers such as hydroxyl (OH), amino (NH_2), carboxyl (COOH), and phosphate (PO_4^{3-}) can form bonds between functional groups and heavy metal ions by electrostatic and coordination interactions, showing high adsorption capacity and removal efficiency (Chen, Huang, Liu, Meng, & Ma, 2020).

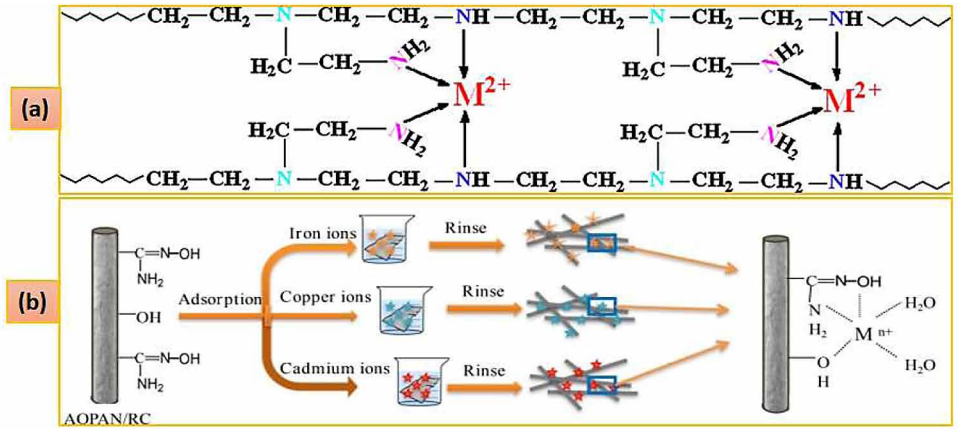
Inorganic materials and organic polymers have been electrospun into nanofibrous membranes as adsorbents for elimination of metals from aqueous solutions. Chitosan (CS) displays effective adsorption ability for heavy metals due to presence of hydroxyl and amino functional groups as coordination sites. The use of chitosan directly for water treatment is unfavorable to metal adsorption and to be reused due to weak mechanical strength and small surface area. Thus, specific surface area and adsorption efficiency of chitosan can be improved when CS is made into nanofibers. Ang *et al.* prepared Chitosan/PVA/zeolite nanofibrous composite via electrospinning method and applied it for Cr(VI), Fe(III), and Ni(II) removal. The results show that the removal efficiency was more than 99% at low concentrations with the order Cr (VI) >Fe (III) > Ni (II). These order resulting from the order of ionic radius for these heavy metal ions Cr (VI) <Fe (III) < Ni (II) (Habiba, Afifi, Salleh, & Ang, 2017). In other study a novel adsorbent based on chitosan/TiO_2 nanofibers by two methods (coating and entrapped methods) were developed. The result revealed that prepared nanofibrous adsorbent by electrospinning method was better than that of coated method due to the maximum adsorption capacities for Pb(II) and Cu(II) metal ions (Razzaz, Ghorban, Hosayni, Irani, & Aliabadi, 2016). Poly(ethyleneimine) has a high affinity for adsorption of heavy metal ions from wastewater (Bessbousse, Rhlalou, Verchère, & Lebrun, 2008). Wang *et al*. synthesized PVA doped PEI nanofibrous membranes using wet-electrospinning method. The adsorbent was applied for removal of Cu(II), Cd(II), and Pb(II) from an aqueous solution. The high adsorption capacity of PVA doped PEI nanofibers for heavy metals can be assigned to the available chelating active sites of the nanofibrous membrane (**Fig. 3a**) (Wang et al., 2011). Feng *et al.* synthesized AOPAN/RC blend nanofiber membranes by combining hydrolysis and amidoximation modification. The nanofiber membranes were used to remove Cd(II), Cu(II), and Fe(III) ions from aqueous solutions. The result revealed that adsorption of AOPAN/RC membranes was for 7.47, 1.13, and 4.26 $mmolg^{-1}$ for Fe(III), Cd(II), and Cu(II) at 25 °C, respectively. The adsorption of Fe(III), Cu(II), and Cd(II) ions on the surface of AOPAN/RC membranes occurs by coordination mechanism (**Fig. 3b**) (Feng *et al.*, 2018). Fang *et al.* prepared Polyurethane/phytic acid nanofibrous membrane by electrospinning. The PU/phytic acid nanofibrous membrane was used for Pb(II) removal. They found the capacity of Phytic acid-modified PU NMF was over 6 times more than Pure PU NFM due to the presence of Phytic acid that contains 6 phosphate groups (Fang, Liu, Wu, Tao, & Fei, 2021). Also, the thiol (-SH) group can capture heavy metal ions through chelation and improved performance of absorbents which result in an increase in adsorption capacity and removal efficiency. Thiol-functionalized cellulose nanofiber membranes were synthesized by Choi *et al*. for removal of Cu(II), Cd(II), and Pb(II) metal ions from water. The result revealed that the maximum adsorption capacities were 49.0, 45.9, and 22.0 mg/g for Cu(II), Cd(II), and Pb(II), respectively. The adsorption of Pd(II), Cu(II), and

Cd(II) ions onto TC nanofibers occurs by chemical adsorption (Choi *et al.*, 2020). Additionally, Li *et al*., produced chitosan nanofibers with an average diameter of 75 nm by electrospinning. The chitosan and chitosan nanofiber were used for the removal of Cr(VI) from water. They found that the maximum adsorption capacity was 131 mg/g, more than twice that of chitosan powders (L. Li, Li, Cao, & Yang, 2015). **Table 2** summarized important publications reporting the use of electrospun nanofiber membranes (ENMs) for the removal of heavy metals polluted water

Table 2. Electrospun nanofiber membranes (ENMs) for removal of heavy metals polluted water

Adsorbent	Metal Ion	pH	Contact Time	Adsorption Capacity (mg/g)	Best Fitted Kinetic	Best Fitted Isotherm	Ref.
Carboxylic-functional nanofibers	Pb(II)	7	120 min	143.27	Pseudo-second-order	Langmuir model	(Zhao, Ma, & Zheng, 2018)
PEI-grafted chitosan electrospun membrane	Cr(VI), Cu(II) Co(II))	2 4 6	60 min 60 min 60 min	138.96 69.27 68.31	Pseudo-second-order	Langmuir model	(D. Yang et al., 2019)
Fe_3O_4/o-MWCNTs/ PA6 hybrid nanofibrous membrane	Pb(II)	6	120 min	49.3	-	Langmuir model	(Bassyouni et al., 2019)
Chitosan grafted PPLLA/ PDA nanofibrous membrane	Cu(II)	6	60 min	270.27	Pseudo second order	Langmuir model	(Zia et al., 2021)
Electrospun PVA/PEI nanofibers	Cr(VI)	4	180 min	150	Pseudo-first and pseudo-second order	Langmuir model	(Zhang et al., 2020)
Hordein/MBA/β-CD nanofiber membrane	Cu(II)	6	12h	88.50	-	Langmuir model	(Guan et al., 2019)
Fum-F/PAN nanocomposite nanofibers	Pb(II)	6.18	68.23 min	357.14	-	Langmuir model	(Moradi et al., 2018)
ZIF-8@ZIF-8/ polyacrylonitrile nanofibers	Cr(VI)	2	90 min	39.68	Pseudo-second-order	Langmuir model	(X. Yang, Zhou, Sun, Yang, & Tang, 2020)
Amine grafted nanofibers (AGNFs)	Cu(II) Pb(II)	- -	8h 8h	166.67 94.34	-	Langmuir model	(Haider, Ali, Haider, Al-Masry, & Al-Zeghayer, 2018)
PVA/SA/PEO/HZSM5 nanofiber	Th(IV) U(VI)	5.5 5.5	240 min 240 min	274.6 144.7	Double exponential kinetic model	Langmuir model	(Talebi, Abbasizadeh, & Keshtkar, 2017)

Figure 3. Mechanistic representation of Cu(II), Cd(II), and Pb(II) adsorption on PVA doped PEI nanofibrous membranes (Wang et al., 2011) (a) Schematic representations of adsorption mechanism of Cd(II), Cu(II), and Fe(III) on electrospun AOPAN/RC blend nanofiber membrane (b) (Feng et al., 2018)



Dyes Adsorption by EPNFs

Dyeing wastewater usually results from different industries such as textile, tannery, cosmetic, food, photographs, and plastic industries (M.A. Khan *et al*., 2020; Moonis Ali Khan *et al.*, 2019). These industries depend on water for many of their processes. Organic dyes can change the properties of water, even at low concentrations. According to some studies, 700,000 tons of dyes are produced annually and 15% of dyes are discharged as waste to environment (Samsami, Mohamadi, Sarrafzadeh, Rene, & Firoozbahr, 2020), (Tkaczyk, Mitrowska, & Posyniak, 2020). The release of colored contaminant to environment causes many problems to humans and other organisms due to their toxicity such as causes cancer and disorder of liver (Altaleb *et al*., 2021). Recently, researchers have made great efforts in developing adsorbents to eliminate dyes from wastewater by using EPNFs. The adsorption efficacy of dyes onto polymeric nanofibers differs according to nature of functional groups onto their surface. Thus, presence of COOH and NH_2 groups on surface of nanofibers plays an important role in interaction between modified nanofibers and anionic/cationic dyes (Vakili *et al*., 2014). Two adsorbents PAN nanofibers and EDA-g-PAN NFs membrane were synthesized using electrospinning and chemical grafting techniques (**Fig. 4a**). These adsorbents were applied for removal of rhodamine B (RB), safranin T (ST), and methylene blue (MB). The results revealed that the adsorption capacities of PAN nanofibers and EDA-g-PAN NFs were (63.46, 41.80, and 35.523) and (65.19, 45.56, and 39.03) for RB, (ST) and MB, respectively. The high adsorption of ST,

MB, and RB onto EDA-g-PAN nanofibers is due to the presence of amino groups compared to the nitrile groups onto PAN nanofibers (Haider *et al*., 2015). Chitosan-coated polyacrylonitrile nanofibrous mat (CPNM) was synthesized by two-step. In the first step, the preparation process of polyacrylonitrile electrospinning, and the second step, chitosan-coated polyacrylonitrile nanofibrous. CPNM and PNM were applied to adsorption of acid Blue-113 dye. The results revealed that adsorption capacities were found to be 1368 and 48.6 mg/g under the same adsorption conditions at 120 h, respectively. The high adsorption capacity of CPNM compared to PNM due to the presence of chitosan on the surface of PNM nanofiber. Similarly, novel composite nanofiber (PVDF/PDA/PPy) were fabricated in three steps. In the first step, the electrospun PVDF nanofiber was coated with polydopamine. In the second step, the self-polymerization of PDA was triggered in a Tris–HCl buffer solution on the surface of PVDF/DA electrospun nanofibers. In third step, deposition of polypyrrole (PPy) particles on electrospun PVDF nanofibers (**Fig. 4b**). PVDF/PDA/PPy was used to remove the anion congo red (CR) and cation dye methylene blue (MB) from wastewater. The absorption intensity of CR and MB dyes was decreased with increasing the equilibrium time which indicated that the adsorption process of CR and MB dyes was improved with increasing the contact time (**Fig. 4c, d**). Color changes of the MB and CR dyes solution with time are given in (**Fig. 4e, f**). They found that the adsorption capacities of CR and MB were 384.6 at pH=1 and 370.4 at pH=13 mg/g, respectively. The high adsorption capacity of PVDF/PDA/PPy composite is due to the introduction of nitrogen-containing groups on the surface of PVDF/PDA/PPy and also improves their hydrophilicity (F. Ma, Zhang, Zhang, Huang, & Wang, 2018). Interestingly, Zhu *et al*. developed PDA/PEI@PVA/PEI NFMs by a combination of PVA/PEI co-electrospinning and ultrathin PDA/PEI coating. PDA/PEI@PVA/PEI NFMs were applied for removal of anionic dyes MB, MO, ponceaus (PS) & CR and cationic dyes crystal violet (CV) & MB. The result revealed that the maximum adsorption capacity for anionic dyes onto PDA/PEI@PVA/PEI NFMs was higher than cationic dyes at pH = 7 and pH = 3 with separation factor of anionic to cationic dyes was 970 due to high-density positive charges from its abundant aminoalkyl (NR_3^+) and amine (NH_3^+) on the surface of PDA/PEI@PVA/PEI NFMs which capture of anionic dyes through electrostatic attraction. Also, they found that the maximum adsorption capacity for MB and PS were 1290 and 1180 mg/g (Z. Zhu *et al*., 2017). Table 2 summarized some important publications reporting the use of ENMs for the removal of dyes.

Figure 4. Schematic representations of the preparation of EDA-g-PAN NFs membrane (a) (Haider et al., 2015), Schematic representations of the modification of the electrospun PVDF nanofibers by PPy (F. Ma et al., 2018) (b) Time-dependent UV–vis spectra of MB dye (c) and CR dye (d) Color changing of the MB (e) and CR dye ion solution (f) in the presence of PVDF/PDA/PPy composite nanofibers (F. Ma et al., 2018)

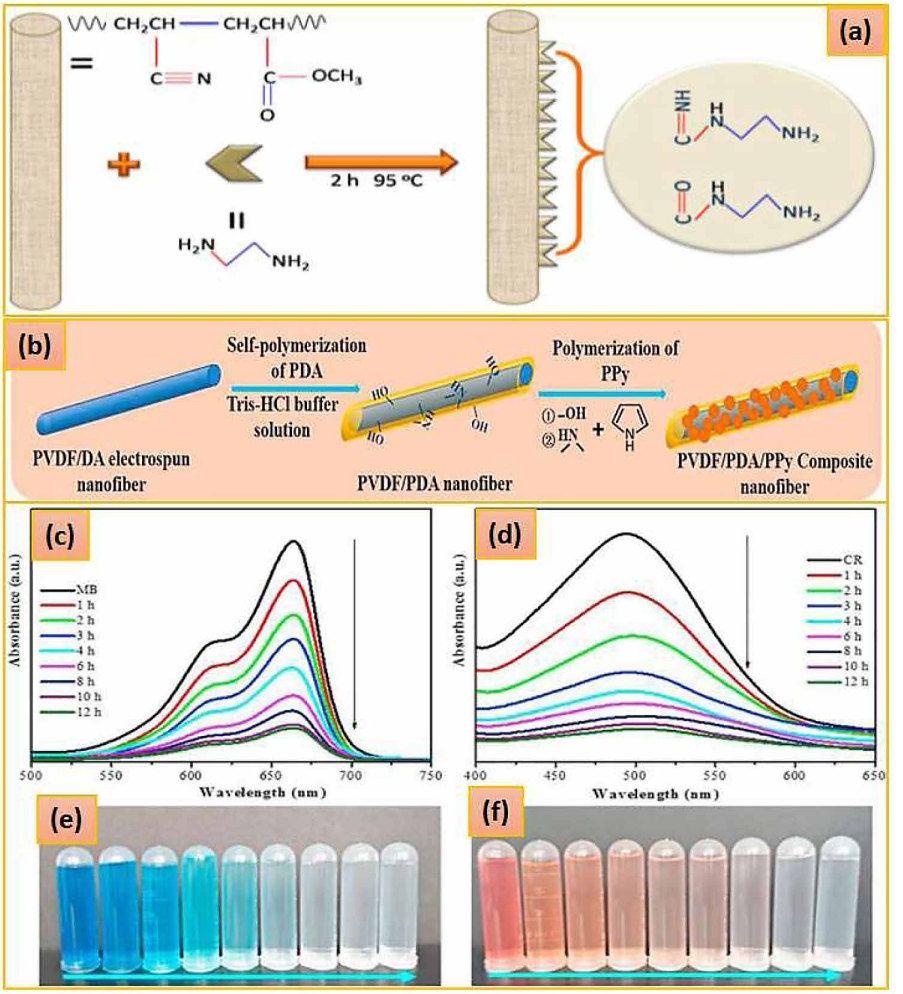


Table 3. Electrospun nanofiber (ENMs) for the removal of dyes

Adsorbent	Dye Ion	Adsorption Conditions				Adsorption Capacity (mg/g)	Typ Process	Best Fitted Isotherm	Best Fitted Isotherm	Ref.
		pH	Contact Time	Dosage (mg)	Conc. (mg/L)					
Polyacrylonitrile (PAN) nanofibers	CR	3	60 min	10	10 -70	133.34	Endothermic	PSO	Langmuir	(Patel & Hota, 2018)
Chitosan nanofibrous membrane	AB-113	ND	120 h	10	50-250	412	ND	PSO	Langmuir	(C. Li *et al.*, 2018)
Nanofiber aerogels (NFAs)	MB	11	40 min	200	200	383	Endothermic	PSO	Langmuir	(Mousavi *et al.*, 2018)
ZIF-8@chitosan/PVA nanofiber	MG	6	150 min	30	10–40	1000	ND	PSO	Langmuir	(Mahmoodi, Oveisi2020)
Polymer-bixin nanofibers	BG MB	6	80 min	ND	2.5–40	254 79	ND	PSO	Langmuir	(Domingues, Orlando, 2020)
GO modified PU nanofibers	MB RB	10 12	168 min 60 min	ND ND	10 10	77.15 109.88	Endothermic	PSO	Langmuir	(Sundaran, Reshmi, 2019)
Aminated PAN/ PVDF composite nanofibers	DR-23	2	90 min	7 – 11	20 -50	357.14	ND	PSO	Langmuir	(Mokhtari-Shourijeh, 2020)
Gelatin/calcium alginate composite nanofibers	MB	6	100 min	20	50 - 900	1937	ND	PSO	Langmuir	(Y. Ma *et al.*, 2019)
DA@PDA nanofiber membrane	MB	6.5	24 h	10	50	88.2	Endothermic	Intraparticle diffusion	Langmuir	(Cheng *et al.*, 2020)

Potential of Electrospun Nanofibers for Rejection of Pathogenic Contamination

The pollution caused by pathogenic microorganisms has been measured as momentous distress regarding water quality throughout the world. Due to exponential enlargement in population, it has been predictable that human population will get to approximately 9 billion by 2050 (Ray, Chen, Li, Nguyen, & Nguyen, 2016). Consequently, the accessibility of hygienic water resources to this huge population will create one of the most serious problems to mankind. The World Health Organization has already addressed that safe drinking water ease of access is worry of approximately 785 million natives and ~2 million people utilize contaminated water for consumption (Bain, Johnston, & Slaymaker, 2020). This polluted water is considered to be accountable for serious types of waterborne illness as well as responsible for ~502,000 deaths worldwide annually (Silva & Scalize, 2020). The presence of bacterial pathogens in drinking water stores is responsible for major intimidation to public health which result outbreak of sicknesses such as gastroenteritis, cholera, giardiasis, cryptosporidiosis, etc. *Shigella dysenteriae, Vibrio cholera*, bacteria from genus Legionella, *Escherichia coli O157:H7* and *Campylobacter jejuni* are major bacteria mixed up with these outbreaks (Fahimirad, Fahimirad, & Sillanpää, 2020).

Additionally, the pathogens such as *Cryptosporidium parvum* and *Giardia lamblia* are very dangerous as their presence in water result grave sicknesses. Consequently, in a lot of nation states, their elimination from water is obligatory. Interestingly, one of the latest model techniques to create nanofiber based membranes with modifiable pore size and allotment of pore is electrospinning method. The outstanding potential of electrospun nanofiber in function, such as uniform fiber morphology with controllable pore size and membrane width, makes them a better alternate to substitute the conservative membranes. Furthermore; interesting uses of electrospun nanofiber in water decontamination and bacterial refutation is thin-film nanocomposite membrane(Fahimirad et al., 2020). Moreover, the functionalized nanofibrous membranes can also be very advantageous in purification of water. Therefore, introduction of materials for instance elemental silver and silver salts, silver-TiO_2 systems as well as ammonium salt-having cationic polymers be able to provoke excellent antimicrobial features to the existing membranes. Admittedly; having high aspect ratio, antimicrobial agents incorporated ENMs can present exceptionally efficient competence in elimination of these contaminants (Homaeigohar & Elbahri, 2014). Unquestionably, the electrospun nano-membranes encompass the prospective ability to efficiently eradicate protozoa also. Similarly, nanofiltration is competent to remove bacteria proficiently. In addition, it is competent to abolish viruses, such as, rotavirus, norovirus, enteric virus and hepatitis A (Tlili & Alkanhal, 2019). Nevertheless; electrospun nanofibers integrated with antimicrobial components have

been produced with excellent antimicrobial properties against diverse microbes. These nanofibers demonstrate novel applications in other processes such as filtration, wound-dressing materials, protective textiles, tissue scaffolds, and biomedical devices (Song, Wu, Qi, & Kärki, 2017) in addition to water decontamination. In a study the silk nanofibers (SNFs) and hydroxyapatite (HAP) materials are used to prepare membranes. These SNF/HAP membranes demonstrated efficient high water flux in comparison with membranes of similar size and thickness. Conclusively, in comparison with conventional water purification systems, the membrane separation process has many features due to simple technology, high-quality water sanitization, low energy utilization, as well as no secondary pollution. Filtration schemes in bionic system possess multi-layer nanoporous membrane made up of biomaterials, which is appropriate for extensive production of water purification membranes with economic cost.

Role of Electrospun Nanofibers in Antifouling

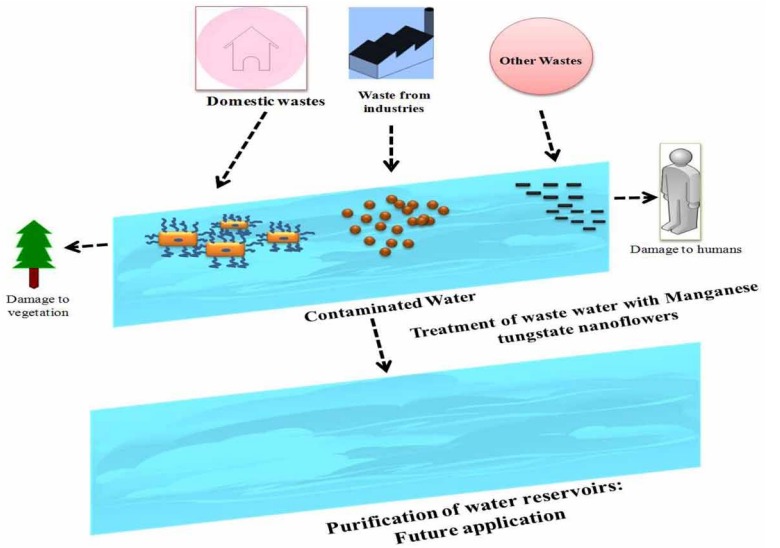
Generally speaking; membrane fouling address to adsorption or deposition of particulate /or colloidal material or solute molecules in treated material as a result of physico-chemical communication or mechanical interaction with crust, ensuing blockage or lessen of pore size. Membrane fouling significantly decreases the life of membrane as well as raise price, in turn seriously influence practical utilization (Hu, Zhang, Zhang, & Yang, 2019). Noteworthy consideration has been accredited to electrospun polymer nanofibrous membrane in wastewater management owing to their inherent benefits as aforementioned (Wan et al., 2014). The integration of efficient moieties for instance inorganic nanoparticles and macromolecular organic compounds may enhance the features of nanofiberous films for water decontamination. Antifouling ability of membrane is regarded as an important feature required for wastewater management. Special strategies for example combination with hydrophilic well-designed nanomaterials, plane grafting, and hydrophilic monomers coating the exterior of membrane have been customized to reduce fouling of membrane (Kiani, Mousavi, Shahtahmassebi, & Saljoughi, 2015). In a very recent study PU/rGO–TiO_2 nanofiber has been reported as efficient resolution to the efficient cleansing of wastewater polluted with MB dye (Sundaran, Reshmi, Sagitha, & Sujith, 2020).

Moreover, membrane fouling also refers inorganic fouling/scaling, organic fouling, particulate/colloidal fouling and biofouling (such as occurrence of microorganisms or biological fouling). It has been observed that fouling as a result of organic; inorganic components as well as microbes may take place concurrently, and these mechanisms may interrelate (Amjad, Zibrida, & Zuhl, 1997). In case of membrane biofouling, the microorganisms first adhere to membrane facade, resulting in the development of biofilm stratum. This biofilm may possibly include diverse category

of microbes (e.g., bacteria, algae, protozoa as well as fungi etc.). Preliminary microbial adhesion is intervened by electrokinetic and hydrophobic communications (Bendinger, Rijnaarts, Altendorf, & Zehnder, 1993), and is commonly preceded by cell duplication and expansion at expenditure of dissolved nutrients in supply water or adsorbed organics on exterior membrane (Costerton et al., 1994). Therefore, biofouling is a grave problem in membrane water and wastewater management process significantly gets affected. Correspondingly, it is complicated to manage as well as considerable financial capital is being devoted to progress of effectual biofouling screening and management. In this direction the electrospun nanofibrous membranes (ENMs) are innovative membrane tools that put forward considerable high flux and prominent refusal rate as compared to conservative membrane systems. As mentioned above, electrospinning engineers nanofibrous membranes with controllable pore size (micro/or nano range), which possibly will be replacement for conventional membrane. Interestingly, these ENMs represent modernism in water and wastewater decontamination by virtue of insubstantial mass, low price, as well as low energy utilization than classical membranes. As described earlier the ENMs own lofty porosity and elevated surface ratio. Their porosity is in general ~ 80%, while conservative membranes possess ~5–35%. The interconnecting organization and utmost permeability of ENMs authorize excellent permeability as compared to their conventional counterparts. In a study the hydrophilicity of composite nanofibrous membranes improved with nanocellulose confirmed by water contact angle size, therefore enhanced anti-fouling characteristics of membranes. On the contrary, occurrence of organic material and traces of its amassing in wastewater pretense chief crisis and current methods for instance coagulation/flocculation and chlorine technology are not capable to give in pleasing outcome. Moreover, these technologies produce additional volumes of sludge, which require additional handling and clearance. Consequently, it has been given to understand that the nanotechnology possesses immense prospective in filtration applications owing to its potential to generate specific structurally controlled materials for such necessities. The significant features of ENMs, are pore size, porosity, and fiber diameter control flux, removal rate, and efficiency of ENMs which can be generated in the fabricated electrospun nanofibers using electrospinning technique.

Conclusively, this chapter briefly highlights fundamental reasons of membrane biofouling as well as makes available an assessment report on current developments of prospective monitoring and organizes techniques for wastewater treatment (**Fig. 5**) regarding identify the enduring concerns and challenges in this field.

Figure 5. Schematic diagram illustrating the use of as-synthesized $MnWO_4$ nanofibers as an example for cleaning of wastewater reservoirs
(Adapted from Musarat Amina Korean J. Chem. Eng. Vol. 33, No. 11)



FUTURE RESEARCH DIRECTIONS

With swift growth of nanoscience, growing consideration has been remunerated to fabrication of electrospun nanofibers. Electrospun nanofibers display significant part in numerous research areas owing to their elevated specific surface area, excellent porosity as well as fine practical capabilities. Therefore, these nanofibers are and will be used in solving various global problems particularly in area of wastewater handling and purification. These electrospun fibers have resolved shortcomings such as lofty energy utilization, poor efficacy, and complicated reuse of conventional process. Conclusively, these electrospun nanomembranes can speedily and sensitively eradicate different pollutants viz, pathogens, monovalent and multivalent anions and cations, salts, minerals as well as surplus suspended materials from wastewater.

CONCLUSION

In conclusion, quick global industrialization and population explosion has resulted in environmental pollution. Consequently, in current times various nations are facing misery owing to water scarcity stimulated by respective pollution, and large amount of money gets exhausted annually owed to pollution troubles in the world.

On one hand the wastewaters contaminated with heavy metals, organic dyes, oils, and other contaminants have a dangerous consequence on individual fitness as well as atmosphere. On the other hand, biofouling symbolize a composite system where quality of feed water, physico-chemical characteristics of nanofibrous membrane as well as working parameters each one plays a function. Biofouling starts with addition of microorganisms to membrane plane resulting in development of a biofilm coating. This chapter underscored some key features. Firstly herein, we introduced important aspects of electrospinning equipment, method as well as research development in fabrication of different types of nanofibers possessing diverse morphology. Mechanism of electrospun nanofiber adsorption and filtration of industrial wastewater has been portrayed. Additionally, current research developments of electrospun nanofiber for wastewater management have been detailed. Lastly, the challenges and probable implications are conversed.

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Chapter 12
Nanomaterials and Pollution Control

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ABSTRACT

With nanoscience, new environmental benefits have emerged to aid pollution control. Nanotechnology is becoming beneficial for air and water pollution control and eradication in the future. Air pollution can be controlled with nano-adsorptive materials, nanocatalysis, and nano filters. For water pollution, nanofiltration and nano sorbents techniques are used. Nanotechnology establishes a framework to manipulate the molecular structure of objects depending on the characteristic to generate new materials. Environmental pollution is being controlled more efficiently and strategically through the application of nanotechnology. The technology deals with numerous contaminants like nitrogen oxides, volatile organic compounds, carbon dioxide, among other harmful gases. The research narrows down to the argument that nanotechnology has a positive impact on environmental protection and provides an effective way to eliminate pollution by developing reliable treatment plans. In this chapter, the authors have briefly discussed the different nontechniques applied to control the pollution.

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INTRODUCTION

The topic of nanomaterials is becoming extremely popular due to the diversification of its usage in numerous areas of science and engineering. With that, the production of nanomaterials is significantly increasing in an enormous scope of utilizations (Varghese et al., 2019). Some of the industries that integrate materials made from nanomaterials into their practice settings include the healthcare industry, electronics, information technology, textile industry, and environmental conservation (Peng et al., 2020). Significantly, nanomaterials and nanotechnology offer a huge benefit through contaminants trace and handling to narrow environmental pollutions (Zhang & Fang, 2010).

WHAT ARE NANOMATERIALS?

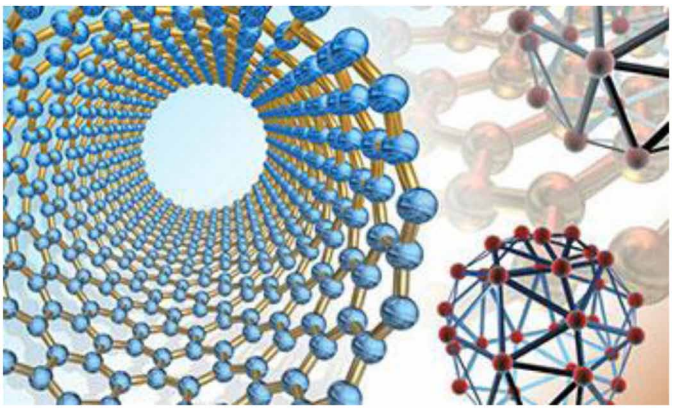
Scientists have not comprehensively established the definition of nanomaterials. However, most scholars define nanomaterials based on their size measured in nanometers (one-millionth of a millimeter) (Yang et al., 2019). Nanomaterials are materials with at least one external dimension and internal structure measuring between one and 100 nanometers (Yang et al., 2019). According to the European Commission, nanomaterials should be named based on the principle that the particle sizer of at least half of the particles in the distribution of number size should measure 100 nanometers or below. "Engineered nanometers" ("ENMs") are materials designed on a small scale to take on exclusive optical, electrical, and magnetic properties. Engineered nanomaterials have both significant and adverse impacts on the health of individuals as well as the environment (Luo & Deng, 2018).

Nanometers occur in different forms, including particles, fibers, and rods (Luo & Deng, 2018). The occurrence of nanometers can be natural or manmade as by-products of reactions involving combustion and engineering procedures to conduct a specific function. The natural occurrence of nanomaterials includes blood-borne proteins required for life and lipids in the blood and body fat, viruses, and spider-, mite silk. Nanomaterials can be created from products including carbon and minerals such as silver (Lin et al., 2018). The physical and chemical characteristics of nanomaterials can vary significantly from their bulk-form counterparts. Hence, nanomaterials that have a similar composition as their bulk counterparts may portray varying physical and chemical characteristics. On the contrary, nanomaterials that have a similar composition as the same bulk materials may have similar physical and chemical properties (Lin et al., 2018). As a result, these materials portray different behaviors

when they are introduced to the human body through skin contact, ingestion, and inhalation to pose varying potential risks. Aggregated nanomaterials may also portray similar properties with single nanoparticles, especially in circumstances when the single nanoparticles have remarkably large surface areas for a specified amount of material. Therefore, nanomaterials have numerous advantages over bulky material forms because of their size and versatility that makes it easy to tailor them for specific purposes (Lin et al., 2018).

In the contemporary market industry, nanomaterials containing products are very popular in different industries for their individual purposes. In the cosmetic industry, for instance, mineral nanoparticles, including titanium oxide that have poor stability offered by conventional chemical ultraviolet protection, are used in sunscreen. In the healthcare industry, equipment made from nanomaterials is mainly used for the targeted delivery of drugs, regenerative medicine, and diagnostic services. On the other hand, the sports industry makes use of nanomaterials such as carbon nanotubes to produce and manufacture baseball bats. Consequently, the bats are made lighter for enhanced performance (Peng et al., 2020). Antimicrobial nanotechnology also utilizes nanotechnology to make towels and mats used by individuals in the sports industry to prevent diseases caused by bacteria. Lastly, nanomaterials are used in the military to manufacture excellent forms of camouflage through their insertion into the soldiers' attires. Titanium dioxide made from nanotechnology is also used to develop sensor systems for purposes of detecting biological agents (Peng et al., 2020).

Figure 1. Titanium dioxide.
Source: (Peng et al., 2020)



PROPERTIES OF NANOMATERIALS

Nanomaterials have exceptional physical and chemical characteristics because of their size and surface area (Corsi et al., 2018). It is essential to understand the physical and chemical properties of nanomaterials to evaluate their associated toxicological and ecological risks. This section discusses the different chemical, physical and optical properties of nanomaterials.

Physical Properties of Nanomaterials

Nanomaterials are made up of three layers, including the surface layer, the shell layer, and the core (Gubicza, 2017). While some nanomaterials consist of single materials, others contain a combination of many materials. The surface layer of nanomaterials is made up of different molecules such as metal ions, surfactants, and polymers. Based on the layers and materials found in nanoparticles, nanoparticles exist in different forms, including suspensions, dispersed aerosols, and colloids (Gubicza, 2017).

Nanomaterials are also characterized based on their size. Most nanomaterials have at least one external dimension measuring less than 100 nanometers (Patil & Burungale, 2020). The size of nanomaterials determines the different properties exhibited by them. For example, copper nanomaterials that measure less than 50 nanometers are hard, non-malleable, and non-ductile compared to bulk copper. At the same time, size determines the super Paramagnetism of magnetic objects, quantum confinement portrayed by semiconductor Q materials, and surface plasm on the resonance of metallic objects. Similarly, the radiation of solar energy in photovoltaic nanomaterials is high compared to solar radiation in thin films of continuous sheets of counterpart bulk cells. This characteristic is attributed to the small size of nanomaterials that increase their capability of absorbing solar radiation (Patil & Burngale, 2020). With an increase in temperature, nanomaterials portray enhanced diffusion. Nanomaterials exhibit this characteristic because of their high surface area to volume ratio. Hence, the process of sintering can easily take place in nanomaterials even at low temperatures compared to large particles. The diffusion characteristic in nanomaterials can cause agglomeration despite its little to no impact on the density of the object (Patil & Burungale, 2020).

Chemical Properties of Nanomaterials

Nanomaterials are characterized based on chemical properties such as structure, composition, the weight of molecules, boiling and melting points, pressure of vapor,

the partition coefficient of octanol-water, reactivity, nature of stability, and solubility in water (Chen et al., 2018).

The major determiners of the size and structure of nanomaterials include the salt and surfactant additives, the concentration of the reactant, temperatures under which the reaction takes place and solvent conditions integrated during the synthesis process.

Nanomaterials take the form of different shapes. These shapes play a significant role in determining cellular uptake, biocompatibility, and retention in body organs and tissues. Nanomaterials also have different shapes, sizes, and agglomeration states that influence their disposition and translocation in an organism (Chen et al., 2018).

The size of nanomaterials plays an important role in determining their rates of circulation and movement in the bloodstream. Size also determines the penetration of nanomaterials across the physiological drug barriers, localizations that are specific to a given cell, and the induction of cellular responses (Chen et al., 2018).

Optical Properties of Nanomaterials

The optical characteristics of nanomaterials are discussed based on the existence of surface plasmon resonance and the nanoscale dimension of nanomaterials (Manera et al., 2018). The optical properties of nanomaterials based on their size occurs due to alterations in the band gap of optical energy. A decrease in particle size of nanomaterials leads to an increase in the optical band gap for semiconductor nanomaterials (Manera et al., 2018). Consequently, nanomaterials interact with electromagnetic radiation based on particle dimensions. This aspect, in turn, provides an opportunity for engineers and technological scholars to develop tailor-made materials for novel optical components (Wood, 2018).

Different mechanisms also influence the optical properties of nanomaterials. For instance, scattering and absorption occur due to incident light on a nanomaterial. Similarly, quantum dots are used to refer to nanomaterials with semiconductor materials. These types of nanomaterials tend to absorb and emit light at different wavelengths based on particle size and shape (Wood, 2018).

NANOTECHNOLOGIES

Nanotechnology is a branch of technology that focuses on manipulating the molecular structure of objects to alter their inherent characteristics to generate new materials with revolutionary operations (Duhan et al., 2017). Richard Feynman first mentioned the application of nanotechnology in 1959 at the California Institute of Technology. In 1974, Norio Taniguichi from Tokyo Science University invented the term to define the processes of semiconductors, including the deposition of

thin films to regulate nanometer orders (Duhan et al., 2017). Norio Taniguichi initially defined nanotechnology as a process that mainly incorporates separation processing, consolidation, and material deformation through the use of one atom or molecule. Since the invention of the term, several technological organizations have come up to describe their understanding of nanotechnology. For instance, National Nanotechnology Initiative in the United States defines nanotechnology as "…the understanding and control of matter at dimensions between approximately 1 and 100 nanometers, where unique phenomena enable novel nanotechnology applications" (Raman Martin, 2017). According to NNI also, nanotechnology utilizes the science of nanoscale, engineering, and technology to incorporate imaging approaches, measure, model, and manipulate matter on a scale. Between the years 2001 and 2013, the NNI program in the US led to the investment of up to $18 billion to present nanotechnology as a key force of competitiveness and economic growth (Raman Martin, 2017). At the same time, Wang et al. (2019) defined nanotechnology based on no size limitations as "the design, characterization, production, and application of structures, equipment, and systems by controlled manipulation of size and shape at the nanometer scale that produces structures, devices, and systems with at least one novel/superior characteristic or property."

There are different types of nanotechnology whose classifications are based on the manner of the procession (from top to down or bottom to up) and their medium of operation. Hence, nanotechnology can be descending (top-down), ascending (bottom-up), dry and wet nanotechnology (Raman Martin, 2017). Dry nanotechnology is utilized in the manufacture of coal, silicon, metal, and semiconductor structures that do not operate effectively under humid conditions. On the other hand, the basis of wet nanotechnology is on existing biological structures in aqueous ecology, including different components of the cell such as membranes and enzymes. In ascending nanotechnology, evaluation is initiated from a nanometric structure through a self-assembly procedure to develop a larger mechanism compared to the initiating mechanism. Lastly, descending nanotechnology involves miniaturizing techniques and structures at the nanometer scale and is the most common approach integrated into the electronics industry. The use of nanotechnology in the environment involves the purification of air with ions and the purification of wastewater using nanobubbles and nanofiltration techniques for heavy metals. Hence, it can be speculated that nanotechnology plays a significant role in developing applications that are environmentally friendly. Nanotechnology also yields optimal outcomes after its implementation in industries such as electronics, energy, biomedicine, food, and textile industry (Raman Martin, 2017).

Nanotechnology is perceived as a significant discipline that fosters the implementation of techniques to enhance the industrial revolution. Its practical application ranges from the development of invisible cancer cell fighting particles,

microprocessors that work at low power-consumption levels, solar panels that produce double energy, and the manufacture of long-lasting batteries. According to Contreras et al. (2017), the application of nanotechnology together with its microscopic universe in the contemporary world plays a significant role in boosting science and operating industries. Since its commencement, the nanotechnology industry has significantly flourished over the past few decades. A report by the Research and Markets on the Global Nanotechnology Market indicates that the industry is expected to increase its value by $125,000 million in the next five years (Contreras et al., 2017).

NANOTECHNOLOGY FUTURE OF ENVIRONMENTAL POLLUTION CONTROL

More efforts in the contemporary world are focused on fighting environmental pollution. The air across the world contains numerous contaminants, including carbon dioxide, chlorofluorocarbons, hydrocarbons, volatile organic compounds, and nitrogen oxides (Chirag, 2015). Water and soil pollution today is also significantly contributed to by organic and inorganic compounds found in sewage water, fertilizers, oil spills, and pesticides. When ingested, inhaled, or comes into contact with the human skin, these pollutants pose adverse impacts to human health. Consequently, scientists and engineers should put more focus on developing more efficient technologies to detect and effectively manage toxic contaminants in the environment. Scientists also argue that nanotechnology may be the new solution for environmental cleaning and enhancing the performance of traditional technologies (Chirag, 2015). The innovation is also considered an effective approach to control environmental pollution by minimizing the release of pollutants into the atmosphere or preventing their formation.

Over the past years, nanotechnology has integrated knowledge from a wide range of fields, including informatics, physics, medicine, and biology, contributing to contemporary science and technology (Chirag, 2015). Hence, scientists began to incorporate nanomaterials in improved systems to facilitate the monitoring and clean up of the environment. Nanomaterials can be used to develop environmental conservation equipment to sense and detect pollutants and advance novel remediation technologies. Nanomaterials have physical and chemical properties such as large surface area, and high reactivates that improve their adsorbent properties of catalysts and sensors. Today, nanotechnology is perceived as an emerging technology because of its capability to facilitate the advancement of well-established equipment with new characteristics and functions in different fields (Umar et al., 2019).

Nanotechnology is anticipated to play a significant role in controlling environmental pollution in the future. Nanotechnologies have the potential to produce innovative equipment with exclusive properties that can be implemented in different fields of environmental protection. The small size and high surface area of nanomaterials can facilitate the production of materials with significant monitoring properties (Umar et al., 2019). As a result, the Physico-chemical properties provide an opportunity of improving highly accurate and highly sensitive nano-sensors equipment. At the same time, the production of equipment from nanomaterials can be specifically designed to facilitate effective reactions with pollutants and degrade them into non-toxic materials. In the future conservation of environmental contamination, nanotechnologies have the ability to replace toxic products utilized with other safety devices. Nanotechnology can also be used in the development of non-structured coating technologies that develop resistance to contaminants and possess self-cleaning properties (Umar et al., 2019).

NANOTECHNOLOGIES IN AIR POLLUTION TREATMENT

Nanotechnology is perceived to demonstrate effectiveness in the treatment and reduction of a wide variety of air pollutants. Nanotechnologies can be used to treat and remedy air pollution through strategies such as the use of nano-adsorptive materials for adsorption, degradation by nanocatalysis, and the use of nano filters to filter and separate air pollutants (Umar et al., 2019).

Use of Nano-Adsorptive Materials to Adsorb Air Pollutants

According to scientists and researchers, nanoscience and nanotechnology are considered effective approaches to solve air pollution problems by improving air quality. The perception holds that nanotechnology can solve current air pollution problems by utilizing nanoscale adsorbents, also known as nano adsorbents (Yunus et al., 2012). For instance, carbon nanostructures are applied in industries as nano-adsorbents that have high selectivity, capacity, and affinity. This is because of the physical characteristics of carbon nanostructures, including average pre diameter, the volume of the pores, and high surface area. Structural bonds in nanomaterials also play a significant role in adsorption properties (Yunus et al., 2012).

Nano-adsorbents have unique properties that enable effective interactions with organic compounds through non-covalent bonds, including hydrogen bonding, electrostatic forces, hydrophobic interactions, and van der Waal forces (Yunus et al., 2012). Carbon nanotubes have been used as adsorbent materials in environmental protection because of their characteristics, including high electrical and thermal

conductivity, high strength, the unique potential for adsorption, and high hardness. Table 1 illustrates different nanostructures and how they are used to treat greenhouse gases through nano-adsorption.

Table 1.

Nanoadsorptive materials	Types of nanoparticles	Target pollutant gases	Removal mechanism
Carbon nanotubes (CNTs)	(SWNTs and MWNTs)	NOx (mixture of NO and NO_2)	NO and O_2 pass through CNTs and NO is oxidized to NO_2 and then adsorbed on the surface of nitrate species.
	(CNTs-APTS), Modified CNTs using 3aminopropyltrietho xysilane (APTS).	CO_2	Surface of CNTs with abundant amine groups that provide numerous chemical sites for CO_2 adsorption which makes CNTs adsorb more CO_2 gases at low temperature range (20-100 °C).
	SWNTs/NaClO	Isopropyl vapor	Physical adsorption by van derWaals forces and chemical adsorption onto adsorbent surface functional groups.
	CNTs deposited on quartz filters	VOCs	It carried out by π- π interactions.
	Si-doped and Boron-doped SWCNTs	CO and CH_3OH gases	Physisorption or chemisorption, the electronic properties of SWCNT improves significantly the gas adsorption.
Fullerene	fullerene B_{40}	CO_2	high adsorption capacity for CO_2 by strong chemisorptions.
	fullerene-like boron nitride nanocage	N_2O	Adsorption and decomposition of N_2O.

Reprinted by permission from Materials Today: Proceedings: (Panahi et al., 2018)

Degradation by Nanocatalysis

Since the early 1900s, indoor pollution has been a topic of significant concern. This is because of the perception that most people spend their time indoors, which predisposes them to the risk of inhaling pollutants compared to when they are outside. Indoor contaminants include the harmful gas VOC, which poses health hazards to human beings (Panahi et al., 2018). Nanotechnology can be used to prevent air pollution in indoor environments in a variety of ways. Semiconducting materials photocatalytic remediation is one effective strategy used to manage indoor pollution through nanotechnology (Panahi et al., 2018). These materials are exposed to light with equal energy as that of the bandgap to result in the electron-hole pair formation. Reaction mainly occurs on the active surface, which is the significant catalyst structure. A decrease in the size of the catalyst leads to an increase in the surface area to increase the efficiency of the reaction. The size of the nanoparticle and the structure of the molecule can be improved by nanotechnology to develop new nano-catalysts that have a higher surface area. Nano-catalysts are considered appropriate materials in improving air quality and reducing pollutants in the air. This is because nano-catalysts permit the rapid and selective transformation of chemicals with optimal product outcomes than conventional catalysts (Panahi et al., 2018). For instance, titanium dioxide nanoparticles have photocatalytic properties to produce self-cleaning coatings used to decontaminate environmental pollutants, including nitrogen oxides and VOCs, into materials that have low toxicity levels/. Carbon nanostructures, including CNTs and graphene nanosheets, have been utilized over the past years to increase titanium dioxide's photocatalytic effectiveness by facilitating the easy movement of electrons.

Use of Nano Filters for Separation and Filtration Purposes

Nano filters are structured membranes with small pores to separate several contaminants from the exhaust. In the contemporary era, scholars focus on improving and optimizing nanostructured membranes used to control air pollution by capturing gas pollutants. Filter media coated with nanofiber is mainly used in industrial plants to remove dust and filter the inlet air for gas turbines. According to Kaur et al. (2017), nanostructured membranes are mainly designed to filter gas pollutants, including VOC vapors. For instance, electrospun polyacrylonitrile (PAN)-based carbon nanofiber membrane that contains properties such as increased microporosity. Numerous nitrogen-containing functional categories have been used as an effective filtration approach to adsorb formaldehyde (Kaur et al., 2017). Silver and copper nanoparticles filters are also extensively used in air filtration technology as antimicrobial agents

for the removal of biological aerosols such as viruses, bacteria, and fungi that predispose individuals to infections.

NANOTECHNOLOGY IN WATER POLLUTION TREATMENT

Over the past years, scientists have focused on considering nanotechnology as a potent approach for water treatment rather than other expensive and time-consuming conventional technologies (Yunus et al., 2012). Hence, the low cost of nanotechnology in water treatment would significantly benefit developing countries like India and Bangladesh, where success is measured through the implementation of new removal techniques. Nanoparticles are effective sorbents because of their large surface area and their ability to be enhanced with different reactor groups to enhance their chemical affinity towards specific compounds. The technology of nanofiltration has gained popularity in contemporary operations to eliminate cations, natural organic materials, organic contaminants, biological pollutants, and nitrates from surface and groundwater. At the same time, nano-sorbents can be used as separation techniques in the process of water purification to eradicate inorganic and organic matter from contaminated matter. Hence, it can be concluded that the major mechanisms used to remove contaminants from contaminated water through nanotechnology include nano-sorbents and nanofiltration (Yunus et al., 2012).

Nanofiltration

Nanofiltration is a membrane process used in water pollution treatment for drinking water and wastewater (Kamali et al., 2019). Nanofiltration is a low-pressure membrane technique used to separate substances measuring 0.001-0.1 micrometer. Nanofiltration is perceived as an effective method used to remove biological pollutants, turbidity, and inorganic compounds. At the same time, nano filters are used to soften hard water, remove dissolved organic materials, and trace contaminants from surface water, treatment of wastewater, and pre-treatment during the desalination of seawater. Nanofiltration can also be combined with reverse osmosis to increase the portability of brackish water (Kamali et al., 2019). Technology advances have led to the development of carbon nanotubes filters to remove pollutants from water through bacteria removal in contaminated water. After use, immediate cleansing of carbon nanotube filters occurs through autoclaving and ultrasonication. In another technology, nanoceramic filters, a combination of nano alumina fiber and micro-glass, are used to remove bioaerosols, including bacteria and viruses, from contaminated water. Nanoceramic fitters remove contaminants from water by retaining negatively charged particles. Their major advantage is they possess an increased ability for

particulates, less clogging, and they can adsorb heavy metals through their chemical properties (Kamali et al., 2019).

Nano Sorbents

Nanoparticles have a large surface area and can be enhanced with different reactor compounds to improve their affinity towards specific compounds (Panahi et al., 2018). These characteristics render nanoparticles as effective sorbents. Hence, research focuses on these properties to develop more efficient sorbents to eliminate organic and inorganic materials from polluted water. Since the evolution of nanotechnology, scientists have developed different nano-agglomerates of mixed oxides, including iron-cerium, iron-manganese, and iron titanium, among others, to remove pollutants in water. Carbon is also considered a versatile adsorbent extensively utilized to remove a wide variety of pollutants such as heavy metals from contaminated water (Panahi et al., 2018). For instance, graphene, a carbon nano sorbent, is a recently researched nanoparticle used in water treatment. However, reduced graphene oxide has antibacterial characteristics that may be used to prevent the formation of biofilm on the surface of filters because of bacterial growth. The growth of bacteria on filter surfaces may result in unwanted odor and taste in water and premature clogging of filters (Pathakoti et al., 2018).

FUTURE RESEARCH DIRECTIONS

The future research direction is to identify the side effects of nanotechnology, especially when it comes to health. Nanotechnology may contribute to health complications that might be detrimental and affect human existence. For example, the inhaled nanoparticles may result in lung inflammation and heart problems which can affect human health. Lung damage can be a complex health complication that might affect health. Nemmar et al. (2017) acknowledged that nanoparticles in diesel fuel additives could emit exhaust which might cause health concerns. As a result, it is important to carry out future research about the negative effects associated with nanotechnology. Similarly, it is important to carry out research in relation to the standardization and legislation of the use of nanomaterials. The scientific research and international levels should focus on standardized research mechanisms related to nanotechnological material. Scientific research should also identify the risks associated with nanotechnology materials.

CONCLUSION

To sum up, the application of nanomaterials and nanotechnology is contributing massively to the acts of pollution control and environmental protection. The popularity of nanoscience in the scientific field sheds light on a very promising future for environmental healing. Finally, nanomaterials offer many possibilities to meet future demands not only in the environmental sector but in other industrial regions as well. Therefore, the investment in nanotechnologies and their research is very efficient and valuable.

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