Phytoconstituent-Based Nanocomplexes for Novel Drug Delivery: Nanoformulation Strategies, Therapeutic Applications, Challenges, And Future Perspectives

Janhavi Ingle[1], Pranjali Wasade[2], Mr. Shubham Kamble[3], Dr. Jagdish Baheti[4]
[1,2] Kamla Nehru college of Pharmacy, Butibori
[3] Assistant Professor Department of Pharmaceutics Institute address: Kamla Nehru college of Pharmacy, Butibori
[4]Principal, Department of Pharmacognosy Institute address: Kamla Nehru college of Pharmacy, Butibori

***Abstract*—In recent years, phytoconstituents have drawn considerable attention due to their antioxidant, anti-inflammatory, antimicrobial, anticancer, antidiabetic, cardioprotective, and neuroprotective activities. The low aqueous solubility, bioavailability, and target site-specific delivery of phytoconstituents limit their physiotherapeutic applications. Nanotechnology has offered an innovative approach to the enhanced stabilization, increased bioavailability, targeted release, and improved targeting of bioactives. This review reports an in-depth understanding of phytoconstituent-based nanocomplexes. It further discusses the therapeutic potential of phytoconstituent-loaded nanocomplexes in the treatment and management of various diseases, including cancer, diabetes, cardiovascular diseases, neurodegenerative disorders, inflammation, and antimicrobial infections. Moreover, the present review highlights recent advances, challenges, and prospects of phytoconstituent-based nanoformulations. Phytoconstituent-based nanocomplexes offer a new horizon in the field of pharmaceutical nanotechnology for the safe, effective, and targeted drug delivery of various phytoconstituents.**
.

***Index Terms*—Phytoconstituents; Nanocomplexes; Nanoformulations; Targeted drug delivery; Bioavailability enhancement; Nanocarriers**

I. INTRODUCTION

Medicinal plants have been the integral part of health care for centuries and even today, they remain one of the most important sources for drug discovery. Many of the medicines that are currently in use were directly isolated from plants or designed based on the lead compounds obtained from plants. The therapeutic activity of medicinal plants is due to their phytoconstituents, such as alkaloids, flavonoids, polyphenols, terpenoids, glycosides, tannins, saponins, and other secondary metabolites, which demonstrate various biological activities, such as antioxidant, anti-inflammatory, antimicrobial, anticancer, antidiabetic, cardioprotective, and neuroprotective properties. The use of phytoconstituents as therapeutic agents is associated with their multitarget mechanism of action and good safety profile. However, despite these benefits, phytoconstituents are used in medicine exhibit poor therapeutic application since these bioactive compounds often possess poor aqueous solubility, low membrane permeability, chemical instability, rapid metabolism, and significant first-pass effect, which reduces their systemic bioavailability and pharmacological activity. (1,2)

The recent developments in nanotechnology have led to novel approaches to overcome these obstacles through nanoscale drug delivery systems. The incorporation of phytoconstituents into nanocarriers increases their solubility, prevents their breakdown due to chemicals or enzymes, facilitates the process of their gastrointestinal absorption, extending systemic circulation, and provides targeted as well as controlled release of drugs. Different types of nanocarriers, such as liposomes, phytosomes, polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, dendrimers, nanoemulsions, and polymeric micelles have shown considerable effectiveness in modifying the pharmacokinetics and pharmacodynamics of biologically active phytoconstituents. Moreover, the developments in surface functionalization have enabled the targeting of diseased sites without any toxicity and increasing therapeutic efficiency. Therefore, nanoformulations containing phytoconstituents have proved effective as therapeutic agents in the treatment of cancer, diabetes mellitus, cardiovascular diseases, infectious diseases, inflammatory diseases, and neurodegenerative diseases. (3,4)

Yet another important innovation has been the use of green nanotechnology that uses plant extracts as nontoxic, sustainable, and affordable reducing and stabilizing agents in nanoparticle synthesis. This approach offers advantages such as reduced toxicity, enhanced biocompatibility, sustainability and cost-effectiveness compared with conventional chemical synthesis. Thus, the convergence of ancient science of herbal medicine with nanotechnology can be considered an important milestone in pharmaceutical sciences since it facilitates the modernization of plant-based therapeutics while preserving their natural pharmacological potential. Further work on the optimization of formulations, large scale production, safety assessment, and regulatory issues will allow for the successful clinical translation of phytoconstituent-based nanomedicines. (5,6)

This review provides a brief introduction to phytoconstituents and the use of nanocomplexes to resolve some of the drawbacks of classical phytochemical treatment. Phytoconstituents and their classification as well as the use of nanocomplexes as carriers for improving the solubility, stability, bioavailability and targeted delivery of bioactive plant compounds. Additionally, therapeutic applications, recent advancements, the current challenges, and future perspectives for phytoconstituent-based nanomedicine are considered.

II. PHYTOCONSTITUENTS: CLASSIFICATION & THERAPEUTIC POTENTIAL

Plant-derived phytoconstituents have long served as an important source of therapeutic agents and continue to contribute significantly to modern pharmaceutical research. The incorporation of these bioactive compounds into nanocomplexes has emerged as a promising approach to overcome their pharmacokinetic limitations while enhancing their clinical efficacy and safety.

1.ALKALOIDS

Alkaloids represent an essential group of natural nitrogen-containing secondary metabolites, primarily extracted from medicinal plants. As a result of high structural diversity and wide spectrum of pharmacological activity, alkaloids are widely applied in the area of both traditional and modern medicine. Several alkaloids isolated from plants such as morphine, quinine, vincristine, vinblastine, berberine, caffeine, nicotine, and piperine, have demonstrated considerable antioxidant, anti-inflammatory, antimicrobial, analgesic, antimalarial, anticancer, and neuroprotective effects, and can be used to treat various diseases. (7)

Despite their promising therapeutic effects, the use of several alkaloids in medicine is significantly hindered by poor physicochemical and pharmacokinetic properties. Poor aqueous solubility, poor gastrointestinal absorption, rapid hepatic metabolism, extensive first-pass elimination, and low oral bioavailability limit their effectiveness as a drug. Besides, some alkaloids demonstrate dose-dependent toxicity that limits their application in medicine and makes it necessary to design new drug delivery systems able to improve bioavailability and minimize side effects. (8)

Nano-drug delivery systems based on nanotechnology have proved to be a useful technique for addressing these problems. The encapsulation of alkaloids in nanocomplexes such as polymer nanoparticles, liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), dendrimers, nanoemulsions, and phytosomes increases solubility, protects active molecules from decomposition, extends systemic circulation time, and ensures the controlled and targeted delivery of drugs. The use of such nanocarriers increases the efficiency of cellular uptake and biodistribution, which, in turn, increases the effectiveness of drugs and decreases their side effects. (9)

In alkaloid-based nanoformulations, such as vinca alkaloids vincristine and vinblastine, much attention has been paid in the treatment of cancers. Nanotechnology-assisted delivery of these chemotherapy agents increases their accumulation in tumors by passive and active targeting, which increases the anticancer activity of these drugs and decreases their toxicity. Moreover, more advanced techniques such as photochemical internalization have shown increased efficiency in the intracellular delivery of vinca alkaloids. (10)

The other example of promising phytoconstituent which could be effectively nanoformulated is piperine, an alkaloid that can be extracted from Piper nigrum (black pepper). Even though piperine is characterized by strong antioxidant, anti-inflammatory, anticancer, and bioenhancing activities, the use of piperine in therapeutic practice is restricted because of poor aqueous solubility and low oral bioavailability. Encapsulation in functionalized nanoparticles, lipid-based nanocarriers, and polymeric systems is found to increase stability, drug release, drug-cell interaction, and anticancer activity along with decreased toxicity for normal cells. pH-responsive nanocarriers have also been developed for selective drug release in the acidic tumor environment, which allows for increasing drug concentration locally and decreasing systemic side effects. (11)

Despite of the fact that nanocomplexes loaded with alkaloids have shown promising results in preclinical trials, there still are several obstacles in the way of practical application of these systems. Manufacturing, stability, reproducibility, regulation issues, long-term safety, and cost-effective production require more attention. Therefore, the future research should be devoted to the optimization of nanocarrier design, molecular interactions between alkaloids and nanocarriers, and clinical trials. (3)

2.FLAVONOIDS

Flavonoids represent one of the most abundant families of plant-based polyphenolic phytochemicals found in abundance in fruits, vegetables, tea, and medicinal herbs. Flavonoids exhibit numerous pharmacological activities, which include antioxidant, anti-inflammatory, antimicrobial, anticancer, cardioprotective, and neuroprotective actions. Thus, they are considered useful phytoconstituents for the prophylaxis and therapy of various diseases. However, their clinical application is hampered due to poor aqueous solubility, poor gastrointestinal absorption, rapid metabolism, instability, and extensive first pass metabolism leading to low oral bioavailability of flavonoids. (12)

Nano-complex-based formulations have been used as a viable approach to deal with the pharmacokinetic hurdles associated with flavonoids. The use of flavonoid-loaded nanocomplex formulations such as liposomes, phytosomes, polymeric nanoparticles, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), nano-emulsions, and polymeric micelles enhances the solubility, stability, permeability, and sustained release of flavonoids along with protection from any sort of enzymatic and chemical degradation. Moreover, surface functionalization of nanocomplexes leads to targeted drug delivery, improved cellular uptake, prolonged circulation time, and tissue targeting, hence improving efficacy and reducing toxicity. (3)

A number of flavonoids like quercetin, apigenin, naringenin, catechins, rutin, and myricetin have been found to exhibit increased pharmacological activities upon their nanoencapsulation. Flavonoid nanocomplexes have been found to show enhanced properties such as anticancer, antioxidant, anti-inflammatory, antimicrobial, and wound healing effects due to increased availability and selective delivery of these drugs to diseased areas. Additionally, nanocomplexes that can co-deliver flavonoids along with other medicinal drugs or imaging agents have made the development of combination and personalized medicines possible, thus emphasizing on their immense potential in phytopharmaceutical studies. (13)

3. PHENOLIC COMPOUNDS

The class of phenolic compounds known as polyphenols is comprised of a large group of natural secondary products isolated from plants, with the feature of having one or more hydroxyl groups bound to aromatic rings. They occur abundantly in fruits, vegetables, tea, coffee, cocoa, cereals, and medicinal plants. Polyphenols are divided according to their chemical structure into flavonoids and non-flavonoids polyphenols, which include phenolic acids, stilbenes, lignans, tannins, and curcuminoids. The bioactive polyphenols include curcumin, resveratrol, epigallocatechin gallate (EGCG), and ellagic acid which are powerful antioxidants with anti-inflammatory, antimicrobial, cardioprotective, neuroprotective, and anticancer effects. (14)

Though polyphenols possess remarkable pharmacological properties, they have poor aqueous solubility, less absorption in the gastrointestinal tract, fast metabolism, instability, and a high rate of first-pass metabolism which lead to limited bioavailability and hence therapeutic ineffectiveness. The drug delivery systems based on nanocomplex have been found to be a reliable method to cope with these issues. Nanocarriers like liposomes, phytosomes, polymeric nanoparticles, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), nanoemulsions, and nanogels help in increasing the solubility, stability, permeability, controlled release of polyphenols, and protection against degradation and enzymatic destruction. (15)

Nanoencapsulation of polyphenols has been found to increase cell penetration ability, extend circulating time, achieve target delivery, and facilitate tissue-specific deposition of polyphenols, which results in increased therapeutic efficacy with minimal systemic toxicity. In addition, multi-functional nanocomplexes which can deliver polyphenols along with the conventional drugs have been found useful for the treatment of cancer and inflammatory conditions among others. (16)

4.TERPENOIDS

Terpenoids, or isoprenoids, belong to the biggest group of secondary plant metabolites with a number of pharmacological actions, namely anticancer, antioxidant, anti-inflammatory, antimicrobial, antiviral, and neuroprotective activity. Some terpenoids, for example, paclitaxel, andrographolide, betulinic acid, artemisinin, and limonene have shown high therapeutic efficacy in treating cancer, infectious diseases, and inflammatory conditions. (17)

However, despite their remarkable biological properties, terpenoids have limited therapeutic applications due to poor water solubility, low bioavailability, fast metabolism, and chemical instability. In order to overcome the mentioned issues, nanocomplexes, liposomes, polymeric nanoparticles, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), nanoemulsions, and polymeric micelles were designed for delivery of terpenoids. Such nanocarriers can increase the solubility of drugs, protect terpenoids from decomposition, increase cellular delivery and drug release, and deliver the drug directly to the target tissue. (18)

The use of nanoencapsulated terpenoids has proven very effective in the treatment of cancer through formulations of paclitaxel, andrographolide, and betulinic acid, which are known for enhanced accumulation in tumors, improved circulation time and anticancer activity. Terpenoids have also found significant antimicrobial and antioxidant applications through the use of green approach in the formation of metal nanoparticles and nanocomplexes for targeted therapy. The above applications of terpenoid nanocomplexes show the increasing use of these complexes in phytopharmaceutical and nanomedicine studies. (19)

5.LIPIDS

Lipid-based nanocomplexes have proven to be one of the most successful and clinically translated nanocarriers for the delivery of phytoconstituents because of their excellent biocompatibility, biodegradability, non-toxicity and high drug loading capacity. These nanocarriers are represented by liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), lipid polymer hybrid nanoparticles, nanoemulsions and phytosomes, all having the capability to encapsulate both hydrophilic and lipophilic phytoconstituents. (20)

Phospholipids, cholesterol, triglycerides, fatty acids, and PEGylated lipids constitute the key structures of lipid nanocomplexes. The most widely used phospholipids are phosphatidylcholine since they can form stable bilayers, which are similar to biological membranes, and promote drug loading, membrane fusion, and cellular uptake. In turn, cholesterol is frequently added to increase the rigidity of lipid membrane, reduce drug loss, and improve the stability of nanoparticles. (21)

There are many ways how lipid nanocomplexes can be used to enhance the pharmacological properties of plant components. Lipid-based nanocomplexes can improve the aqueous solubility of phytoconstituents, stabilize them against enzymatic degradation and oxidative processes, prolong the circulation in the body, increase their absorption from the intestine, and enable controlled and sustained drug release. Moreover, the surface modification with PEG, antibodies, peptides, or other targeting moieties provides the opportunity for both passive and active targeting of drugs, which increases their accumulation at the disease site and decreases the toxicity in the rest of the body. (22)

Numerous phytoconstituents such as curcumin, quercetin, resveratrol, berberine, silymarin, and paclitaxel have been reported to exhibit significantly better pharmacokinetic behavior and therapeutic performance due to encapsulation within lipid nanocomplexes. This is attributed to increased cellular uptake, bioavailability, and drug release from lipid nanocomplexes. Apart from that, there has been significant potential shown for the ability of lipid nanocomplexes to cross biological barriers such as the blood-brain barrier. This has opened up further uses of lipid nanocomplexes in neurological disorders and targeted cancer treatment. (23)

The immense clinical success of lipid nanoparticles is illustrated by several FDA-approved formulations such as liposomal anticancer drugs and lipid nanoparticle-based mRNA vaccines. These have already made lipid nanocomplexes into efficient and scalable drug delivery systems. Current research aims at developing stimuli-sensitive and ligand-targeting multifunctional lipid nanocomplexes which will be able to deliver phytoconstituents together with conventional drugs or nucleic acids. (24)

Limitations of Conventional Phytoconstituents (25)

- Poor aqueous solubility: Many phytoconstituents are hydrophobic, resulting in limited dissolution in biological fluids and reduced absorption.
- Low oral bioavailability: Extensive first-pass metabolism and poor gastrointestinal absorption significantly decrease the systemic availability of phytochemicals.
- Chemical and physiological instability: Many bioactive compounds are susceptible to degradation by light, heat, oxygen, pH variations, and digestive enzymes before reaching the target site.
- Rapid metabolism and elimination: Fast biotransformation and clearance shorten the biological half-life of phytoconstituents, reducing their therapeutic effectiveness.
- Limited membrane permeability: Poor permeability across biological membranes restricts efficient transport into target tissues and cells.
- Lack of target specificity: Conventional formulations distribute drugs non-selectively, leading to reduced drug concentration at the disease site and increased off-target effects.
- Poor pharmacokinetic profile: Unfavorable absorption, distribution, metabolism, and excretion (ADME) characteristics often limit clinical efficacy.
- Dose variability and inconsistent therapeutic response: Differences in phytochemical composition, extraction methods, and formulation quality may result in inconsistent pharmacological effects.
- Poor patient compliance: Frequent dosing is often required because of rapid drug clearance and limited duration of action.
- Limited ability to cross biological barriers: Conventional phytoconstituents often fail to efficiently penetrate barriers such as the blood-brain barrier, reducing their effectiveness in treating neurological disorders.
- Low stability during storage: Many phytoconstituents undergo oxidation or degradation during storage, leading to reduced potency and shorter shelf life.
- Challenges in clinical translation: Variability in phytochemical composition, poor standardization, and inadequate pharmacokinetic performance hinder the successful transition of many phytoconstituents from laboratory research to clinical practice.

Nanotechnology-Based Drug Delivery Systems

Overview of Nanotechnology

Nanotechnology is a multi-disciplinary area that focuses on the development and implementation of various materials and structures at the nanometer scale (1 to 1000 nm) in order to modify their physicochemical and biological properties. As far as the pharmaceutical sciences are concerned, nanotechnology is considered a highly advanced technique that allows improving the delivery of drugs due to the enhancement of their solubility, stability, bioavailability and efficacy. Through nanotechnology-based drug delivery systems, medications can be protected from degradation, and controlled release of a substance in a targeted way is possible. Moreover, the use of nanotechnology allows increasing cellular uptake and reducing systemic toxicity.

Application of Nanotechnology in Phytopharmaceutical Research

Phytopharmaceutical research includes the investigation of plant materials in the field of developing new drugs. The application of nanotechnology allows enhancing the clinical efficacy of phytoconstituents that demonstrate low water solubility, low permeability and rapid metabolism. Nanocomplexes such as liposomes, phytosomes, polymeric nanoparticles, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), dendrimers, nanoemulsions and nanogels are used to increase the delivery of phytoconstituents.(3)

Advantages of Nanocomplexes (25)

- Enhanced solubility: Improves the aqueous solubility of poorly water-soluble phytoconstituents.
- Increased bioavailability: Enhances gastrointestinal absorption and systemic availability of bioactive compounds.
- Protection from degradation: Shields phytoconstituents from enzymatic, chemical, and environmental degradation, improving stability.
- Controlled and sustained drug release: Provides prolonged therapeutic action while reducing dosing frequency.
- Targeted drug delivery: Facilitates selective delivery to specific tissues or cells, minimizing off-target effects.
- Improved cellular uptake: Nanosized carriers promote efficient transport across biological membranes and intracellular delivery.
- Reduced systemic toxicity: Localized drug delivery lowers adverse effects on healthy tissues.
- Enhanced pharmacokinetic profile: Optimizes absorption, distribution, metabolism, and elimination (ADME) characteristics.
- Ability to cross biological barriers: Enhances penetration across barriers such as the blood-brain barrier and mucosal membranes.
- Higher therapeutic efficacy: Increases drug concentration at the target site, leading to improved clinical outcomes.
- Co-delivery of multiple agents: Enables simultaneous delivery of phytoconstituents with synthetic drugs, genes, or imaging agents for synergistic therapy.
- Surface functionalization: Nanocomplexes can be modified with ligands, antibodies, or polymers to achieve active targeting and improved circulation time.
- Improved patient compliance: Sustained release and reduced dosing frequency contribute to better treatment adherence.
- Versatility: Suitable for delivering a wide range of hydrophilic, lipophilic, and macromolecular therapeutic agents.

III. TYPES OF NANOCOMPLEXES

1.LNPs (Lipid nanoparticles)

One of the highly advanced and clinically promising nanocomplexes, used for the delivery of therapeutic agents, especially phytoconstituents is Lipid nanoparticles (LNPs). Due to the excellent biocompatibility, biodegradability, low toxicity and high drug-loading capacity, LNP is regarded as a suitable nanodelivery system that could enhance the therapeutic properties of phytoconstituents. The composition of LNPs includes physiological lipids that mimic natural biological membrane, ensuring high efficacy in encapsulating both hydrophilic and lipophilic phytoconstituents while maintaining their integrity against enzymatic and chemical degradation. Thus, LNPs considerably increase the solubility, stability, bioavailability and pharmacokinetics of poorly absorbed phytochemicals. (1)

Two major classes of LNPs are SLNs (solid lipid nanoparticles) and NLCs (nanostructured lipid carriers). SLNs involve lipids that stay in solid state at physiological temperature, guaranteeing great physical stability, high efficiency in drug encapsulation and sustained drug release. NLCs are the second generation lipid nanoparticles that are prepared from the mixture of solid and liquid lipids, forming incomplete lipid matrix, which allows increasing the drug loading and reducing the leakage during storage. These lipid nanoparticles demonstrated great potential for delivering poorly soluble phytoconstituents, like curcumin, resveratrol, quercetin and berberine.(22)

Another key group is that of liposomes which are phospholipid-based vesicles which can encapsulate both aqueous soluble and lipid soluble substances. Liposomes enhance the stability of drugs, increase circulation times and ensure targeted delivery through active and passive means. Furthermore, lipid-polymer hybrid nanoparticles combine the benefits of lipid-based nanoparticles and polymer nanoparticles. These particles have been proven effective in the delivery of drugs to the target sites without the associated toxic effects since they enable the targeting of certain sites where drugs should be delivered. This has been applied in treating cancer, inflammatory conditions and infectious diseases. (26)

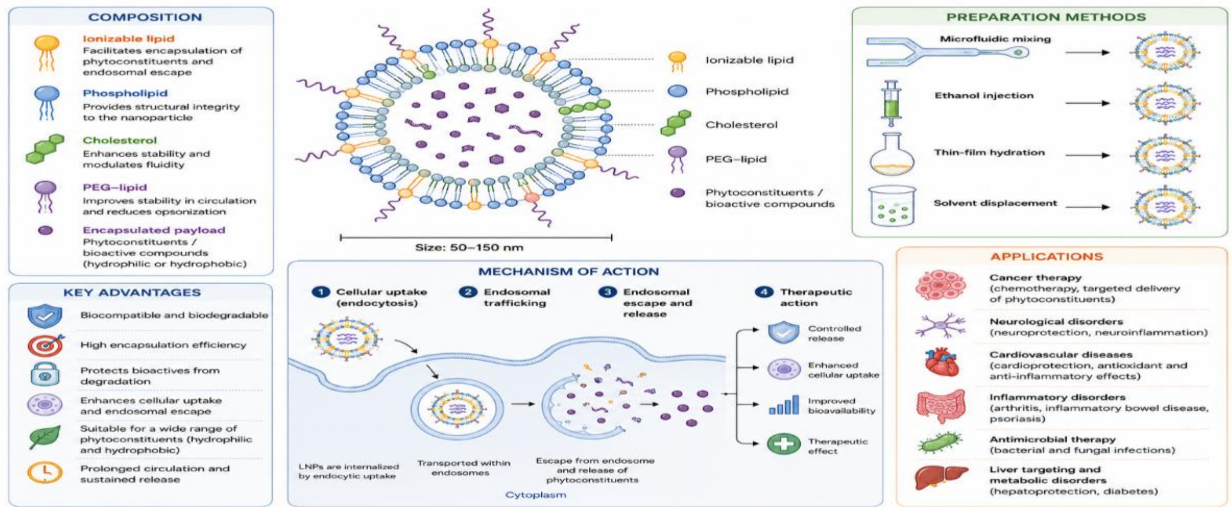


Figure a. Overview of Lipid Nanoparticles as Nanocarriers for Phytoconstituent Delivery

Among recent developments in LNP technologies, there have been improvements in surface PEGylation, ligand conjugation, and microfluidic engineering, which make it possible to achieve high precision in controlling LNP particle size, encapsulation efficiency, and drug release profiles. Additionally, LNPs have become increasingly recognized as nucleic acids delivery systems, as is evidenced by their use in mRNA vaccines and gene therapy, making these nanocomplexes applicable in delivery purposes other than drug delivery. Taken together, all these features render lipid nanoparticles the most promising nanocomplexes in the context of enhancing clinical applicability of phytoconstituent-based medicines.(15)

2. PNPs (Polymeric nanoparticles)

Polymeric nanoparticles (PNPs) are highly versatile nanocomplexes which are widely used for phytoconstituent delivery due to their biocompatibility, biodegradability, physical stability, and modifiable physicochemical properties. They are usually prepared using natural polymers like chitosan, gelatin, alginate, and dextran, as well as artificial ones like PLGA, PLA, and PCL. Their small size and surface features allow for effective loading with different phytoconstituents, thus increasing their solubility, stability, bioavailability, and effectiveness. (27)

Several methods, such as nanoprecipitation, solvent evaporation, emulsion-diffusion, ionic gelation, and microfluidics, are used for PNPs production to ensure precise particle size and high drug loading capacity. Different preparation methods facilitate the adjustment of drug loading and release features according to particular purposes of using the nanoparticles. Unlike traditional formulation, PNPs deliver controlled and sustained drug release, thus keeping the therapeutic drug concentration in blood for prolonged time and lowering the dosage administration frequency. The described feature is especially useful in the case of unstable phytoconstituents, such as curcumin, quercetin, berberine, and resveratrol, that rapidly eliminate from the body. (28)

One of the key benefits of PNPs is their targeted drug delivery due to the functionalization of nanoparticles' surface with antibodies, peptides, aptamers, or other ligands. Functionalized nanoparticles help to concentrate the active drug component at the site of disease without causing any side effects elsewhere. Moreover, polymeric nanoparticles may be designed as responsive systems delivering the drugs by the effect of certain physiological factors, such as low pH, increased enzymatic activity, temperature change, or reduction. Smart nanocomplexes have proven themselves effective in cancer therapy by targeted delivery of phytoconstituents to the target cells while reducing systemic adverse effects. (28)

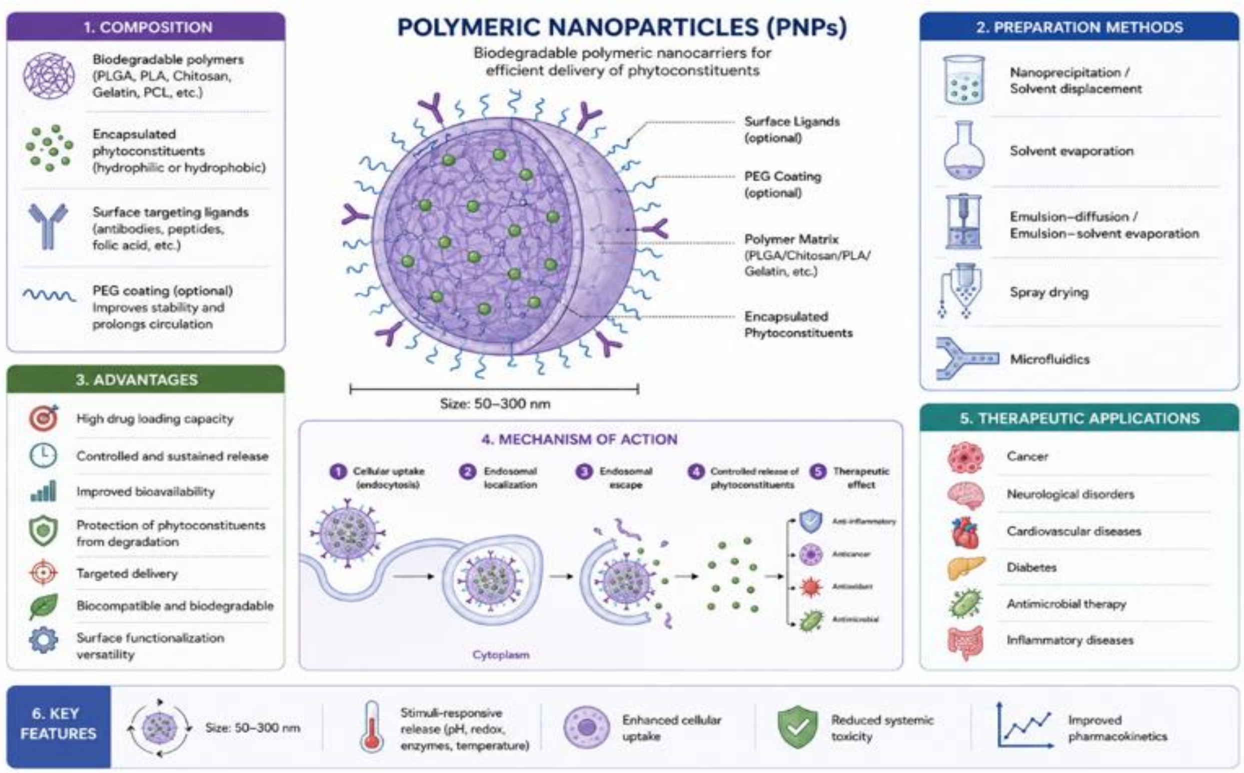


Figure b. Overview of polymeric nanoparticles as nanocarriers

With regard to recent advancements in polymer science, the biomedical applications of PNPs have been enhanced due to improvements in their stability, circulation and intracellular delivery. The properties such as ability to circumvent biological barriers, protection against premature degradation of phytoconstituents entrapped in their structure and efficient cellular delivery make them suitable carriers for treatment of cancer, inflammatory conditions, infectious diseases and neurodegenerative ailments. Although PNPs exhibit great promise as carriers of phytoconstituents in medical practice, certain concerns such as large scale production, reproducibility, approval and safety need to be considered in order to successfully translate PNPs into clinical application. However, despite aforementioned issues, PNPs still represent some of the most promising nanocomplexes for enhancement of pharmacological activity of plant-derived phytochemicals. (29)

3. NANOEMULSION

Nanoemulsions represent nanosized colloidal carrier systems consisting of two phases that are immiscible, oil and water phase stabilized by surfactants and cosurfactants. Sizes of droplets vary in range of 20-200 nm. Due to their large surface area, high kinetic stability and optical clarity, nanoemulsions have become promising nanocarriers for poorly water-soluble phytoconstituents. These systems considerably improve solubility, stability, dissolution profile, oral bioavailability and efficiency of phytochemicals including curcumin, quercetin, resveratrol, essential oils, and carotenoids. (30)

Nanoemulsions can be made through high energy processes like high-pressure homogenization and ultrasonication or low energy techniques like spontaneous emulsification and phase inversion. Such an emulsification method results in uniformly distributed nanosized droplets with good encapsulation efficiency and stable formulations. In contrast to regular emulsions, nanoemulsions show high resistance to coalescence, creaming, sedimentation, and phase separation. Thus, shelf life is increased, and the phytoconstituents entrapped in them are protected against degradation. (31)

The smaller droplet size of nanoemulsions leads to increased absorption, membrane permeability, and cellular uptake, resulting in lymphatic delivery, which reduces the first-pass effect on lipophilic phytoconstituents. Besides, nanoemulsions have sustained drug release characteristics, thus prolonging the period of drug activity and decreasing the dosing schedule. Furthermore, the surface of nanoemulsions can be modified with targeting agents, which enable active and passive drug targeting. This will increase the delivery of drugs to the disease tissue by utilizing EPR effect, etc. (31)

In recent times, the new developments include stimuli-responsive nanoemulsions, Pickering nanoemulsions, double nanoemulsions, and microfluidic-based production, which increase the stability, efficiency, reproducibility, and scaling-up process of the formulation. Also, nanoemulsions can encapsulate different phytoconstituents or phytochemicals along with regular drugs to provide a synergy effect in the treatment of cancer, inflammatory diseases, infections, and neurodegenerative diseases. Due to their easy preparation, large-scale production possibility, and high biocompatibility, nanoemulsions have emerged as one of the most effective nanocomplexes for phytopharmaceutical drug delivery systems. (30)

4. Solid Lipid Nanoparticles (SLNs)

Solid lipid nanoparticles (SLNs) are the first generation of lipid-based nanodelivery systems that were created to overcome the problems related to the delivery of insoluble phytoconstituents. These are biocompatible solid lipid nanoparticles dispersed in an aqueous surfactant phase, whose size lies between 50 and 1000 nm. These nanodelivery systems increase the solubility, stability, and bioavailability of phytoconstituents and protect them against degradation. (22)

SLNs are usually produced using techniques like high-pressure homogenization, ultrasonication, solvent emulsification, and microemulsion. Depending on the preparation technique used, the drug can either be a part of the homogeneous matrix, enriched shell, or enriched core of the SLN. SLNs have successfully been employed to transport phytoconstituents like curcumin, quercetin, resveratrol, and berberine. This improves their gastrointestinal absorption, increases their circulation times, and allows for targeted delivery. They also play an important role in the topical administration where their occlusive nature helps improve skin hydration and facilitates deep penetration of herbals. (32)

However, there are several drawbacks associated with SLNs including their relatively poor drug loading ability and tendency of drug expulsion in case of crystallization of lipids upon storage. However, recent developments in the composition of the lipid and its surface functionalization have greatly improved the stability and effectiveness of SLNs.(32)

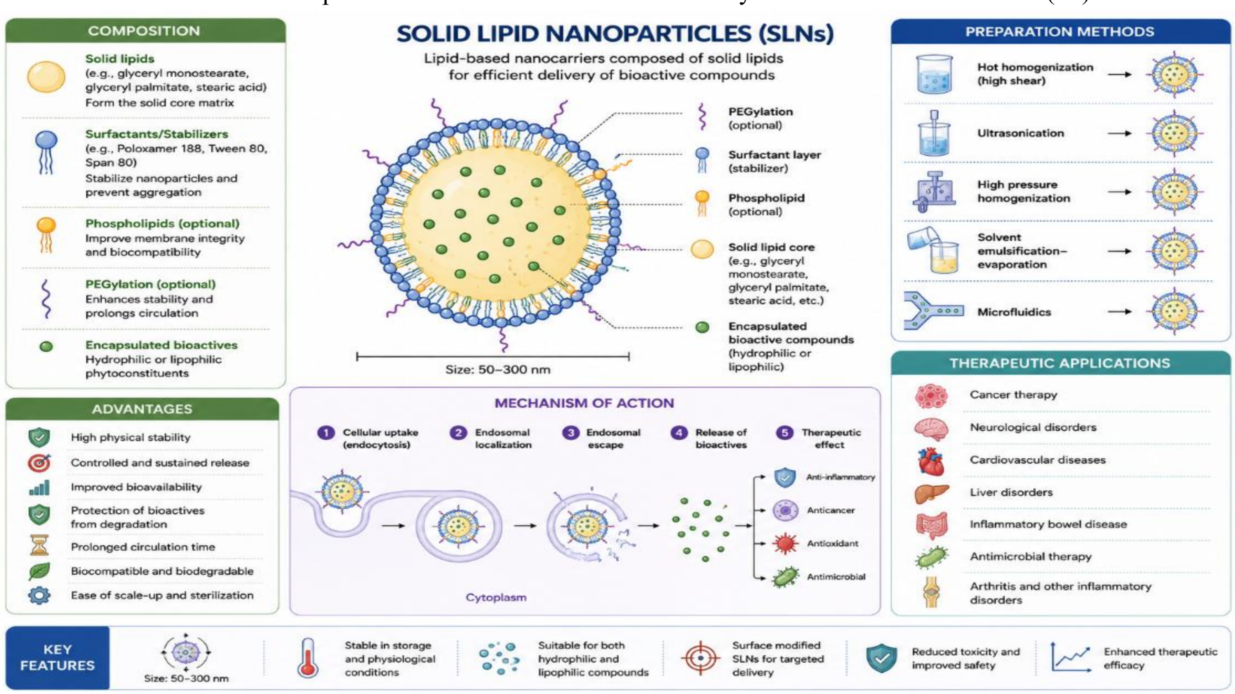


Figure c. Overview of solid lipid nanoparticles

5. Nanostructured Lipid Carriers (NLCs)

Nanostructured lipid carriers (NLCs) are considered next-generation lipid-based nanocarrier systems that have been designed to address the deficiencies of solid lipid nanoparticles (SLNs) such as poor drug loading and tendency of drug expulsion during storage. NLCs are made up of a combination of solid and liquid lipids resulting in an incomplete lipid matrix which allows more room for the inclusion of biologically active molecules. NLCs are ideal for carrying poorly soluble phytochemicals like curcumin, quercetin, resveratrol, berberine, and silymarin due to their improved characteristics. (22)

NLCs are usually produced by employing methods such as high-pressure homogenization, microemulsion, solvent emulsification–evaporation, ultrasonication, and hot or cold homogenization. Their small size increases the solubility, gastrointestinal permeability, and cellular uptake of drugs while offering protection against enzyme and oxidative destruction of the phytochemicals incorporated in the carrier. As compared to other formulation approaches, NLCs offer advantages such as enhanced bioavailability, increased systemic circulation, and controlled release. (33)

Another key benefit associated with NLCs is their ability to undergo surface functionalization using polymers, antibodies, peptides, or any other targeting ligands in order to deliver drugs selectively to diseased tissues, thus decreasing the risks of any adverse effects and increasing drug accumulation in the target site. Such properties make NLCs useful in the development of formulations for cancer therapy, inflammatory diseases, neurological diseases, skin diseases, and antibacterial treatment, as they can significantly enhance the pharmacodynamics and pharmacokinetics of incorporated phytoconstituents. In addition, biocompatibility, low toxicity, scalability, and physical stability of NLCs make them an interesting choice for pharmaceutical and nutraceutical preparations. (34)

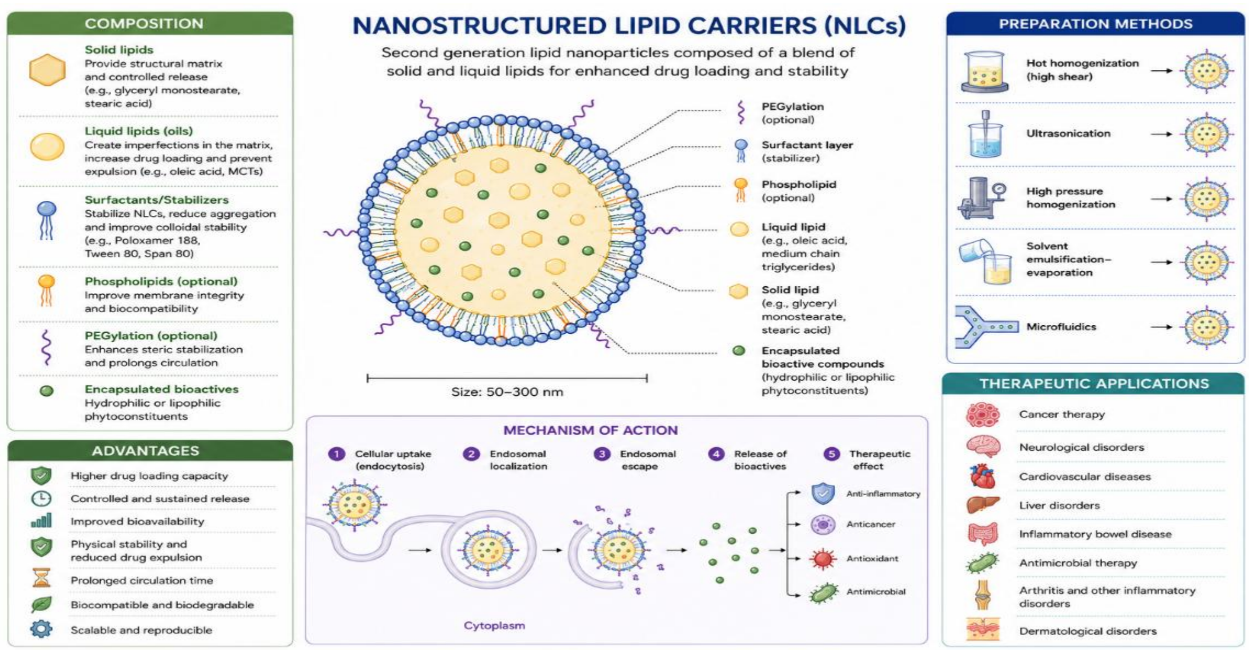


Figure d. overview of NLCs

In recent studies, researchers proved the possibilities of usage of stimuli-responsive and ligand-functionalized NLCs for precise drug delivery. Stimuli-responsive NLCs can respond to physiological stimuli such as pH, enzymes, or redox conditions, which will result in the drug release in the required place and improve therapeutic application. Moreover, NLCs can help to deliver simultaneously multiple phytoconstituents or phytochemicals and synthetics, which will have synergic effects on the body while reducing adverse reactions. These advantages position NLCs as one of the most promising nanocomplexes for enhancing clinical use of plant-derived bioactive compounds. (22)

5.Dendrimers

Dendrimers are highly branched nanosized polymer nanocarriers that have a well-organized three-dimensional structure including a core, repeated branching and multiple surface groups. The monodispersity, high surface area, and adjustable physiochemical properties of dendrimers offer an excellent platform for phytoconstituent transport and delivery. Encapsulation of hydrophobic drugs into the internal cavity of the dendrimers and functionalization of the surface groups with specific chemical moieties allow improving solubility, biocompatibility, and targeting of the drugs. Thus, dendrimers increase the stability, bioavailability and release rate of poorly soluble phytochemicals. (35)

The main strength of dendrimers is the ability of delivering drugs selectively to the diseased tissues. The surface modification with different ligands (for example, folic acid, antibodies, peptides or sugars) allows targeting specific receptors, thereby increasing the efficiency of the drug and reducing the toxicity. Nanoformulations based on dendrimers were widely used for delivery of phytoconstituents like curcumin, quercetin and resveratrol leading to higher solubility, prolonged circulation and better drug delivery. In oncology PAMAM dendrimers have shown promising results in delivery of antitumor drugs via active targeting approaches. (36)

Apart from traditional drug delivery, dendrimers also serve as carriers for nucleic acids, proteins, and imaging agents. The positively charged surface of dendrimers makes them effective for complexation with DNA, siRNA, and mRNA, offering protection against enzymatic degradation and intracellular delivery. Moreover, metal nanoparticles coated with dendrimers, especially gold and silver nanoparticles, have been explored in nanomedicine since dendrimers work as nanoreactors which control the size of particles, prevent aggregation, and increase colloidal stability. Dendrimer nanocomplexes find applications in targeted drug delivery, bioimaging, biosensors, and catalytic systems. Recently developed stimuli-responsive dendrimers release the loaded drug under the influence of stimuli like pH, enzymes, and redox environment. Such kind of stimuli-responsive dendrimers finds application in precision medicine and cancer therapy. Though there are many challenges regarding scaling up process, cost, and safety, dendrimers still remain one of the most versatile nanocarriers for future phytoconstituent delivery systems. (35)

6. NANOGELS

Nanogels are three-dimensional polymeric nanoparticles that can encapsulate hydrophilic as well as hydrophobic phytoconstituents and therefore nanogels are considered as one of the most versatile nanocarriers for drug delivery systems. The high water content, soft structure, biocompatibility, and high drug loading capacity make these nanoparticles useful for the efficient delivery of bioactive compounds. Nanogels can be activated by physiological stimuli such as pH, temperature, enzymes, and reduction/oxidation states for site-specific and controlled drug delivery. Due to such attributes, they have received significant focus as carriers for herbal-based drugs in nanomedicine. (37)

Nanogels may be prepared through such processes as inverse miniemulsion polymerization, self-assembly, radiation cross-linking, and chemical cross-linking. The nanoparticles' small size facilitates their efficient penetration into tissues; the polymeric matrix protects the phytoconstituents from early destruction and extends their circulation time. Moreover, the presence of ligands, antibodies, or peptides on the surface of nanogels leads to the increase in targeting ability and efficacy. The response to stimuli in the environment helps control the release of the drug in a timely fashion and minimize toxicity and maximize efficacy. (37)

The nanogel preparations have proven to be quite promising in the treatment of different diseases, including cancers, inflammation, diabetes, neurodegeneration, and infectious diseases. The research on the delivery of various phytoconstituents, such as curcumin, quercetin, resveratrol, and EGCG, has been actively conducted in oncology. The use of nanogels increases the tumor accumulation and cellular uptake of drugs, extends their effect, and minimizes toxic reactions. In wound healing, the use of hyaluronic acid and chitosan-based nanogels promotes the tissue regeneration due to the prolonged release of growth factors and phytochemicals. Other applications of nanogels include their use in transdermal, ocular, oral, pulmonary, and intranasal drug delivery due to their excellent mucoadhesive nature and bio-barrier crossing ability. In addition, their ability to encapsulate proteins, peptides, nucleic acids (siRNA and DNA), and imaging agents has increased their potential use in gene delivery and vaccine delivery. (38)

7. Metallic Nanoparticles (MNPs)

Metallic nanoparticles are nanomaterials that are usually in the size range of 1 – 100 nm, which is made up of metals or metal oxides. Their remarkable physicochemical properties such as surface area, surface chemistry, optical activity, and magnetic property makes them suitable for drug delivery nanocarrier. MNPs in formulations of phytoconstituents improve the solubility, stability, cellular absorption, bioavailability, and drug delivery. Furthermore, the ability to synthesize the particles through green eco-friendly technique by plant extract has broadened their scope in nanomedicine. (39)

Gold Nanoparticles (AuNPs)

Gold nanoparticles are one of the widely studied nanomaterials for use as nanocarrier owing to their superior biocompatibility, chemical stability, and surface modification capacity. AuNPs could be conjugated with phytoconstituents such as curcumin, quercetin, EGCG, and resveratrol for better efficacy. AuNPs have found immense application in targeted cancer therapy, photothermal therapy, bioimaging, biosensing, and drug delivery. (40)

Silver Nanoparticles (AgNPs)

The silver nanoparticles have excellent antimicrobial, antioxidant, anti-inflammatory, and anticancer activities. They are synthesized through green synthesis methods using extracts from various plants as reducing and stabilizing agents. They are widely used in wound healing, antimicrobial coatings, tissue engineering, and cancer therapy owing to their membrane-disrupting ability that inhibits biofilm formation while improving the activity of the phytoconstituents enclosed in them. (41)

Iron Oxide Nanoparticles (Fe_3O_4NPs)

Iron oxide nanoparticles are known to be superparamagnetic, which implies that an external magnetic field can attract them to specific tissues. Iron oxide nanoparticles are commonly used in magnetically targeted drug delivery, MRI, hyperthermia therapy, and cancer therapy. With phytoconstituents incorporated in them, the iron oxide nanoparticles enhance their targeting ability without causing any damage to healthy tissues. (42)

Metal Oxide Nanoparticles

Metal oxide nanoparticles, which include ZnO, TiO_2, CuO, and CeO_2 nanoparticles, have excellent photocatalytic, antioxidant, and antimicrobial properties. They have gained significant attention in the delivery of phytoconstituents in the treatment of bacterial infections, inflammation, skin diseases, diabetes, and cancer among others. (43)

IV. THERAPEUTIC APPLICATIONS

1. Cancer

Cancer is among the leading causes of morbidity and mortality around the world, and the drawbacks of traditional chemotherapy, such as poor selectivity, toxicity, and multidrug resistance, have made researchers develop new treatment methods. Natural products like curcumin, quercetin, resveratrol, and epigallocatechin gallate (EGCG) have been widely studied for their ability to halt the development of cancer cells using different pathways, which include induction of apoptosis, blocking of cell proliferation, angiogenesis inhibition, and modification of cellular signaling pathways. Though having beneficial pharmacological effects, these substances are limited in their use due to poor solubility, low bioavailability, high metabolism, and insufficient targeting in the tumor area. (44)

Nanotechnology delivery systems have proved to be the most efficient way of dealing with these issues. Nanostructured systems, including lipid nanoparticles, polymeric nanoparticles, liposomes, phytosomes, dendrimers, and nanoemulsions, increase the solubility, stability, and pharmacokinetics of the phytoconstituents and allow targeted delivery of drugs. Due to the enhanced permeability and retention (EPR) effect, these nanosystems accumulate mainly in tumor areas. (45)

Some studies have proven the benefits of nano-formulated phytoconstituents in the treatment of cancers. Some of the examples include folate-modified nanoparticles incorporating curcumin or quercetin, which have improved intracellular uptake and specific targeting of cancer cells. Nanoformulation of resveratrol has also been found to have increased stability and sustained drug release due to which it shows enhanced anticancer activity. Chitosan nanoparticles of ellagic acid also show increased cytotoxicity against breast cancer cells along with increased antitumor activity than the free compound.

Besides, some studies have suggested that the co-delivery of phytoconstituents with chemotherapy drugs like doxorubicin using nanocarrier results in synergetic anticancer activity with reduced side effects. (46)

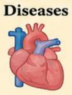
Overall, nanotechnology-based delivery systems offer enhanced therapeutic properties to phytoconstituents.

2.Cardiovascular Diseases

Cardiovascular diseases (CVDs) continue to be among the most prominent causes of death throughout the world with oxidative stress, inflammation, dysfunction of the endothelium, and lipid accumulation being key components in their pathogenesis. Such phytoconstituents as quercetin, curcumin, and resveratrol are known for the documented cardioprotective activity, which includes antioxidant, anti-inflammatory, anti-apoptotic, and vasoprotective effects. Nevertheless, their therapeutic properties are frequently hindered by poor aqueous solubility, poor oral bioavailability, fast metabolism, and insufficient tissue distribution. The nanoformulation technologies have been proven as efficient ways to address these issues by increasing stability, bioavailability, and targeted delivery of these substances. (47)

Lipid nanoparticles, polymeric nanoparticles, liposomes, and nanogels are among the number of nanocarriers tested in cardiovascular drug delivery. Nanoencapsulated resveratrol was found to have increased stability and bioavailability, thus providing more protection from the oxidative stress and inflammation of the vessel walls caused by atherosclerosis. Quercetin-loaded lipid-based nanoparticles were shown to accumulate in atherosclerotic areas, which prevented lipid deposits, inflammatory reaction, and progression of the plaque. The nanoformulations were also used to limit chemotherapy-related cardiotoxicity, when the plant extract-loaded metal oxide nanoparticles proved to be cardioprotective due to decreased production of reactive oxygen species and apoptosis of cardiomyocytes. (48)

Furthermore, stimuli-responsive nanocarriers also hold a great deal of potential in treating vascular diseases. The use of pH- and ROS-responsive nanocarriers facilitates drug delivery at specific sites of vascular tissue inflammation, making it possible to achieve greater efficacy with lower systemic side effects. Targeted drug delivery systems have been found to possess the potential to prevent vascular inflammation, neointimal hyperplasia, and also enhance arterial function. Overall, nano-formulated phytocompounds appear to be a good choice for the prevention and treatment of cardiovascular diseases. (49)

Disease	Phytoconstituent(s)	Nanoformulation Type	Key Mechanism / Target	Outcome / Therapeutic Benefit
Cancer 	Curcumin, Quercetin, Resveratrol, EGCG, Apigenin, Ellagic acid	• Liposomes • Polymeric nanoparticles • Solid lipid nanoparticles • Nanogels • Dendrimers • Metallic nanoparticles	• Induces apoptosis • Inhibits cell proliferation • Suppresses angiogenesis • Modulates signaling pathways (PI3K/Akt, NF-κB, MAPK) • Overcomes multidrug resistance	• Enhanced tumor targeting and accumulation • Improved bioavailability and stability • Increased cytotoxicity to cancer cells • Reduced systemic toxicity • Synergistic effect with chemotherapeutic drugs
Diabetes 	Berberine, Curcumin, Quercetin, Resveratrol, Epigallocatechin gallate (EGCG)	• Nanoemulsions • Polymer nanoparticles • Lipid nanoparticles • Nanogels • Phytosomes	• Enhances insulin sensitivity • Regulates glucose metabolism • Inhibits α-glucosidase and α-amylase • Reduces oxidative stress and inflammation	• Improved glycemic control • Enhanced oral bioavailability • Prolonged drug release • Protection of pancreatic β-cells • Reduced diabetic complications
Neurological Disorders 	Curcumin, Resveratrol, Quercetin, EGCG, Berberine, Huperzine A	• Solid lipid nanoparticles • Nanostructured lipid carriers • Liposomes • Polymeric nanoparticles • Nanogels	• Antioxidant and anti-inflammatory • Reduces amyloid aggregation • Protects neurons from apoptosis • Modulates neurotransmitters • Enhances blood–brain barrier penetration	• Improved brain targeting and delivery • Enhanced neuroprotection • Reduced oxidative stress and neuroinflammation • Amelioration of cognitive and motor function
Cardiovascular Diseases 	Resveratrol, Quercetin, Curcumin, Catechins, Ginsenosides	• Lipid nanoparticles • Nanoemulsions • Polymeric nanoparticles • Nanogels • Phytosomes	• Antioxidant and anti-inflammatory • Improves endothelial function • Reduces lipid accumulation • Anti-atherosclerotic and anti-hypertensive effects	• Improved cardiac function • Reduced oxidative stress and inflammation • Plaque stabilization and reduced atherosclerosis • Enhanced bioavailability and safety
Antimicrobial Therapy 	Curcumin, Berberine, Thymol, Eugenol, Allicin, Catechins	• Silver nanoparticles • Liposomes • Chitosan nanoparticles • Nanoemulsions • Dendrimers	• Disrupts microbial cell membrane • Inhibits biofilm formation • Interferes with microbial enzymes • Enhances antimicrobial activity against resistant strains	• Enhanced antibacterial, antifungal and antiviral activity • Overcomes drug resistance • Synergistic effect with antibiotics • Lower required dose and reduced toxicity

3.Neurological Disorders

Neurological disorders such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, and other neurodegenerative conditions are characterized by progressive neuronal damage, oxidative stress, chronic inflammation, and abnormal protein aggregation. Several phytoconstituents, including curcumin, resveratrol, quercetin, epigallocatechin gallate (EGCG), and berberine, possess significant neuroprotective, antioxidant, and anti-inflammatory properties. However, their therapeutic application is often limited by poor aqueous solubility, low oral bioavailability, rapid metabolism, and limited ability to cross the blood-brain barrier (BBB). Nanoformulation strategies have emerged as an effective approach to overcome these limitations by enhancing drug stability, improving BBB penetration, and enabling sustained and targeted delivery to neuronal tissues. (50)

Among the various nanocarriers, lipid nanoparticles, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), polymeric nanoparticles, liposomes, and nanogels have demonstrated considerable potential for brain-targeted delivery of phytoconstituents. Their nanoscale size facilitates transport across the BBB through mechanisms such as receptor-mediated endocytosis and adsorptive transcytosis, resulting in increased drug accumulation within the brain and prolonged therapeutic action. (51)

Nanodelivery systems loaded with curcumin have exhibited better neuroprotective properties by preventing the aggregation of amyloid-beta proteins, oxidative damage, and neuroinflammation in Alzheimer's disease animal models. Likewise, nanoparticulate systems encapsulating resveratrol and quercetin have been found to exhibit better antioxidant properties and have prevented neurodegeneration and dopaminergic neuron apoptosis in models of Parkinson's disease. Not only does nanoparticulation improve the pharmacodynamics of drugs but also enables sustained release with minimal systemic toxicity. (52)

Moreover, nanoparticulate systems functionalized with targeting ligands like transferrin, lactoferrin, or peptides have been evaluated for delivering neuroprotective drugs selectively across the BBB. This not only helps in increasing efficacy but also minimizes off-target effects. Thus, nanoparticulate systems of phytoconstituents are very promising for improving neurological disorders. (52)

4. Antibacterial Therapy

The increasing resistance of pathogens against different antibiotics has necessitated the development of alternate antimicrobial therapies. Natural products exhibit broad-spectrum antibacterial properties because of their ability to affect the permeability of bacterial membranes, enzyme inhibition, protein synthesis inhibition, and biofilm formation inhibition. The application of these drugs has been limited by their poor water solubility, instability, poor bioavailability, and degradation rate. The use of nanoparticles in drug formulation has provided an excellent method of overcoming these problems through increased stability, targeted delivery, and antibacterial activity. (53)

Phytoconstituents like curcumin, quercetin, resveratrol, rutin, phloridzin, ursolic acid, punicacortein A, alkaloids, flavonoids, and saponins have exhibited enhanced antimicrobial potential after being used in nanocomplexes. Lipid, polymer, metal and nanoemulsions increase the efficiency of bioactive compounds against bacterial cells, and this increases the inhibition of both gram-positive and gram-negative bacteria. (54)

In terms of metallic nanocomplexes, the green-synthesized silver nanoparticles (AgNPs) synthesized from plant extracts exhibit impressive antibacterial activity against pathogens like Staphylococcus aureus, Escherichia coli, and Pseudomonas aeruginosa. The phytochemicals in medicinal plants act as reducing and stabilizing agents in nanoparticle synthesis, besides their antimicrobial potential. Similarly, zinc oxide nanoparticles (ZnO NPs) synthesized using plant extracts exhibit potent antibacterial effects through the generation of reactive oxygen species, membrane disruption, and inhibition of bacterial growth. (55)

Nanotechnology also improves the effectiveness of phytoconstituents in fighting biofilm because of enhanced permeability through mature biofilms and sustained drug release at the infected sites. Hybrid nanocomplexes formulated from phytoconstituents and metallic nanoparticles are more effective in antibacterial therapy than the use of free phytoconstituents and have potential of circumventing bacterial resistance with reduced doses. Therefore, phytoconstituent based nanocomplexes are a promising approach to the formulation of safe and effective antibacterial drugs. (56)

5.Inflammatory Conditions

Inflammation is one of the main pathological conditions in several chronic ailments like arthritis, inflammatory bowel disease (IBD), psoriasis and other autoimmune disorders. Despite the powerful antioxidant and anti-inflammatory effects of phytoconstituents such as curcumin, quercetin, resveratrol, rutin and piperine, their medical usage is limited because of problems in solubility, bioavailability, metabolic rates and inability to accumulate at inflamed tissue sites. Nanoformulation methods have therefore been employed in an attempt to address these issues and increase therapeutic effectiveness of phytoconstituents. (1)

Several types of nanocomplexes that include lipid nanoparticles, polymeric nanoparticles, nanogels, dendrimers and metal-organic framework (MOF) based nanoparticles have been considered for the targeted delivery of anti-inflammatory phytoconstituents. These nanocarriers protect encapsulated compounds from premature degradation, prolong circulation time and ensure sustained drug release at the site of inflammation improving the therapeutic action. (57)

MOF-based nanoformulations encapsulating phytoconstituents such as rutin and piperine have demonstrated enhanced anti-inflammatory activity by reducing oxidative stress, leukocyte infiltration, and tissue edema in preclinical models. Likewise, folate-functionalized nanoparticles selectively target activated inflammatory cells, improving drug accumulation at inflamed tissues while minimizing systemic adverse effects. Such targeted delivery has shown promising results in experimental models of arthritis and other chronic inflammatory disorders. (58)

In addition, nanogels and dendrimer-based nanocomplexes provide high drug-loading capacity and enable the simultaneous delivery of multiple phytoconstituents for combination therapy. For example, curcumin-loaded dendrimers have been reported to significantly reduce the expression of pro-inflammatory cytokines, including TNF-α and IL-6, thereby attenuating inflammation in inflammatory bowel disease models. Overall, phytoconstituent-based nanocomplexes offer an effective strategy for improving the safety, bioavailability, and therapeutic efficacy of natural anti-inflammatory agents in the management of chronic inflammatory diseases. (59)

Challenges Faced by Phytoconstituent Nanocomplexes (60)

Although nanotechnology has made significant improvements in the efficacy of phytoconstituents owing to increased solubility, stability, bioavailability, and targeted delivery, many problems still exist that prevent their efficient translation into clinical practice. Some of the factors contributing to these problems include complicated formulations, inability to produce them on a large scale, concerns about safety, regulatory issues, and expensive manufacturing processes.

1.Limited Drug Loading and Encapsulation Efficiency: Phytoconstituent encapsulation efficiency depends on the physicochemical nature of both the active agent and the nano-carrier system. Phytochemicals that are either highly hydrophilic or lipophilic can pose problems for drug loading efficiencies, which may impact efficacy. Moreover, early leakage of drugs while in storage is another issue that may affect efficacy.

2. Stability During Storage: Nanocomplexes are known to be sensitive to particle agglomeration, drug release, oxidation, and particle size alterations with prolonged storage time. External environmental conditions like temperature, pH, moisture, and exposure to light can further affect the stability of the formulation, thus limiting shelf-life and efficacy.

3. Toxicity and Biocompatibility Concerns: While most nanocarriers are synthesized by biocompatible materials, some synthetic polymers, surfactants, metal nanoparticles, and surface modifying agents could be cytotoxic, oxidative, and elicit an undesirable immune response. Toxicological assessment is critical to establish clinical utility.

4. Scale-Up and Manufacturing Challenges: Though most plant extract nanoparticles have been successfully produced in laboratories, there is still difficulty in achieving uniformity in particle size and drug loading during their production on an industrial scale.

5.Regulatory and Quality Control Issues: The lack of standardized regulations for nanomedicines is a significant hindrance to their commercialization process. Differentiation in the methods used to characterize, evaluate quality, and conduct safety assessments causes complications in regulation across various nations.

6. High Production Cost

The preparation of advanced nanocomplexes often requires specialized equipment, high-purity raw materials, and sophisticated manufacturing techniques. These factors increase production costs and may limit their affordability for routine clinical use.

7. Limited Clinical Translation: Most phytoconstituent-loaded nanocomplexes have demonstrated promising results in laboratory and animal studies; however, relatively few have progressed to human clinical trials. Insufficient long-term safety data, manufacturing challenges, and regulatory complexities continue to delay their clinical translation.

Future Perspectives of Phytoconstituent-based Nanocomplexes

The future of phytoconstituent-based nanocomplexes is highly promising due to rapid advances in nanotechnology, biomaterials, and precision medicine. Continued research is expected to address the current limitations associated with safety, large-scale production, and clinical application, thereby improving the therapeutic potential of plant-derived bioactive compounds. In the future, nanocomplexes will use the stimuli-responsive system which will release the phytoconstituents specifically triggered by certain stimuli, such as pH value, temperature, enzymes, and redox condition. Personalized nanomedicine will help develop personalized treatment with taking into consideration the genetic profile and disease manifestations. Moreover, surface functionalization of nanocomplexes with ligands, antibodies, peptides, and aptamers will improve tissue-targeting, facilitate the accumulation of drugs in the disease area, and prevent off-target actions. Combination of phytoconstituent nanocomplexes with advanced technologies, namely, gene therapy, RNA-based therapy, and immunotherapy, can bring synergy benefits especially in cancer, neurological, and inflammatory diseases treatment. (4)

The future research is also anticipated to focus on environmentally safe and sustainable synthetic procedures employing biodegradable materials and plant-based approaches for the development of safer and more economical nanocarriers. Nanocomplexes having ability to bypass physiological barriers like GI tract and the blood brain barrier will enhance the scope of use of phytoconstituents in systemic and neurological diseases. Standardization and scalability in the manufacturing process will also become critical for commercial production of these nanoformulations. Studies focusing on toxicity, pharmacokinetic, pharmacodynamic properties, biodegradation and immunogenicity are critical in order to determine their safety profile. Establishment of guidelines for quality control and characterization will help in their approval and commercialization. Despite the fact that most phytoconstituent loaded nanocomplexes have shown promising preclinical results, clinical trials are still needed to validate their efficacy and safety in humans. Furthermore, the incorporation of artificial intelligence and machine learning in the formulation development process will aid in the quick optimization of nanocomplex formulations, prediction of the drug-carrier interaction, and enhanced formulation performance. It is expected that the future multifunctional nanotechnology platforms that incorporate diagnostic and therapeutic aspects will allow for the diagnosis of diseases, drug delivery, and treatment response monitoring simultaneously. (61)

V. CONCLUSION

Phytoconstituents possess remarkable therapeutic potential; however, their clinical application is often limited by poor solubility, low bioavailability, rapid metabolism, and inadequate targeted delivery. This review highlights the role of nanocomplexes in overcoming these limitations by enhancing the stability, bioavailability, controlled release, and site-specific delivery of plant-derived bioactive compounds. A number of nanocarriers such as liposome nanoparticles, polymeric nanoparticles, nanoemulsions, solid lipid nanoparticles, nanostructured lipid carriers, dendrimers, nanogels, and metallic nanoparticles have been found to hold great potential in increasing the therapeutic properties of phytoconstituents. Moreover, nanoformulations have shown promising applications in the management of cancer, diabetes, cardiovascular diseases, neurological disorders, inflammatory conditions, and microbial infections by improving efficacy while minimizing systemic toxicity. Despite encouraging preclinical and emerging clinical evidence, challenges related to large-scale production, long-term safety, regulatory approval, and commercialization remain to be addressed. Overall, the integration of phytoconstituents with nanotechnology has opened new avenues for the development of efficient drug delivery systems, providing improved therapeutic performance and promising opportunities for future clinical applications.

REFERENCES

[1] Ansari, P., Reberio, A. D., Ansari, N. J., Kumar, S., Khan, J. T., Chowdhury, S., Mohamed, F., El-Mordy, A., Hannan, J., Flatt, P., Abdel-Wahab, Y., & Seidel, V. (2025). Therapeutic Potential of Medicinal Plants and Their Phytoconstituents in Diabetes, Cancer, Infections, Cardiovascular Diseases, Inflammation and Gastrointestinal Disorders. Biomedicines, 13. https://doi.org/10.3390/biomedicines13020454

[2] Riaz, M., Khalid, R., Afzal, M., Anjum, F., Fatima, H., Zia, S., Rasool, G., Egbuna, C., Mtewa, A. G., Uche, C. Z., & Aslam, M. A. (2023). Phytobioactive compounds as therapeutic agents for human diseases: A review. Food Science & Nutrition, 11, 2500 - 2529. https://doi.org/10.1002/fsn3.3308

[3] Parvin, N., Aslam, M., Joo, S., & Mandal, T. K. (2025). Nano-Phytomedicine: Harnessing Plant-Derived Phytochemicals in Nanocarriers for Targeted Human Health Applications. Molecules, 30. https://doi.org/10.3390/molecules30153177

[4] Kumari, S., Goyal, A., Gürer, E. S., Yapar, E. A., Garg, M., Sood, M., & Sindhu, R. (2022). Bioactive Loaded Novel Nano-Formulations for Targeted Drug Delivery and Their Therapeutic Potential. Pharmaceutics, 14. https://doi.org/10.3390/pharmaceutics14051091

[5] Singh, H., Desimone, M., Pandya, S. R., Jasani, S., George, N., Adnan, M., Aldarhami, A., Bazaid, A. S., & Alderhami, S. A. (2023). Revisiting the Green Synthesis of Nanoparticles: Uncovering Influences of Plant Extracts as Reducing Agents for Enhanced Synthesis Efficiency and Its Biomedical Applications. International Journal of Nanomedicine, 18, 4727 - 4750. https://doi.org/10.2147/ijn.s419369

[6] Jadoun, S., Arif, R., Jangid, N. K., & Meena, R. (2020). Green synthesis of nanoparticles using plant extracts: a review. Environmental Chemistry Letters, 19, 355-374. https://doi.org/10.1007/s10311-020-01074-x

[7] Omar, F., Tareq, A. M., Alqahtani, A., Dhama, K., Sayeed, M., Emran, T., & Simal-Gandara, J. (2021). Plant-Based Indole Alkaloids: A Comprehensive Overview from a Pharmacological Perspective. Molecules, 26. https://doi.org/10.3390/molecules26082297

[8] Losada-Barreiro, S., Celik, S., Sezgin-Bayindir, Z., Bravo-Fernández, S., & Bravo-Díaz, C. (2024). Carrier Systems for Advanced Drug Delivery: Improving Drug Solubility/Bioavailability and Administration Routes. Pharmaceutics, 16. https://doi.org/10.3390/pharmaceutics16070852

[9] Liu, Y., Liang, Y., Jing, Y., Xin, P., Han, J., Du, Y., Yu, X., Zhu, R., Zhang, M., Chen, W., & Y. (2024). Advances in Nanotechnology for Enhancing the Solubility and Bioavailability of Poorly Soluble Drugs. Drug Design, Development and Therapy, 18, 1469 - 1495. https://doi.org/10.2147/dddt.s447496

[10] Khan, T., & Gurav, P. (2018). PhytoNanotechnology: Enhancing Delivery of Plant Based Anti-cancer Drugs. Frontiers in Pharmacology, 8. https://doi.org/10.3389/fphar.2017.01002

[11] Li, J., Leung, S., Chan, E. H. Y., Jiang, C., Ho, E. Y., & Zuo, Z. (2025). Significantly Increased Aqueous Solubility of Piperine via Nanoparticle Formulation Serves as the Most Critical Factor for Its Brain Uptake Enhancement. International Journal of Nanomedicine, 20, 3945 - 3959. https://doi.org/10.2147/ijn.s506827

[12] Zhao, J., Yang, J., & Xie, Y. (2019). Improvement strategies for the oral bioavailability of poorly water-soluble flavonoids: an overview.. International journal of pharmaceutics, 118642 . https://doi.org/10.1016/j.ijpharm.2019.118642

[13] Zhao, J., Yang, J., & Xie, Y. (2019). Improvement strategies for the oral bioavailability of poorly water-soluble flavonoids: an overview.. International journal of pharmaceutics, 118642 . https://doi.org/10.1016/j.ijpharm.2019.118642

[14] Rana, A., Samtiya, M., Dhewa, T., Mishra, V., & Aluko, R. (2022). Health benefits of polyphenols:

A concise review.. Journal of food biochemistry, e14264 . https://doi.org/10.1111/jfbc.14264

[15] Ashfaq, R., Rasul, A., Asghar, S., Kovács, A., Berkó, S., & Budai-Szűcs, M. (2023). Lipid Nanoparticles: An Effective Tool to Improve the Bioavailability of Nutraceuticals. International Journal of Molecular Sciences, 24. https://doi.org/10.3390/ijms242115764

[16] Vieira, I., Tessaro, L., Lima, A. K. O., Velloso, I. P. S., & Conte-Junior, C. (2023). Recent Progress in Nanotechnology Improving the Therapeutic Potential of Polyphenols for Cancer. Nutrients, 15. https://doi.org/10.3390/nu15143136

[17] Yang, W., Chen, X., Li, Y.-L., Guo, S., Wang, Z., & Yu, X. (2020). Advances in Pharmacological Activities of Terpenoids. Natural Product Communications, 15. https://doi.org/10.1177/1934578x20903555

[18] De Matos, S. P., Teixeira, H., De Lima, Á. A. D., Veiga-Junior, V., & Koester, L. (2019). Essential Oils and Isolated Terpenes in Nanosystems Designed for Topical Administration: A Review. Biomolecules, 9. https://doi.org/10.3390/biom9040138

[19] Sharmila, A., Bhadra, P., Kishore, C., Selvaraj, C. I., Kavalakatt, J., & Bishayee, A. (2025). Nanoformulated Terpenoids in Cancer: A Review of Therapeutic Applications, Mechanisms, and Challenges. Cancers, 17. https://doi.org/10.3390/cancers17183013

[20] Dutt, Y., Pandey, R., Dutt, M., Gupta, A., Vibhuti, A., Raj, V., Chang, C.-M., & Priyadarshini, A. (2023). Liposomes and phytosomes: Nanocarrier systems and their applications for the delivery of phytoconstituents. Coordination Chemistry Reviews. https://doi.org/10.1016/j.ccr.2023.215251

[21] Albertsen, C. H., Kulkarni, J., Witzigmann, D., Lind, M., Petersson, K., & Simonsen, J. (2022). The role of lipid components in lipid nanoparticles for vaccines and gene therapy. Advanced Drug Delivery Reviews, 188, 114416 - 114416. https://doi.org/10.1016/j.addr.2022.114416

[22] Jacob, S., Rao, R., Gorain, B., Boddu, S. H. S., & Nair, A. B. (2025). Solid Lipid Nanoparticles and Nanostructured Lipid Carriers for Anticancer Phytochemical Delivery: Advances, Challenges, and Future Prospects. Pharmaceutics, 17. https://doi.org/10.3390/pharmaceutics17081079

[23] Patel, P., Garala, K., Singh, S., Prajapati, B., & Chittasupho, C. (2024). Lipid-Based Nanoparticles in Delivering Bioactive Compounds for Improving Therapeutic Efficacy. Pharmaceuticals, 17. https://doi.org/10.3390/ph17030329

[24] Wang, S., Chen, Y., Guo, J., & Huang, Q. (2023). Liposomes for Tumor Targeted Therapy: A Review. International Journal of Molecular Sciences, 24. https://doi.org/10.3390/ijms24032643

[25] Nyamba, I., Sombié, C., Yabré, M., Zimé-Diawara, H., Yameogo, J., Ouédraogo, S., Lechanteur, A., Semdé, R., & Evrard, B. (2024). Pharmaceutical approaches for enhancing solubility and oral bioavailability of poorly soluble drugs.. European journal of pharmaceutics and biopharmaceutics : official journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik e.V, 114513 . https://doi.org/10.1016/j.ejpb.2024.114513

[26] Mehta, M., Bui, T. A., Yang, X., Aksoy, Y. A., Goldys, E., & Deng, W. (2023). Lipid-Based Nanoparticles for Drug/Gene Delivery: An Overview of the Production Techniques and Difficulties Encountered in Their Industrial Development. ACS Materials Au, 3, 600 - 619. https://doi.org/10.1021/acsmaterialsau.3c00032

[27] Elmowafy, M., Shalaby, K., Elkomy, M. H., Alsaidan, O., Gomaa, H., Abdelgawad, M., & Mostafa, E. M. (2023). Polymeric Nanoparticles for Delivery of Natural Bioactive Agents: Recent Advances and Challenges. Polymers, 15. https://doi.org/10.3390/polym15051123

[28] Beach, M. A., Nayanathara, U., Gao, Y., Zhang, C., Xiong, Y., Wang, Y., & Such, G. K. (2024). Polymeric Nanoparticles for Drug Delivery. Chemical Reviews, 124, 5505 - 5616. https://doi.org/10.1021/acs.chemrev.3c00705

[29] Tang, Z., He, C., Tian, H., Ding, J., Hsiao, B., Chu, B., & Chen, X. (2016). Polymeric nanostructured materials for biomedical applications. Progress in Polymer Science, 60, 86-128. https://doi.org/10.1016/j.progpolymsci.2016.05.005

[30] Harwansh, R., Deshmukh, R., & Rahman, A. (2019). Nanoemulsion: Promising nanocarrier system for delivery of herbal bioactives. Journal of Drug Delivery Science and Technology. https://doi.org/10.1016/j.jddst.2019.03.006
[31] Wilson, R. J., Li, Y., Yang, G., & Zhao, C. (2021). Nanoemulsions for drug delivery. Particuology. https://doi.org/10.1016/j.partic.2021.05.009
[32] Montoto, S. S., Muraca, G., & Ruiz, M. E. (2020). Solid Lipid Nanoparticles for Drug Delivery: Pharmacological and Biopharmaceutical Aspects. Frontiers in Molecular Biosciences, 7. https://doi.org/10.3389/fmolb.2020.587997
[33] Khan, S., Sharma, A., & Jain, V. (2022). An Overview of Nanostructured Lipid Carriers and its Application in Drug Delivery through Different Routes. Advanced Pharmaceutical Bulletin, 13, 446 - 460. https://doi.org/10.34172/apb.2023.056
[34] Mall, J., Naseem, N., Haider, M. F., Rahman, M. A., Khan, S., & Siddiqui, S. N. (2024). Nanostructured lipid carriers as a drug delivery system: A comprehensive review with therapeutic applications. Intelligent Pharmacy. https://doi.org/10.1016/j.ipha.2024.09.005
[35] Wang, J., Li, B., Qiu, L.-G., Qiao, X., & Yang, H. (2022). Dendrimer-based drug delivery systems: history, challenges, and latest developments. Journal of Biological Engineering, 16. https://doi.org/10.1186/s13036-022-00298-5
[36] Chauhan, A. (2018). Dendrimers for Drug Delivery. Molecules : A Journal of Synthetic Chemistry and Natural Product Chemistry, 23. https://doi.org/10.3390/molecules23040938
[37] Delgado-Pujol, E. J., Martínez, G., Casado-Jurado, D., Vázquez, J., León-Barberena, J., Rodríguez-Lucena, D., Torres, Y., Alcudia, A., & Begines, B. (2025). Hydrogels and Nanogels: Pioneering the Future of Advanced Drug Delivery Systems. Pharmaceutics, 17. https://doi.org/10.3390/pharmaceutics17020215
[38] Yin, Y., Hu, B., Yuan, X., Cai, L., Gao, H., & Yang, Q. (2020). Nanogel: A Versatile Nano-Delivery System for Biomedical Applications. Pharmaceutics, 12. https://doi.org/10.3390/pharmaceutics12030290
[39] Soni, V., Raizada, P., Singh, P., Cuong, H., S., R., Saini, A., Saini, R., Van Le, Q., Nadda, A., Le, T., & Nguyen, V. (2021). Sustainable and green trends in using plant extracts for the synthesis of biogenic metal nanoparticles toward environmental and pharmaceutical advances: A review.. Environmental research, 111622 . https://doi.org/10.1016/j.envres.2021.111622
[40] Hammami, I., Alabdallah, N., Jomaa, A. A., & Kamoun, M. (2021). Gold nanoparticles: Synthesis properties and applications. Journal of King Saud University - Science, 33, 101560. https://doi.org/10.1016/j.jksus.2021.101560
[41] Jangid, H., Singh, S., Kashyap, P., Singh, A., & Kumar, G. (2024). Advancing biomedical applications: an in-depth analysis of silver nanoparticles in antimicrobial, anticancer, and wound healing roles. Frontiers in Pharmacology, 15. https://doi.org/10.3389/fphar.2024.1438227
[42] Devi, H., Boda, M. A., Shah, M. A., Parveen, S., & Wani, A. (2018). Green synthesis of iron oxide nanoparticles using Platanus orientalis leaf extract for antifungal activity. Green Processing and Synthesis, 8, 38 - 45. https://doi.org/10.1515/gps-2017-0145
[43] Nikolova, M., & Chavali, M. (2020). Metal Oxide Nanoparticles as Biomedical Materials. Biomimetics, 5. https://doi.org/10.3390/biomimetics5020027
[44] García-Oliveira, P., Otero, P., Pereira, A., Chamorro, F., Carpena, M., Echave, J., Fraga-Corral, M., Simal-Gandara, J., & Prieto, M. (2021). Status and Challenges of Plant-Anticancer Compounds in Cancer Treatment. Pharmaceuticals, 14. https://doi.org/10.3390/ph14020157
[45] Din, F., Aman, W., Ullah, I., Qureshi, O. S., Mustapha, O., Shafique, S., & Zeb, A. (2017). Effective use of nanocarriers as drug delivery systems for the treatment of selected tumors. International Journal of Nanomedicine, 12, 7291 - 7309. https://doi.org/10.2147/ijn.s146315
[46] Wahi, A., Bishnoi, M., Raina, N., Singh, M., Verma, P., Gupta, P. K., Kaur, G., Tuli, H., & Gupta, M. (2023). Recent updates on nano-phyto-formulations based therapeutic intervention for cancer treatment. Oncology Research, 32, 19 - 47. https://doi.org/10.32604/or.2023.042228
[47] Hesari, M., Mohammadi, P., Khademi, F., Shackebaei, D., Momtaz, S., Moasefi, N., Farzaei, M., & Abdollahi, M. (2021). Current Advances in

the Use of Nanophytomedicine Therapies for Human Cardiovascular Diseases. International Journal of Nanomedicine, 16, 3293 - 3315. https://doi.org/10.2147/ijn.s295508
[48] Yang, F., Xue, J., Wang, G., & Diao, Q. (2022). Nanoparticle-based drug delivery systems for the treatment of cardiovascular diseases. Frontiers in Pharmacology, 13. https://doi.org/10.3389/fphar.2022.999404
[49] Liu, Y., Li, C., Yang, X., Yang, B., & Fu, Q. (2024). Stimuli-responsive polymer-based nanosystems for cardiovascular disease theranostics.. Biomaterials science. https://doi.org/10.1039/d4bm00415a
[50] Moradi, S. Z., Momtaz, S., Bayrami, Z., Farzaei, M., & Abdollahi, M. (2020). Nanoformulations of Herbal Extracts in Treatment of Neurodegenerative Disorders. Frontiers in Bioengineering and Biotechnology, 8. https://doi.org/10.3389/fbioe.2020.00238
[51] Mishra, K., Rana, R., Tripathi, S., Siddiqui, S., Yadav, P., Yadav, P., & Chourasia, M. K. (2023). Recent Advancements in Nanocarrier-assisted Brain Delivery of Phytochemicals Against Neurological Diseases. Neurochemical Research, 48, 2936 - 2968. https://doi.org/10.1007/s11064-023-03955-3
[52] Naqvi, S., Panghal, A., & Flora, S. (2020). Nanotechnology: A Promising Approach for Delivery of Neuroprotective Drugs. Frontiers in Neuroscience, 14. https://doi.org/10.3389/fnins.2020.00494
[53] Susanti, D., Haris, M. S., Taher, M., & Khotib, J. (2022). Natural Products-Based Metallic Nanoparticles as Antimicrobial Agents. Frontiers in Pharmacology, 13. https://doi.org/10.3389/fphar.2022.895616
[54] Sharma, D., Gautam, S., Singh, S., Srivastava, N., Khan, A., & Bisht, D. (2025). Unveiling the nanoworld of antimicrobial resistance: integrating nature and nanotechnology. Frontiers in Microbiology, 15. https://doi.org/10.3389/fmicb.2024.1391345
[55] Almomani, H., Massadeh, M. I., Almasri, M., Balawi, D. A., Aolymat, I., Hamed, S., Albiss, B., Ibrahim, L., Balawi, H. A., & Mahmoud, S. A. H. A. (2024). Anti-Bacterial Activity of Green Synthesised Silver and Zinc Oxide Nanoparticles against Propionibacterium acnes. Pharmaceuticals, 17. https://doi.org/10.3390/ph17020255
[56] Nandi, S., & Basu, T. (2022). Nano-Antibacterials Using Medicinal Plant Components: An Overview. Frontiers in Microbiology, 12. https://doi.org/10.3389/fmicb.2021.768739
[57] Conte, R., Marturano, V., Peluso, G., Calarco, A., & Cerruti, P. (2017). Recent Advances in Nanoparticle-Mediated Delivery of Anti-Inflammatory Phytocompounds. International Journal of Molecular Sciences, 18. https://doi.org/10.3390/ijms18040709
[58] Plachá, D., & Jampílek, J. (2021). Chronic Inflammatory Diseases, Anti-Inflammatory Agents and Their Delivery Nanosystems. Pharmaceutics, 13. https://doi.org/10.3390/pharmaceutics13010064
[59] Jogpal, V., Sanduja, M., Dutt, R., Garg, V., & T. (2022). Advancement of nanomedicines in chronic inflammatory disorders. Inflammopharmacology, 30, 355 - 368. https://doi.org/10.1007/s10787-022-00927-x
[60] Teja, P. K., Mithiya, J., Kate, A. S., Bairwa, K., & Chauthe, S. (2021). Herbal nanomedicines: Recent advancements, challenges, opportunities and regulatory overview.. Phytomedicine : international journal of phytotherapy and phytopharmacology, 96, 153890 . https://doi.org/10.1016/j.phymed.2021.153890
[61] Petrović, S., Bita, B., & Barbinta-Patrascu, M. (2024). Nanoformulations in Pharmaceutical and Biomedical Applications: Green Perspectives. International Journal of Molecular Sciences, 25. https://doi.org/10.3390/ijms25115842