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CHAPTER 1

Pharmaceutical Nanosciences and their Application in the Delivery of Various Phytoconstituents

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Abstract: Nanoscience provides numerous opportunities for pharmaceutical scientists. Due to the continuing progress of nanoparticle-based medicines, the opportunity to treat and combat difficult diseases, especially with herbal remedies, can be achieved. The use of herbs is effective when their active constituents reach the intended target. However, the flavonoids, tannins, and terpenoids present in herbs are hydrophilic and unable to pass through cell lipid membranes. Therefore, their absorption is poor,resulting in reduced availability and biological efficacy, increased dosage, andfrequency of use. Nanoengineering has verified that nanoparticles have significantpotential as drug carriers. Size reduction methods and technologies produce a widevariety of nanostructures, which are indicative of specific physicochemical and biological properties. This delivery system plays an essential role in increasing thesolubility, bioavailability, pharmacological effect, stability, effectiveness, selectivity, and drug specificity of its bioactive constituents. Nanoscale models such as phytosomes, liposomes, nanoemulsions, nanoparticles, solid lipid nanoparticles, andethosomes are used to deliver various bioactive constituents at adequate doses to thetarget during the entire treatment period. Phospholipid complex techniques have recently been introduced to overcome these barriers either by enhancing theirdissolving capacity or their potential ability to traverse biological membranes andprotect the active herbal constituents against degradation. Therefore, this chapterdiscusses the application of nanoscience for delivering various phytoconstituents inorder to achieve therapeutic targets.

Keywords: Herbal medicine, Nanotechnology, Phytoconstituents.

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INTRODUCTION

Nanotechnology is a science that changes the dimensions of matter at the nanoscale level. Recently, this branch of science has been indispensable to the pharmaceutical and drug industries because of its potential to play a crucial role in improving human life. These scientific applications are related to the medicalfield and include the therapeutic applications of drug delivery, enhancing drug efficacy, reducing side effects, and improving circulation and stability [1]. The majority of phytoconstituents are declared active if they are proven to have a confirmed impact on the treatment of specific diseases or pain relief and are classified as organic constituents. The active organic constituents demonstrate lowbioavailability while being predominantly non-water soluble, unstable, and the most toxic.

Nanoparticles are frequently used as therapeutic and diagnostic agents because of their advanced and essential drug delivery systems. For example, materials incorporating protein or nucleic acids require a carrier system that potentially enhances their effectiveness and shields them from undesired decreation [2]. The potency of the drug nanoparticle delivery system is directly associated with its small particles and huge surface area, thus indicating increased solubility and the capacity to pass through the blood-brain barrier (BBB), enter the respiratorysystem, and be captivated across the close connections of skin epithelial tissue cells [3].

Formulations based on herbal medicines or their active phytoconstituents remain subjected to numerous limitations [4]. Nevertheless, they are considered a major source because of their less severe side effects compared to those of synthetic drugs and the deep-seated public belief in their ability to cure or prevent various diseases. Several methods are employed to overcome these limitations, including dissolving in non-polar solvents, making injection preparations, and increasing their solubility by changing the active phytoconstituents into their salt form.These methods have several drawbacks, such as high solvent toxicity, their uncertain activity when in salt form, the presence of bioactive drug forms, and the lack of bioavailability. Consequently, special technology, namely nanotechnology, needs to be employed as a solution. With the application of nanotechnology, herbal medicines can deliver their active phytoconstituents to specific targets. These nanoparticle techniques are designed and delivered with various sizes, forms, compositions, functions, and physical/chemical modifications to suit the distinctiveness of the targeted organs and the specific drug used. The dosage forms of nanoparticles include fullerenes, emulsions, microemulsions, liposomes, liquid crystals, dendrimers, quantum dots, nanoparticles, gels, solid lipid nanoparticles, among others. This chapter will,

therefore, briefly focus on herbal medicine nanoparticles to overcome several formulation deficiencies associated with phytoconstituents in herbs.

PHYTOCONSTITUENTS IN HERBAL MEDICINE

Phytoconstituents found in herbs are commonly referred to as secondary metabolites, namely phenolics, terpenoids, alkaloids, and anthraquinones. These compounds have high curative value, but their bioavailability and solubility are low, while their toxicity and instability may hinder their medicinal use [5].

Phenolic

Almost all plants contain phenolic compounds which are aromatic in character and contain more than one hydroxyl substituent. The main compounds are phenols, many of which are found in polyphenols, and among which more than 8,000 compounds have been identified. Based on their primary chemical structures, polyphenols are divided into stilbenes, phenolic acids, flavonoids, and lignans. Flavonoids are one of the naturally occurring polyphenols, with morethan 6,000 compounds being identified. They include flavones, flavonols, flavans,flavanones, dihydroflavanols, isoflavons, and biflavones [6]. Compounds within this class execute a protective function against free radicals, cardiovascular disease, cancer, inflammation, microbial contamination, viruses, allergies, and ulcers, among other diseases [7]. Other phenolic compounds include quinones, xanthones, coumarins, polymer lignins, and tannins. Phenylpropanoid dimers or lignans containing two C6-C3 bound by C-8 carbon centres have antiviral, anticancer, anti-inflammatory, antimicrobial, antioxidant, immunosuppressive, and hepatoprotective properties and are used in osteoporosis prevention [8].

Polyphenols have properties that are challenging to address due to the presence of several phenyl rings in the compound, the number of hydroxyl groups in the aromatic cycle, and the bioavailability of polyphenols in food that depends on pre- and post-harvest conditions and interactions with other compounds. Since these class compounds demonstrate extremely limited absorption ability, poor solubility in water, and rapid metabolism, they need to be made into several types of pharmaceutical formulations with the potential to increase bioavailability. Certain polyphenols have low stability and, therefore, selecting the liposome form for polyphenol encapsulation is considered appropriate. However, it is also important to note the characteristics of each polyphenol, which have various molecular structures within which the ring and hydroxyl numbers affect their solubility [7]. One example is that of a podophyllotoxin employed as an anti-mitotic whose high toxicity limits its use [9]. To overcome this problem, modification of the podophyllotoxin structure is undertaken in the hope that its toxicity will be reduced.

Resveratrol is a polyphenol compound contained in *Vitis vinifera*, labrusca, and muscadine [10], which possesses anti-oxidant, anti-cancer, anti-inflammatory, and cardioprotective properties [11]. Due to being moderately water-soluble, resveratrol demonstrates full bioavailability, photosensitivity [12], and rapid metabolism [13]. Multiple nanoencapsulation of resveratrol, polymer nanoparticles, Zein-based nanoparticles, nanoemulsions, liposomes, cyclodextrins, and resveratrol have been reported to enhance bioavailability and pharmacokinetics [14 - 19]. The polyphenol will improve solubility and chemical stability if formulated with dipalmytoyl-phosphatidylcholine or distearoyl-phosphatidylethanolamine-polyethylene glycol 2000. It also prolongs efficacy andimproves protection from UV B when combined with P90G or dicetyl phosphate [7].

Curcumin (diferuloyl-methane) is moderately soluble in water, has low bioavailability and is produced in the formulation of liposomes, phospholipid vesicles, and polymer-based nano formulations [20, 21]. Oral bioavailability is nine times higher when curcumin is combined with piperine, which functions asan absorption enhancer [22]. In addition, curcumin colloid nanoparticles(theracurmin) are 27 times more effective and can inhibit alcohol poisoning [23]. Curcumin formulated in liposomes using soybean phosphatidylcholine, film hydration, and extruction (MLV) will prolong the antioxidant protective effect.On the other hand, when formulated using dimyristoyl phosphatidylglycerol and lyophilisate, it enhances the bioavailability while reducing the incidence of protease cancer and exerting an antiangiogenic effect [7].

Quercetin, a natural flavonoid in various vegetables and fruits, is 100 times more water-soluble after being formulated as a polymer nanoparticle suspension dosage form [24]. Ampelopsin, produced from *Ampelopsis grossedentata,* has anti-oxidant, anti-inflammatory, anti-hypertensive, anti-microbial, hepatoprotective, anti-carcinogenic properties, and cough-relieving effects. This compound is moderately water-soluble with very low permeability and is consequently packaged in microemulsions to increase bioavailability, solubility, and penetration [25]. Quercetin is formed in liposomes using dipalmytoyl-phosphatidylcholineand lecithin that increases solubility, bioavailability, and anti-tumor and antioxidant properties [7]. *Origanum dictamnus* extract contains anti-oxidant and anti-microbial substances due to large amounts of coumarin and flavones, which are formed into liposomes to increase their activity [26].

Encapsulation, which protects phytoconstituents, can be used to reduce the instability of the active ingredient, retard its degradation, and increase activity. For example, quercetin formed in liposomes with PEG in plasma has a life span exceeding five hours [27], whereas quercetin formulated in polymer nanoparticles

form demonstrates increased anti-oxidant activity, while quercetin encapsulated in Eudragite nanoparticles (polymer nanoparticles) is very stable [28].

Certain other polyphenols, such as catechin, fisetin, dehydro-silymarin, and silymarin, increase bioavailability, solubility, chemical stability, while several activities in liposome form use epikuron/Tween, dioleoyl phophatidylchooline/PEG 2000, soybean phosphatidylcholine, lecithin, and mannitol [7].

The application of a lipid bilayer in liposomes increases catechin permeability. It occurs because of the geometric relationship between lipids in liposomes and insoluble encapsulation drugs (catechins) [7]. To date, no system has generalized the composition and encapsulation of lipids. A significant body of research has concentrated on the modification of liposome surfaces and their composition in enhancing the incorporation of insoluble drugs and well-defined target locations.

Terpenoid

Terpenoids represent the most widespread group of natural compounds, with morethan 40,000 having been identified so far. In general, the structure of terpenes is formed from isoprene units with its constituent groups in the form of cyclic unsaturated hydrocarbons at varying degrees of oxygen. Terpenoids are grouped on the basis of the number of isoprene units; monoterpenes (one isoprene), sesquiterpenes, diterpenes (two isoprenes), sesquiterpenes, triterpenes (three isoprenes), and tetraterpenes (four isoprenes). A variety of terpenoids have been found to have anti-cancer, anti-alzheimer [29], anti-microbial, anti-fungal, anti-parasitic, anti-allergic, anti-spasmodic, anti-hyperglycemic, anti- inflammatory, and immunomodulatory properties [30].

Monoterpenes constitute the main class of terpenoids that contain one isoprene unit found in floral aromas, plants containing essential oils, and aromatic plant resins [31], which act as anti-tumor agents. Thymoquinone is an active anti-oxidant, anti-inflammatory, and anti-cancer constituent of *Nigella sativa* [32, 33]. However, the compounds have limitations, such as poor solubility, extreme lipophilicity, and light and heat-instability that hinder pharmaceutical applications. Triterpenoids have more than 90 carbon skeletons with oxidative modification and skeleton glycosidation resulting in greater diversity [34]. Ursolicacid (UA) and oleanolic acid (OA) are natural triterpenoids obtained from no less than 120 plants. OA has hepatoprotective, anti-inflammatory, anti-hyperlipidemic,anti-tumor, and anti-viral qualities, whereas UA has anti-inflammatory, anti- hyperlipidemic, anti-hyperglycemic, hepatoprotective, anti-carcinogenic,neuroprotective, and anti-ulcer properties [35]. Their bioavailability is severely restricted by an extremely limited solubility in water.

Cucurbitacins are bitter, toxic, oxidized tetracyclic triterpenoids. These compounds can be obtained from the Rubiaceae, Cucurbitaceae, Desfontainiaceae, Scrophulariaceae, Begoniaceae, Elaeocarpaceae, Polemoniaceae, Thymelaeaceae, Primulaceae, Brassicaceae, Sterculiaceae, Datiscaceae, and Rosaceae families. These compounds function as heterologous chemical secretions that protect plants from external biological threats [36], and their anti-pyretic, anti-inflammatory, anti-tumor, anti-microbial, and analgesic characteristics are useful [37].

Triptolide is an epoxide diterpenoid isolated from *Tripterygium wilfordii* and useful in treating polycystic kidney diseases, pancreatic carcinoma, autoimmune, rheumatism, leukemia, and psoriasis even though this compound demonstrates poor solubility and high toxicity. Triptolide is prepared in a microemulsion system as poly [DL-lactic acid] [38] nanoparticles, which are biocompatible and biodegradable for transdermal preparations. Since one side effect of Triptolide is irritation of the gastric system, it is encapsulated in SLN to minimize this effect [39].

Cryptotanshinone is a member of the quinoid diterpene class contained in the root of *Salvia miotiorrhiza* Bunge and has applications as an anti-inflammatory, anti-bacterial, cytotoxic, anti-oxidative, anti-angiogenic and anti-parasitic, but has poor bioavailability due to water solubility. The bioavailability of cryptotanshinone administered orally will increase when prepared in solid nano lipid formulation [40].

Thymoquinone is a monoterpene extracted from *Nigella sativa* seeds that have anticancer properties [41], poor solubility, and strong hydrophobicity. The preparation of an encapsulating thymoquinone formula with polymers [42], liposomes [43], and cyclo-dextrin [44] can overcome this problem.

Alkaloid

The structural framework for alkaloids containing nitrogen atoms as part of the heterocyclic ring structure supports significant biological activity, for example, ephedrine for asthma, morphine for analgesics, and vinblastine as an anticancer treatment. The alkaloids, vinblastine, vincristine, and vinorelbine disrupt the microtubule network, causing metaphase capture in dividing cells [45], allowing for the preparation of a controlled release formulation that would endure for a long time. However, these compounds have side effects that include hema tological toxicity, wheezing, dyspnea, vomiting, nausea, constipation, fever, chest pain, and tumors. Investigators have recently reported that the application of liposome nanocarrier preparations of vinca alkaloids alleviates these side effects [45, 46].

Tetrandrine is a bis-benzylisoquinoline alkaloid that induces anti-tumor activity and constitutes a non-selective calcium channel blocker. Since this compound has poor water solubility, its incorporation into the SLN system [47] can improve the formula. Paclitaxel in the gelatin nanoparticle formula is an extremely effective treatment for bladder cancer because the release rate of the active ingredient and its solubility in aqueous media becomes easier [38]. This active ingredient has been certified by the FDA as an effective and non-toxic cancer treatment marketed under the tradename Abraxane.

Anabasine is a piperidine alkaloid derived from the highly toxic *Nicotiana glauca* tree but whose toxicity decreases after formulation with supramolecular nano-encapsulation [48]. Trigonelin is introduced into the chitosan nanoparticles through the formation of an ion complex between the trigonelin's anionic carboxylic acid group and the chitosan cationic amine group to form particles less than 500 nm in size, which inhibit tumor cell invasion [49].

The Epiisopiloturine in *Jaborandi epiisopiloturine* leaves affects adult and young *Schistosoma mansoni* in addition to their eggs and is difficult to dissolve. Therefore, the structure of the liposomes is induced to increase solubility through the addition of dipalmitoylphosphatidylcholine (DPPC)/cholesterol.

Anthraquinone

Anthraquinone constitutes a group of secondary metabolite compounds that occur in abundance in natural materials. Anthraquinones are quinone derivatives of anthracents with a basic structure of 9,10-anthraquinone dicetone. The presence of methoxyl, methyl, hydroxyl, and carboxyl groups attached to the core structure of 9,10-anthracenedione produces anthraquinone derivatives, which have a wide spectrum of medicinal properties [50].

This group contains the largest number of natural pigments, including 700 compounds, 200 of which are isolated from plants (roots, rhizomes, fruits, and flowers), while the rest are derived from mosses and fungi [51]. They are widely employed due to their anti-tumor, anti-inflammatory, diuretic, antiarthritic, antifungal, antibacterial, antimalarial, antioxidant, and laxative properties [52].

Hypericin, a naphthodianthrone (anthraquinone) compound that is a natural photosensitizer, demonstrates high hydrophobicity but limited solubility. The formulation of hypericin solid lipid nanoparticle (Hy-SLN) and the hypericin polymeric nanoparticle suspension is evolved to acquire preferable photodynamic and photoprotection [53].

Photodynamic therapy has many drawbacks, including poor water solubility and photosensitizer drug toxicity; thus anthraquinone derivatives derived from biotechnology and prepared classic nanocapsule formulations containing polycoating (PLGA) are capable of increasing photosensitizer cell uptake while also being non-toxic [54].

Radix rhei contains less efficient rhein, chrysophanol, physcione, emodin, and aloeemodin. These compounds are formulated in the form of liposomes by ethanol injection method with the result that the entrapment efficiency of the liposomal encapsulation is high [55].

NANOTECH FOR THE DELIVERY OF DIFFERENT PHYTOCONSTITUENTS

The problems faced with regard to herbal formulations are those of moderate solubility in water, poor bioavailability, instability, and toxicity. Nanotechnology is effective in overcoming a number of the difficulties arising from the use of both synthetic and natural drug molecules. This technology has produced acceptable formulas, such as embedded active phytochemicals. Various nanoparticle systems such as encapsulation in the nanocarrier system and the deliverance of active compounds have been applied to support formulations. The different kinds of nanoparticles are dendrimers, solid lipid nanoparticles, liposomes, inorganic nanoparticles, microemulsions, polymer nanoparticles, and nanoflora, among others. This combination of technologies is able to achieve the last stage of active compound examination, thus enhancing the healthcare system.

Nano/submicro medicines ranging in size from 1 to 1000 nm, including liposomes, microspheres, solid lipid nanoparticles, nanoemulsions, andmicroemulsions (Fig. **1**), are frequently employed as herbal medicines, both topically and systemically [56]. This system features controlled hydrophobic and hydrophilic drug delivery, high drug-carrying capacity, superior stability [56, 57], higher surface area proportional to volume [57, 58], and has a small size that supports high skin interactions, increases skin penetration and extends the turnover number of molecules to the targeted sites through active targeting [57,59,60]. Numerous nanoparticle systems composed of biodegradable andbiocompatible materials can be applied to encase toxic drugs and transport themto specific sites around the body.

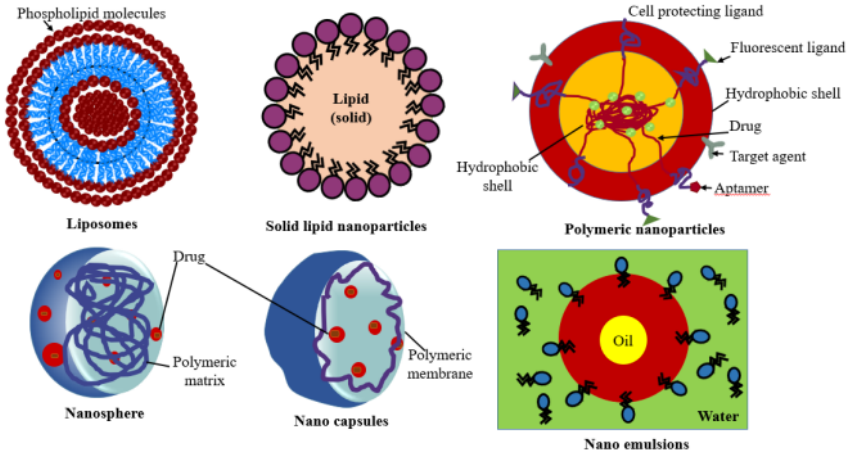

Fig. (1). Overview of nano/sub-microcarriers in herbal medicine [59].

Liposome

Liposomes are tiny vesicles consisting of one or more concentric lipid bilayers (phospholipids) between which an aqueous medium is present. The name 'liposome' is derived from the Greek terms, 'lipo', which means 'fat' and 'soma,' which translates as 'body.' Therefore, liposomes are described as round objects which are predominantly composed of lipids. Liposomes are categorized as cationic, neutral, or anionic because of their type of surface charge. Variations in shape, size and amount of lamellae contained in liposomes lead to their respective classification as unilamellar liposomes (ULs), small unilamellar vesicles (SUV, 25–100 nm), multilamellar vesicles (MLV), large unilamellar vesicles (LUV, 100 nm to 1 m), multivesicular vesicles (MVV). Liposomes are easily produced by disrupting the lipid membrane in an aqueous medium through a sequence of extrusion (sonication) processes combined with a freezing-thaw process.

Liposomes demonstrate strong biocompatibility and can improve physicochemical characteristics in pursuance of their lipid contexture and value. Vesicles are obtained from natural phospholipids that surround the water core. Liposomes are capable of trapping both hydrophilic and lipophilic medications in the aqueous phase and lipidic bilayer with the result that lipophilic drugs will be highlyefficient given the integrity of the membrane bilayer [33]. Plants and phytoconstituents that have been formulated using a liposome system can be seen in Table **1**.

Table 1. Liposome in several plants [4].

Plants	Carrier system	Methods	Effects
Cratylia mollis lectin	Soybean-phosphatidylcholine, cholesterol, and stearylamine	Positively charged surfaces	Degraded toxicity and escalated antitumor activity
Quercetin	Egg phosphatidylcholine & cholesterol	Negatively charged surfaces	Efficiency is between 60%–80%
Silymarin	Lecithin and cholesterol	Reverse evaporation	Improved bioavailability and absorption
Breviscapine	Phosphatidylcholine, cholesterol, phosphatidylglycerol and triolein/ tricaprylin	Double emulsification	Prolonged sustained delivery
Camptothecin	3.5-bis (dodecyloxy) benzoic (PO)-polyethylene glycol	Coating the surface	More efficient
A. arborescens essential oil	Hydrogenated and non-hydrogenated soy phosphatidylcholine	Positively charged MLVs and SUVs	A great ability to entice EO (60%-74%)

Liposomes play an important role as a drug carrier system because they can encapsulate polar and non-polar compounds, are stable, have a lengthy shelf life, are manageable, and their biocompatibility and degradability can be regulated. Specific disadvantages of liposomes are their short half-lives and their vesicle integrity being unsuitable for non-polar drugs. Phytosomes are phospholipids of nanoparticles covalently attached to phytochemicals [61].

Liposomes are flexible because they have a lipid structure that can be adjusted to drugs and a surface that can be converted for a specific target and time. The composition is adjusted to increase drug solubility within the encapsulation system [7].

Microemulsion

Microemulsion (ME) constitutes a fluid system consisting of a simple, transparent emulsion with alcohol or medium chains (hexanol, pentanol) dissolved in an aqueous medium and including surfactants produced by the titration method. The presence of surfactants makes the system conditions thermodynamically stable with internal phase droplets at the nanoscale (10-100 nm). The active ingredients in the ME system will become distinct from the dispersion medium *via* the membrane or interface and transferred to an environment that can improve solubility, modular stability, and bioavailability profile. The increased solubility and stability of ME are capable of delivering active constituents with different levels of lipophilic/ hydrophilicity in the same formulation [62].

An example of the use of microemulsions is that of the triptolide compound contained in the vine *Tripterygium wilfordii* Hook. F (Celastraceae). This plant has anti-inflammatory, anti-neoplastic, anti-fertility, and immunosuppressive properties, but its water solubility is very poor, and it is toxic. It is formulated in isopropyl myristate TP as oil phase, aqueous water phase, and Tween 80: 1,2-propylene glycol as surfactant: co-surfactant in order to increase the permeation profile and anti-inflammatory test [63]. In addition, *Syagrus romanzoffiana* (Cham.) Glassman (Arecaceae) pulp extract is formulated in an o/w nanoemulsion system with squalane as an oil phase and a couple of ethoxylated surfactants with oleic alcohol as non-ionic surfactant, which can increase its antioxidant activity.

Solid Lipid Nanoparticles and Nanostructured Lipid Carriers

Solid lipid nanoparticles (SLN) are colloid vehicle systems (50–1,000 nm) containing pure triglycerides and are combined with other colloid systems (emulsions, liposomes, and polymer nanoparticles) to eliminate shortages of active ingredients [64]. SLN has high physicochemical stability and provides protection against the degradation caused by labile drugs [65]. The resulting structures of this system are solid lipids or mixtures, which are stabilized by surfactants [66].

The nanostructured lipid carrier (NLC) is a colloid system that comprises a lipid and solid-phase mixture to form an irregular liquid lipid matrix, increase the encapsulation efficiency, and minimize the active particle excretion during encapsulation [67]. The solid lipid phases of the NLC system feature glyceryl dilauric, stearic acid, hydrine, cetyl alcohol, and glyceryl monostearate, while the liquid phases involve caprylic/capric acid, oleic acid, and glyceryl monodicaprylic. Generally, the manufacture of NLC systems requires 5% of the active ingredient to form part of the initial precursor mixture in order to produce adrug efficiency of approximately 3%-4% orally and 70% topically [68].

The methods of SLN and NLC formulation include high-pressure homogenization (HPH), emulsification-sonification, microemulsions, and solvent evaporation-emulsification techniques.

- HPH method involves melting the lipids so that the medicine is homogeneously dispersed in the liquid lipid. It is subsequently added to the hot surfactantsolution and homogeneously dispersed (pre-emulsified) by means of a sharp mixer. The nanoemulsion is then cooled at room temperature to form crystals. The cold HPH method is the same as its hot counterpart, but the crystallization process uses liquid nitrogen, rendering this technique safe for hydrophilic or thermolabile drugs.

- The emulsification-sonification method involves dissolving the active ingredient in a thawed solid lipid, adding a warm water surfactant solution, and, finally, dispersing it homogeneously using a high shear mixer. The oil emulsion formed is separated using a sonicator probe according to the nanoemulsion size and then cooled.
- The microemulsion method dissolves the active ingredient in solid lipid and aqueous surfactant/cosurfactant solution that is added during light agitation to produce a clear microemulsion. It is then dissolved in cold water (2-10°C)through light agitation and immediately crystallized to form SLN.
- The solvent-evaporation-emulsifying method works by dissolving lipids in an organic solvent, such as chloroform/cyclohexane, and emulsifying them with aqueous surfactants under continuous stirring.

The results of the utilization of nanostructured lipid carriers and solid lipid nanoparticles in several plants are mentioned in Table **2**.

Table 2. Nanostructured Lipid Carriers and Solid Lipid Nanoparticles in several plants [4].

Constituents	SLN/NLC formulation	Methods	Effects
Quercetin	SLNs (glyceryl monostearate, & soy lecithin)	Emulsification-sonification	Controlled release, increases bioavailability fivefold and enhances absorption within the intestines
	SLNs (glyceryl dibehenate & oleic acid)	Microemulsification	Increases efficiency (92.33%), stability and oral bioavailability
	NLCs (glyceryl monostearate, stearic acid, & soy lecithin)	Emulsion evaporation-sonification	Promotes permeation, increases the number of substances that resist in both epidermis and dermis, and enhances anti-inflammatory and anti-oxidant activities
	NLCs	Probe ultrasonication	Excellent stability
Triptolide (*Tripterygium wilfordii*)	SLNs (tristearin glyceride & stearic acid)	Microemulsification	Improves solubility and absorption into the skin.
Camptothecin	SLNs (cetyl palmitate & polysorbate 80)	Microemulsification	Increases bioavailability
Curcuminoid	SLNs (stearic acid and glyceryl monostearate)	Microemulsification	Improves stability

Inorganic Nanoparticles

Inorganic nanoparticles are present in inorganic compounds such as ceramics, silver, carbon, and gold. These systems are classified as follows:

- Transition metal nanoparticles (Au, Ti, Pt)
  Transition metals serve as medications in cases where excitation by a radiance occurs, which damages DNA and/or modifies proteins, increases lipid peroxidation, and destroys the cell microenvironment causing death. This method can be utilized for the treatment of cancer, carriers of site-specific toxic drugs [69], and potent catalysts.
- Ceramic nanoparticles (oxides, nitrides, and carbides with silica)
  The system can be used as a hollow or core-shell coated with a biodegradable and biocompatible polymer that enhances targeted delivery properties.
- Carbon nanoparticles.

Liquid Crystalline Systems

Liquid crystal (LC) is a distinct phase between crystalline solid and isotropic liquid (mesophase) in the condensed structure. Mesophases, being cubic or hexagonal, are classified into lyotropic liquid crystals (LLCs) and thermotropic liquid crystals (TLC) [70]. TLC is a mesophase molecule that requires a specific temperature to be converted into an isotropic liquid. On the other hand, LLC is an amphiphilic molecule micelle with a tiny polar oxtail (hydrophilic) and a large apolar oxtail (hydrophobic). Mesophase can be identified using low-angle X-ray scattering (SAXS), low-angle neutron scattering (SANS), cryofracture electron microscopy, neutron diffraction, and reflected light microscopy [71].

LC application of herbal medicine is highly advantageous because it is stable, and interacts easily and optimally with specific targets to create a reliable, effective, and safe drug delivery system, whose distribution is even with the selected administration route and has minor side effects [72]. Vegetable oil is the most useful plant component for the development of this LC system because of its low molecular weight and poor viscosity. Vegetable oils produce low occlusion leading to their easy penetration in the skin and increased loading of therapeutic agents [73].

Santos and Rocha-Filho proved the effect of carbon bond length and the number of ethylene oxide groups on the stability of the nonionic emulsion in vegetable oils and recommended the use of such oils derived from apricot (*Prunus armeniaca*), pequi (*Caryocar brasiliense*), avocado (*Persea americana*), cupuassu(*Theobroma grandiflorum*), Brazil nuts (*Bertholletia excelsa*), mari-gold (*C. officinalis),*

andiroba (*Carapa guyanensis*), passion fruit (*Passiflora edulis*), and Buriti (*Mauritia flexuosa*). For the LC lamellar crystal stage, polyoxyethylene stearyl ether (Steareth-2; HLB: 4.7) and polyoxyethylene cetyl stearyl ether (Ceteareth-5; HLB: 9.2) acted as surfactants and distilled water as the waterphase. Liquid crystal systems can be used to overcome formulation limitations in plants and phytoconstituents (Table **3**).

Table 3. Liquid crystalline systems in several plants [4].

Plants	Carrier System	Methods	Effects
Andiroba (*Carapa guyanensis* Aubl.)	• Oily phase: dicetyl phosphate, cetearyl alcohol, ceteth-10 phosphate • Aqueous phase: distilled water & PEG-12 Dimethicone	Silicone (surfactant)	Formulation viscosity, or rheological stability
Peach essential oil (*Prunus persica*)	LCs	Oil in water emulsions (o/w)	Improve physical stability
Annatto oil (*Bixa orellana*)	• Aqueous phase: Distilled water • Surfactant: oleth-20	Hydrophilic/lipophilic balance (HLB)	Constructs LC
Marigold oil (*Calendula officinalis*)	• Aqueous phase: Distilled water • Surfactant: nonionic	HLB	Stable formulation
Marigold oil (*C. officinalis*)	• Aqueous phase: Distilled water • Surfactant:polyoxyethylene alkyl/stearyl ethers	Lamellar LC phases	Stability

POLYMER NANOPARTICLES

Polymer nanoparticles are polymer-based formulations whose biodegradability and biocompatibility render them suitable as drug delivery systems because they are easy to control and target [74]. The colloid system of nanoparticles acts as a vector to manage the drug delivery and target it on a specific location. This system can escalate constituent solubility, reduce the therapeutic dose, and improve the absorption of its active components. This system can be applied tothe blood because it involves non-activate neutrophils, is steady, non- immunogenic, non-toxic, non-thrombogenic, non-inflammatory, and avoids the reticuloendothelial route. Natural ingredients are produced in this system because of their ability to provide several active compounds with a similar carrier, , supplya continuous delivery system, and reduce side effects.

Polymer nanoparticles fall within a diameter scale of 10–1,000 nm to facilitate the release of active substances to the target, increase bioavailability, and mitigate side effects [75]. The shape of the nanoparticles is differentiated according to their composition and structural organization in the form of nanocapsules (NCs) and

nanospheres (NSs). NCs have an oil core and are encased in a polymeric membrane which soaks up the active constituents before they are dispersed throughout the oil base. NSs have a polymer structure that retains or absorbs the active ingredients. The types of polymers widely applied are copolymers with glycolic acid (PLGA) and poly-L-lactic acid (PLA) [76].

The polymer nanoparticle method is categorized as a dispersed monomer method using alkyl cyanoacrylate, *in situ* polymerization method, and polymer deposition methods using polylactic acid-co-glycolic/PLGA, acrylic/methacrylate esters, poly-caprolactone/PCL, polylactic acid/PLA, and methacrylic acid copolymers (Table **4**). The product obtained through the application of these three methods is the aqueous colloid suspension, which has the disadvantage of experiencing precipitation and being physicochemically unstable. This can be overcome by sublimation (freeze-drying) which dehydrates the substance and prevents particle aggregation [74]. Physicochemical characterizations such as morphological assessment, particle size, molecular weight allocation, zeta potential, pH establishment, drug dose in nanostructures, drug delivery kinetics, and long-term stability should be carried out after nanoparticles have been formulated.

Table 4. Polymer Nanoparticles in several plants [4].

Plant/Constituents	Parts	Carrier System	Effects
Phytolacca decandra	Root	PLGA-encapsulated forms (NPD)	Bioavailability is increased, and optimum chemopreventive treatment of lung cancer initiated
Ocimum sanctum	Leaves	Sodium alginate chitosan nanoparticles (OSN)	More effective and durable antimicrobial activity
Curcuma longa (curcumin)	Rhizome	poly(ethylene glycol) mono-acrylate, N-vinyl-2-pyrrolidone, and N-isopropylacrylamide	A significant measured distribution of 50 nm is easily dispersed in aqueous media.
		Encapsulated in PLGA nanospheres	The encapsulation effectiveness is 90.88%, the average particle size is 45 nm and is dissolved in an aqueous without surfactant.
Magnolia officinalis (honokiol)	Bark, leaves	HN-loaded polymeric nanoparticles	Low hydrophobicity and free HN
Gelsemium sempervirens J. St.-Hil (coumarin)	Leaves	Polymeric nanocapsules	Enhanced bioavailability to that of the free active constituent

(Table 4) cont....

Plant/Constituents	Parts	Carrier System	Effects
Harungana madagascariensis Lam. Ex Poir	Leaves	Poly (D,L-lactide-co-glycolide) (PLG) nanoparticles	Bacterial growth is reduced
Cuscuta chinensis Lam.	Seed	Nanosuspension	Antioxidant activity is increased
Ginkgo biloba (quercetin)	Leaves	• Polyvinyl alcohol (PVA) • Eudragit® E (EE) of Nanoprecipitation	Improved yield and the efficiency of encapsulation exceeds 99%.
Camptotheca acuminata Decne (camptothecin)	Bark	Hydrophobically modified glycol chitosan (HGC)	Loading efficiency exceeds 80%
Polygala senega	Rhizome	Encapsulated by PLGA.	Bioavailability is increased

Dendrimers

Dendrimers are branched macromolecules with a highly symmetrical/regular nano-size and a structure both homogeneous and monodispersed. Dendrimers are also described as nano-sized globular molecules possessing unique 3D shapes Fig.(**2**), characterized by low dispersity and multivalence with compositions that can be modified according to the desired purpose. Their structure is divided into core, branched repetitive unit layers, and corona. This drug delivery system is preferred due to its flexibility, shape, functional group, size, and a number of generations. Moreover, it is highly attractive [77].

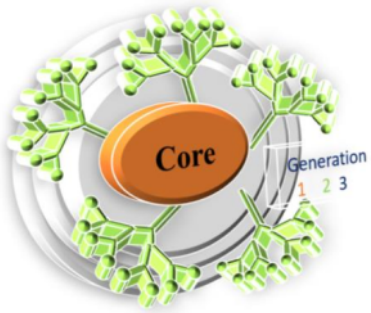

Fig. (2). 3D dendrimer shapes [78].

The mechanism of dendrimer release in drug administration involves the following sequence: (1) drug molecules are trapped in the dendrimer cavity precipitating an increase in hydrophobic molecule solubility, (2) drug molecules are conjugated with functional groups on the outer shell and their delivery rate is controlled. This system has advantages such as the ability to increase the diameter linearly and to

achieve a rounder shape [76]. In addition, dendrimers can prevent Aβ peptide fibrillation by blocking aggregation. This is evidenced by Wasiak *et al*. by modifying the aggregation of Aβ peptide and MAP-Tau protein in cationic phosphorus dendrimers [78]. Both peptides are the main conducive agents for DA. The presence of a desiccant in the dendrimers system may also reduce the toxicity of aggregated Aβ peptides. The formulation of nanoparticles of phytoconstituents can be seen in Table **5**.

Table 5. Nanoparticle formulation on phytoconstituents [79].

Phytoconstituents	Nano/Submicrocarriers	Effects
Curcumin	SLNs	Oral bioavailability is more effective
Curcuminoids	SLNs	The release of curcuminoids as anticancer and antioxidants is prolonged.
Quercetin	Solid lipid nanoparticles SLNs	Five times greater QU-SLN bioavailability
	NLCs	NLCs have a prolonged-release, and high potency for the dermal release system.
	Liposomes	Antioxidant activity is increased, and the drug release is 74 times higher.
Glycyrrhizin acid	Nanoparticles	The bioavailability of anti-inflammatory and antihypertensive activity is improved.
Taxel	Nanoparticles	Continuous blood circulation and huge accumulation in tumors.
Camptothecin	Nanoparticles	Anticancer activity is improved.
Berberine	Nanoparticles	Sustained drug release and anticancer activity (Fukuda).
Silymarin	Liposome	More effective than silymarin suspension
Artemisinin	Nanocapsule	Anticancer activity

THERAPEUTICAL APPLICATION

Nanoparticle drug formulation development has proved beneficial in the treatment of several diseases such as cancer, AIDS and HIV, in addition, to advances in nutraceutical delivery and diagnostic testing. Nanoparticle size varies from 100 to 500 nm. Nanoparticles can be improved to become intelligent systems, excellent therapeutic and imaging packaging agents, and assuming stealth properties by manipulating the size, surface characteristics, and materials used. This system can conduct drugs to the target tissues and provide controlled-release therapy according to a continuous target in order to reduce the degree of drug toxicity and improve patient compliance [80].

Cancer

Cancer is a complex disease that is difficult to cure due to the ability of malignant cells to divide and multiply rapidly and uncontrollably. The types of cancertherapy commonly administered to patients, both through drugs and chemotherapy, produce side effects that destroy normal cells such as those in the intestinal epithelium and hair follicles [81]. Nanoparticle development offers the prospect of a breakthrough in chemotherapy through medication delivery to the site of a tumor or a specific cell group to prevent toxic impact on another healthy organ and other tissues [82]. Micelles represent the optimum means of dissolving an insoluble drug because the nucleus is hydrophobic while the shell is hydrophilic. The PEGylated micelle surface enhances the ability of thenanocarrier to pass through tumor blood vessels and inflamed tissue by passive transport, thereby delivering a higher dose of tumor therapy. Examples of polymermicelles, including anti-cancer medications are NC-6004, NK105, NK012, NK911, SP1049C [83], and Genexol-PM [84].

Dendrimer system-based nanoparticle therapy can increase the cytotoxic drug therapeutic index through the use of biocomponents and the reduction in PEGylation, glycosylation, acetylation, and various amino acids [85, 86]. Nanoparticles, namely carbon nanotubes (CNTs), contain allotropic forms of carbon with a cylindrical frame and a number of sheets in concentric**,** which can be categorized as carbon nanotubes with associated walls (SWCNTs) and multiwalled carbon nanotubes (MWCNTs) [87, 88]. Carbon nanotubes have a highly hydrophobic hollow interior through which water-insoluble medications can easily pass.

Rheumatoid

Rheumatoid arthritis (RA) is an autoimmune inflammatory disease of the joints due to persistent polycarticular inflammation in synovial tissues, which causes progressive deterioration of the articular cartilage and bone [89]. RA occurs due to both genetic and environmental factors [90] and an abnormal immune response leading to synovial inflammation and joint damage.

Currently available pharmaceutical drugs are administered *via* conventional dosage forms and provide therapeutic advantages to only a suboptimal level, thus posing challenges and barriers to the treatment of RA. This requires a new drug delivery strategy design for the development of a useful, targeted and safe drug delivery system with enhanced therapeutic performance [89, 91]. Nanomedicines can act as the carriers of drug delivery for effective RA management because they have unique drug delivery characteristics and are considered a very promising alternative to conventional drug therapy [92]. Among the several available RA

drug delivery routes, topical nanomedicines are more advantageous because of their greater skin retention ability, targeted specific actions, reduced drug doses, lower side effects, increased acceptance, and higher patient adherence [91].

Oral administration of pomegranate extract is an effective treatment for cartilage damage because the extract contains ellagitannins, quercetin, ellagic acid, gallic acid, and polyphenols [93], which support downregulatory activities against JNK-MAPK and NF-jB. Thymoquinone (TQ) from *Nigella sativa* seeds has been shown to produce beneficial effects on inflammatory disorders including IBD,RA, and osteoarthritis [94] through the inhibition of serum IL-1β and TNF-αlevels in RA [95]. Resveratrol is a natural polyphenol compound obtained from grape skin (*Vitis vinifera*) and Polygonum cuspidatum root. Intra-articular resveratrol injection has been demonstrated to have potent effects against arthritis by slowing IL-1-induced apoptosis, ROS, tumor protein (p53), LTB-4, PGE2, andMPPs in animal models [96]. Hesperidin is a citrus flavonoid reported to have therapeutic benefits *vis-a-vis* arthritis through the inhibition of secondary leg swelling and downregulation of TNF-a production, IL-1, and IL-6 [97]. Curcumin is a tetraterpenoid obtained from Curcuma longa, which has anti-inflammatory, antioxidant, and anticancer properties [98]. Green Tea Extract (GTE) produces antiarthritic effects due to the presence of nontoxic epigallocatechin-3 gallate (EGCG) through the inhibition of IL-1-induced delivery of glycosaminoglycans and nitric oxide synthase stimulated by IL-1 (iNOS), nitric oxide, and JNK action [99]. Celastrol is a pentacyclic triterpene of *Trypterygium wilfordii* and has antitumour and anti-inflammatory effects through the downregulation of caspase-1 and inhibition of NF-jb activation [100]. Gambogic acid (GA) is a polyprenylated xanthone containing resin derived from Garcinia hanburyi and Garcinia Morella as an antiarthritic molecule by inhibiting the secretion of IL-1b and TNF. Synomenine is an alkaloid obtained from *Sinomenium acutum*. It is effective for RA therapy by suppressing IL-6, MMP-2, and MMP-9 in an animal model of rheumatism [101]. Centella asiatica contains asiaticoside, madecassoside, centelloside, and asiatic acid (triterpenoids), which are active as anti-inflammatory [102].

The consolidation of phytoconstituents like resveratrol, gambogic acid, thymoquinone, selastrol, hesperidin, curcumin, and polyphenols in a dose-dependent manner has great potential in RA pharmacotherapy through inflammatory mediators such as cytokines, NF-kb, nitric oxide (NO), chemokines, arachidonic acid (AA), adhesion molecules, and lipoxygenase (LOXs). Phytoconstituents have several limitations, such as non-uniform dosage, poor bioavailability, higher metabolism, and greater distribution characteristics. Limited data is available on the concentration of polyphenols in human tissue [103], *i.e.*, 2-20%. The majority of polyphenols are metabolized directly by methylation,

glucuronidation, sulfation, and elimination by the liver, resulting in low bioavailability [103]. Oral administration of cumin causes low plasma levels as opposed to intravenous administration [22]. Resveratrol is metabolized by the small intestines, with its rapid metabolism [104] being detected in serum and plasma at a concentration of 491 90 ng/ml. Quercetin is detectable in plasma in glucuronides and sulfates unconjugated forms [105]. Herbs for RA have limited solubility and permeability, which have a higher metabolism, and have bothunsuitable doses and poor bioavailability [104, 105]. This bioactive incorporation has low water solubility and high metabolism. These drawbacks can be overcome by using nano/submicrocarrier-based drug delivery technology, which maximizes increased bioavailability, greater stability, and greater efficacy without systemic side effects [91].

To overcome the limitations of curcumin, solid lipid nanoparticles are used to effectively lower leg volume through the regulation of the oxide-inflammatory cascade and immunomodulators [106]. The development of proniosomes containing curcumin (curcumin incorporated into a nanoemulsion gel) by the transdermal route can increase skin permeation fourfold [107]. Poly (lactide-c--glycolide) (PLGA) polymer-assisted nanoparticles on thymoquinone increase the entrapment efficiency to 97.5 [108]. Microemulsion-based hydrogel on synomenine is able to suppress leg swelling through the inhibition of TNF-α, IL- 1, and PGE_2 [109]. Total paeony glucoside (TGP) incorporated into the microemulsion can increase poor oral bioavailability (3-4%) [110], leading to stability in GIT [111]. The development of nanosphere-based hydrogels and solid lipid nanoparticles in Tetrandrine has been proven to increase effectiveness [112]. In addition, the ethosome of this compound has a skin permeation of 2.1 times higher than its liposome form [113]. *Tripterygium wilfordii* Hook F (TWHF) containing triptolide (TP) is incorporated into a microemulsion based hydrogel to increase its narrow therapeutic index [114]. The medical nano/submicrons loaded in the phytoconstituent to reduce limitations in RA therapy are mentioned inTable **6**.

Table 6. Nano/submicron loading to reduced limitations on RA therapy [91].

Phytoconstituents	Nano/submicrocarriers	Remarkable Effects
Curcumin	Solid lipid nanoparticles	Extremely effective for the treatment of arthritis in rats by significantly reducing paw volume through the down-regulation of oxide-inflammatory and immune-modulatory cascade
	Nanoemulsion gel	Fourfold higher skin permeation and skin retention compared to curcumin solution in oil
	Proniosomes	Higher permeation through rat skin detected.

(Table 6) cont.....

Phytoconstituents	Nano/submicrocarriers	Remarkable Effects
Thymoquinone	Polymeric nanoparticles	97.5% entrapment efficiency (EE) is achieved. Furthermore, higher potency as compared to thymoquinone alone is obtained.
Sinomenine	Microemulsion-based hydrogel	Greater beneficial effects are produced by suppressing paw swelling through the inhibition of TNF-á, IL-1, and PGE_2
Total glucosides of paeony (TGP)	Microemulsion	Bioavailability and stability-related problems are overcome by micro-emulsion, which also enhances drug stability in GIT and absorption
Tetrandrine	Nanospheres-based hydrogel	Absorption enhanced
	Solid lipid nanoparticles	Absorption enhanced
	Ethosomes	2-to-1 higher skin permeation in comparison to liposomes
Triptolide (TP)	Microemulsion-based hydrogel	High efficacy against RA is achieved. Furthermore, no significant toxicity was discovered during the study.
	SLNs	Rat paw volume is significantly reduced, and a protective effect against hepatotoxicity is achieved

Nutraceutical Delivery

Nutraceuticals are standardized components derived from food and consumed as a complement to allopathic therapies, which provide additional health benefits and reduce the risk of chronic disease [115]. The bioavailability and efficacy of nutraceuticals administered orally are influenced by the interaction of the matrix with food, their solubility in water, epithelial permeability, and degradation/metabolism [116]. They are lipophilic molecules that are soluble in fat (A, D, E, and K), and polyunsaturated lipids. Nanoparticle formulations in nutraceuticals [116, 117] can reduce their limitations, enabling their use as anti-inflammatories, antioxidants, antiapoptotic, and antiangiogenics.

The nanotechnology applications of nutraceutical preparations relate to nutrient delivery, food contact materials, nutrient bioavailability, security devices, sensor diagnostics, vitamin and mineral fortification, and nanoencapsulation of flavor and aromas [118], while a summary of the potential formulations of nutraceuticals as nanomaterials can be seen in Table **7**.

Table 7. Nutraceutical formulations [118].

Phytoconstituents	Nano/submicrocarriers	Remarkable Effects
Hydrophobins (Hyd)- Vitamin D_3	Nanoencapsulation	• A potential nano-transport of hydrophobic nutraceuticals to food beverage enrichment has been discovered using Hyd. • Hyd provides significant vitamin D3 care.
Folic acid with whey protein and commercial resistant starch	Nanoencapsulation	Greater encapsulation efficiency increases folic acid stability. Bioactive stabilization is enhanced.
DL-á-tocopheryl acetate and â-carotene	Pluronic-127 and poly--caprolacotne envelop nanocapsule through emulsification- diffusion method (EDM)	EDM is a promising method for the preparation of nanoparticles for use in food materials
Vitamin D_3 entrapped with whey protein NPs of different calcium concentrations	Nanoencapsulation	Vitamin D3 with significant stability can be used in the clear beverage instead of as an enrichment agent.
Calcium and folic acid	Duel nutraceutical nanomaterial	To provide a good supply of nutrients important to human health
â-carotene, folic acid, curcumin and ergocalciferol	Protein-polysaccharide soluble nanocomplex	To intensify antioxidant activity
Carotenoids	Lipid nanocarriers	The high potency of clinical applications of novel delivery systems for lipophilic plant extracts
CoQ10	Lipid-free nanoformulation	Effective transportation to increase the oral bioavailability of CoQ10
Long-chain fatty acids and CoQ10	Nanoemulsion	Nanoemulsion delivery systems increase the oral bioavailability of lipophilic nutraceuticals
Omega-3-fatty acids and oil-soluble vitamins	Biopolymeric nanogels	• Encapsulation and shield bioactive applied only to food-grade substance • The fabricated system remedies issues surrounding food and beverage quality
Curcumin	Organogel-based nanoemulsion	Digestion of nanoemulsion is rapid and complete The oral bioavailability of curcumin improves Applied to dietary supplements, functional foods, and pharmaceutical industries
á-tocopherol	Supercritical assisted nanosuspension	Improves dissolution rate, bioavailability and stability

(Table 7) cont....

Phytoconstituents	Nano/submicrocarriers	Remarkable effects
(-)-epigalocatechin-3-gallate	Protein-polyphenol coassemblies: Lactoferrin based NPs	• LF-EGCG-nanoparticles and submicrometer have a purpose as EGCG protective transport to supervise other bioactive materials release. • LF-EGCG has the potency to develop food formulation based on LF as a carrier of bioactive constituents
Eugenol and clove oil	COM and EM oil titration–precipitation	The formulation in microemulsion provides an oral delivery system for clove oil in homogenous, water-based, and thermodynamically stable doses
Dextran and isoflavone genistein	Enzymatic-assisted inclusion complexation method	• DMSO-water inclusion protocol is more suitable for delivering genistein into enzymatically hydrolysed dextran • Increase the delivery of nutraceuticals by 11- to 141-fold due to the creation of novel H-bonds and the interaction of Van der Waals forces

The impact of nanotechnology on modern life is both profound and powerful. The technological speed of nanomedicine use is achieved by utilizing several kinds of nanoparticles in the prevention, diagnosis, and treatment of a wide range ofcomplex illnesses.Herbal medicines that had been previously struggled with formulation and delivery of their active ingredients are now starting to use the benefits of nanotechnology.Cosmetochem's Herbasec® has been launched as a liposomal standardized extract for use in cosmetics due to its antioxidant effect in preventing aging. Several other plants are also employed in the production of nanomedicines, such as white hibiscus, green tea, aloe vera, white tea, guarana, and liquorice root. There are also several naturally-produced phytochemicals usedas ingredients of nanomedicines such as triterpenes in *Centella asiatica*, visnadin in *Ammi visnaga*, silymarin and Silybin in milk thistle, vhamitenosides in Hawthorn blossoms, escin ß-sitosterol in horse chestnut, sericoside in *Terminalia sericea*, ginsenosides in *Panax ginseng*, polyphenols in grape seeds and green tea,ginkgo flavon glucosides, ginkgolides, and bilobalide in *Ginkgo biloba* [74]. This proves that phytoconstituents represent the future of nanotechnology related to drug delivery, and a new era of re-exploring and investigating the full potency of traditional herbs has begun. The advantages of nanoscience in analyzing herbal medicines include:

- increased solubility and bioavailability of active ingredients
- reducing the side effects and toxicity of active ingredients
- enhancing the stability of active ingredients with regard to targets

- improving the biocompatibility and reducing the toxicity of the formulations
- increasing nanoparticle safety, and the therapeutic index of the drug

CONCLUSION

Poor absorption of certain phytoconstituents because they are hydrophilic and unable to pass through cell lipid membranes can be overcome by applying nanoengineering such as phytosomes, liposomes, nanoemulsions, nanoparticles, solid lipid nanoparticles, and ethosomes in increasing solubility, bioavailability, pharmacological effect, stability, effectiveness, selectivity, and drug specificity of the bioactive constituents.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

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