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Review Article

SYNERGY OF SCIENCE AND TRADITION: A NANOTECHNOLOGY-DRIVEN REVOLUTION IN NATURAL MEDICINE

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ABSTRACT

Usage of plants to treat various ailments is part and parcel of our tradition and culture. Most marketed formulations are directly or indirectly derived from plants only. Herbal plants are potential therapeutic agents against most life-threatening diseases. Despite these advantages, herbal medicines fail clinical trials due to their low aqueous solubility and low bioavailability. To get the maximum benefits out of herbal plants, we must incorporate medicinal herbs in nanotechnology. The nanotechnology approach not only protects herbal medicines in the body but also aids in delivering the same to the site of action with sustained release. The formulation of herbal nanomedicines will be a breakthrough in treating life-threatening diseases and will also aid in the delivery of drugs that conventionally cannot cross the Blood-Brain Barrier (BBB). The review summarizes the recent advancements of the various nanocarriers loaded with herbal extracts/Phytoconstituents developed to treat various diseases, especially cancer. It also highlights the regulatory requirements for herbal nanomedicines.

Keywords: Formulation, Herbals, Nanomedicine, Permeability, Phytoconstituents, Solubility

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INTRODUCTION

"Herbs, Herbal Materials, Herbal Preparations, and Finished Herbal Products that contain as active ingredients parts of plants, or plant materials, or combinations"-World Health Organization (WHO) [1].

From ages back, flora has been the source of food and the making of daily needy items; from the paper we use to the tables and chairs that we make, it has gained much importance in human life. From ancient times, plants have been used to diagnose and treat various diseases and it is also been used as prophylaxis agent. It is well known in India as the Siddha and Ayurveda System of Medicine [2]. Nowadays herbal medicines are gaining a foothold in the pharmaceutical sector for their enhanced effect and reduced side effects [3]. The importance of THM was derived from years of Experience in drug design and development and it was recognized in the year 2015, The Nobel Prize was awarded to Youyou Tu for identifying Artemisinin, an Antimalarial Compound [4]. Nanoformulations particles range from 100 nm in size. These have gained popularity because of their performance physiochemically and biologically, and they also compact the major drawbacks of the conventional, which are not specific, larger in size, less solubility, and bioavailability. Various nanostructures like polymer nanoparticles, nanoliposomes, nano-micelles, carbon nanotubes, and lipid nanoparticles are now being researched and used widely.

Nanomedicines have been widely used in cancer diagnosis and treatment, from the classical nanoparticles to the recent development of nucleic acid-based nanoconstructs, engineered viral nanoparticles, virus-modified exosomes, extracellular vesicles, and new semiconductors all these have paved the way for the next phase of the nanomedicine [5]. Entirely novel therapeutic and diagnostic modalities emerged as a result of the supramolecular assembly of simpler components which has been developed based on nanotechnology. The recent application of nanomedicine is in immunotherapy, as it has been successful in tumor-targeting and subcellular-targeting. It also can change the way biologics interact with the target immune cells [6].

Though herbal medicines offer massive pharmacological and therapeutic actions, it has limited usage due to numerous disadvantages such as high molecular weight, thereby not crossing lipid membrane, leading to low absorption and bioavailability, reduced efficacy, accumulation in other parts of the body leading to unwanted effects, and degradation easily, which results in poor efficacy and bioavailability [7]. Many herbal medicines are formulated with nanocarriers as it has a unique nature and promising therapeutic action with fewer side effects. It is necessary to formulate herbal medicine with nanocarriers, firstly to prevent the degradation of the former from the acidic environment of the stomach and also to prevent the same from getting metabolized by the liver [8]. Second, both nanomedicine and herbal medicine have similar goals, that is, to reduce adverse reactions and improve therapeutic actions by integrating multiple low-dose therapy to treat diseases, especially cancer. Third, nanomedicine and herbal medicine work in complementary ways; for example, nanotechnology improve the characterization of natural phytoconstituents, on the other hand, there are many barriers in the body to the targeting of nanomedicines in the body, the pathological state or biological microenvironment plays a crucial role in the targeting and this leads to surface modification of nanomedicine and hinders the transport *in vivo.* To compact these issues, traditional medicine practice may be taken as inspiration and regulate the same in the body environment [9].

This article highlights to society that nanotechnology improves the safety and efficacy of herbal medicines. Though it has been used for ages, there are drawbacks which include drug interactions, poor bioavailability, and toxicity; therefore the integration of herbal medicine and nanotechnology will address the drawbacks and will prove to be beneficial to society, especially in cases of diseases that the current treatment strategies are not that very effective. Integrating the two disciplines will increase the therapeutic space and practical demand for the co-application of nanoscience and traditional herbal medicine [10].

The articles selected for the present review article were reviewed from several scholarly databases, such as Taylor and Francis, Elsevier, PubMed, ScienceDirect, Google Scholar, Nature, etc., in chronological order from 2005 to 2023. The search strategy included keywords such as Formulation, Herbals, Nanomedicine, Permeability, Phytoconstituents, Solubility, which are organized in chronological order to structure the review article comprehensively.

Delivery of phytoconstituents using nanocarriers

The nanotechnology strategy to be used to deliver Herbal extracts/Phytoconstituents will improve the efficacy, and reduce the dose and adverse effects [11]. Advantages and disadvantages are listed in table 1. Using the nanocarriers promises activity and reduces the challenges associated with conventional delivery systems. Fig. 1 briefly explains the nanocarriers used to deliver the Herbal extracts/Phytoconstituents. Table 1 represents the advantages and disadvantages of herbal nanomedicines.

Table 1: Advantages and disadvantages of herbal nanomedicines

Merits	Challenges	References
Decreased side effects and adverse consequences.	Challenges in Pharmacology and Safety.	[2]
Enhanced stability.	Herbal nano-formulation's physical stability.	[3]
Increased permeability.	Targeted drug delivery.	[7]
Improved solubility of phytoconstituents.	Difficulties posed by Biological Barriers.	[8]
Bioavailability.	Standardization of Herbal Nano-formulation.	[9]
Controlled release.	Intricate molecular nature of Herbal extracts.	[10]

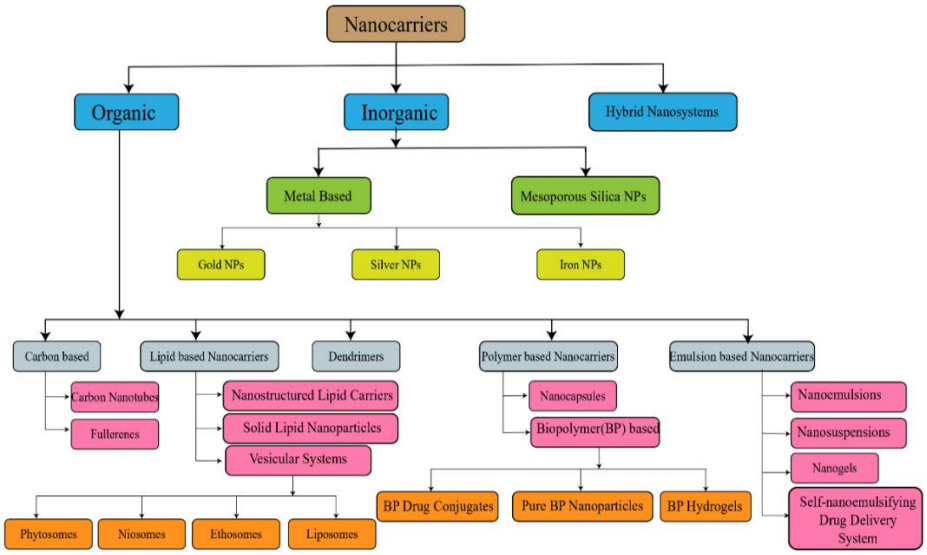

Fig. 1: Nanocarriers used to deliver the herbal extracts/Phytoconstituents [11]

Organic nano-based: carbon-based

Nanotubes

Carbon nanotubes are sheets of graphite rolled up that are tubular and needle-shaped. They can be used as carriers for various proteins, genes, and drugs. They are classified as Single-Walled Carbon Nanotubes and Multi-Walled Carbon Nanotubes [12]. The carbon in the carbon nanotubes shows sp2 hybridization. It is known to have high tensile strength, high surface area, large aspect ratios, elastic in nature, flexibility, and good mechanical strength. The synthesis of CNTs requires vacuum condition, and the methods used for synthesis are, Chemical Vapour Deposition, laser ablation method, plasma-enhanced CVD, Thermal synthesis process, and, discharge method, these methods are known to produce an enormous amount of CNTs [13].

Singh *et al.* argue that conventional dosage forms of curcumin, a natural compound with anti-cancer properties, have several shortcomings, including low aqueous solubility, poor bioavailability, and rapid degradation in the body. To address these shortcomings, they have developed a novel drug delivery system based on polysaccharide-functionalized single-walled carbon nanotubes (SWCNTs). The authors developed a method to functionalize SWCNTs with chitosan and alginate polysaccharides. The functionalized SWCNTs were then loaded with curcumin. The curcumin-loaded SWCNTs showed high drug-loading efficiency and sustained drug release. *In vitro*, cytotoxicity studies showed that the curcumin-loaded SWCNTs were significantly more effective at killing lung cancer cells than free curcumin. The curcumin-loaded SWCNTs were also taken up more efficiently by lung cancer cells. The authors conclude that polysaccharide-functionalized SWCNTs are a promising drug delivery system for curcumin in lung cancer treatment [14]. Fig. 2 depicts the structure of carbon nanotubes.

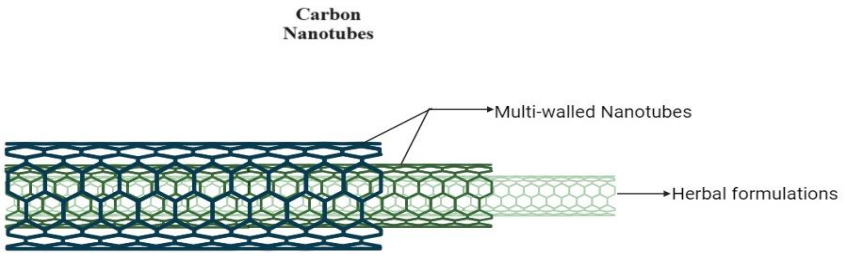

Fig. 2: Carbon nanotubes [12]

Fullerene

Fullerenes are football-like shaped and made of 60 carbon atoms (20 hexagons with C_5-C_6 double bonds, 12 pentagons with C_5-C_5 single bonds) [15]. They consist of fused rings and conjugated bonds with sp^2 and sp^3 bond hybridization, with the average bond length of the single bond being 0.145 nm and the average bond length of the double bond being 0.141 nm. They are 1-10 nm in diameter, having a cage-like structure. It aids in the solubility and bioavailability of the drug which is entrapped in the cage [16].

Artemisinin is a Chinese herb used in the treatment of malaria worldwide, its partially synthetic derivative is Artesunate, which in studies, has shown that it has cytotoxic activity against the tumor cells. Studies have shown that TfR (Transferrin receptors) concentration is high in cancer cells, so this can be used as drug targeting. When AS, a common anti-malarial medication, was physically adsorbed onto HA-C60-Tf, a multifunctional tumor-targeting drug delivery system with high water solubility, tumor-targeting efficacy, and PDT ability was created by Zhang *et al.* Therefore, this approach (HA-C60-Tf/AS) can deliver medications to tumor tissue as well. The unique anti-tumor properties of AS and Tf also caused this delivery strategy to significantly increase the drug's pharmacological efficacy at the target location while significantly lowering AS toxicity in non-target organs.

To simultaneously transmit AS and iron ions into tumor tissue, as well as specifically target cancer cells, a fullerene-based multi-functional nanoparticle called HA-C60-Tf/AS was designed. The nano-scale formulation demonstrated negligible toxicity and could function as both an active-targeting drug delivery vehicle as well as a potent PDT agent. With a high loading efficiency of 162.4%, AS, which is used to treat malaria, may be successfully loaded on HA-C60-Tf to create a drug delivery system for the treatment of cancer. There may be a new multi-mechanism for treating tumors that uses HA-derivatized C60 as drug carriers with the co-delivery of AS and Tf. This new strategy was demonstrated in the *in vitro* and *in vivo* investigations using HA-C60-Tf/AS with laser irradiation [17]. Fig. 3 represents the structure of Fullerenes.

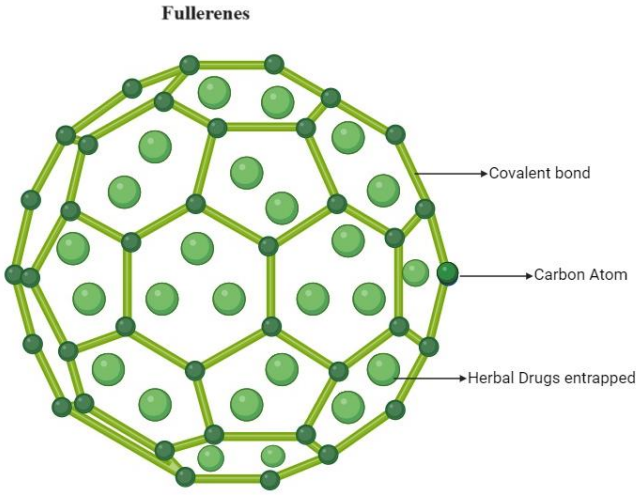

Fig. 3: Fullerenes [15]

Dendrimers

These are the nanoparticles that are extensively branched, three-dimensional polymers, and have a well-defined structure. A variety of monomers are used to synthesize the dendrimers [18]. They are made up of three main parts: Core, Branches, and Surface groups. Unique properties of dendrimers include a High surface-to-volume ratio, Modifiable surface chemistry, Well-defined structure, and size, high aqueous solubility, and biocompatibility which has attracted scientists to work with it [19].

Ge *et al.* used smart dendrimers to deliver Celastrol (anticancer drug), which delivers the drug directly to the mitochondria of the cells. The dendrimers were made of Polyamidoamine (PAMAM) dendrimers modified with polyethylene glycol (PEG) and EpCAM aptamers. Various shortcomings were addressed in delivering Celastrol to the cancer cells as it has a short half-life, poor bioavailability, and low specificity. They were found to enhance the *in vivo* and *in vitro* activity of Celastrol and it was found to be non-toxic and safe to the normal cells. Overall, this improved the safety and efficacy of Celastrol as an Anti-cancer agent [20].

Lipid-based: solid lipid nanoparticles

Solid lipid nanoparticles are nanoparticles made of water, solid lipids, and surfactants. They are spherical and their size range ranges from 10-1000 nm. The drug is entrapped inside its solid lipid core. Solid lipid nanoparticles are biocompatible, biodegradable, stable, and versatile [21]. Loading the herbal extract into the solid lipid core offers numerous advantages such as improved bioavailability, controlled and targeted release, and protection of the drug from degradation [22]. Solid lipid nanoparticles can be prepared by various methods like high speed/pressure homogenization, ultrasonication, super-critical fluid evaporation method, etc [21].

Shi *et al.* formulated solid lipid nanoparticles loaded with frankincense and myrrh oil as the synergistic effects showcased anti-tumour action. Both frankincense and myrrh oil were unstable and had poor aqueous solubility which limited their bioavailability, adding to this the phyto-components were light, air, and temperature-sensitive which made them unsuitable to administer in a conventional dosage form. The solid lipid nanoparticles were prepared by high-pressure homogenization using Compritol 888 ATO, soybean lecithin, and tween 80. Formulated SLNs were subjected to various evaluation studies and it enhanced the anti-tumor activity in H22-bearing Kunming mice. So hydrophobic oils can be loaded into SLNs for better therapeutic efficacy [23]. Fig. 4 represents structure of solid lipid nanoparticles.

Nanostructured lipid carriers

These nanolipids are composed of solid and liquid lipids with surfactants and co-solvents and a size range of 10-100 nm. NLCs improve the stability, bioavailability, and efficacy of the herbal drugs and their delivery to the target site. Compared to SLNs, NLCs offer better advantages like increased drug loading, and more stable, and can be administered through various routes [24].

Soni *et al.* developed and optimized Nanostructured lipid carriers loaded with sulforaphane which showed potent activity against human lung cancer cells. Sulforaphane is poorly soluble in water and has low oral bioavailability, and it is not stable in an acidic

environment of the stomach, so delivering it through a conventional dosage form is difficult, so it was formulated as nanostructured lipid carriers. It was formulated using the melt emulsification ultrasonication technique with had particle size of 120 nm and, zeta potential of-20 mV, and it showed sustained release of the drug over 24 h. The antitumor activity of the SFN-loaded NLCs was evaluated against human lung cancer cells (A549 cells) *in vitro* and *in vivo*. The results showed that the SFN-loaded NLCs significantly inhibited the growth and proliferation of A549 cells *in vitro*. The SFN-loaded NLCs also showed potent antitumor activity in a xenograft mouse model of lung cancer, proving as a potential treatment strategy [25]. Fig. 5 depicts the structure of nanostructured lipid carriers.

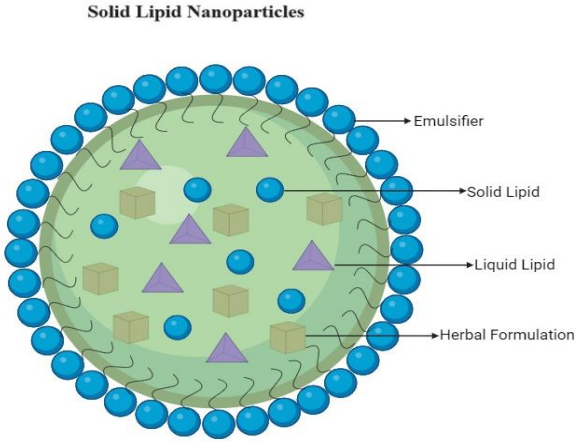

Fig. 4: Solid lipid nanoparticles [21]

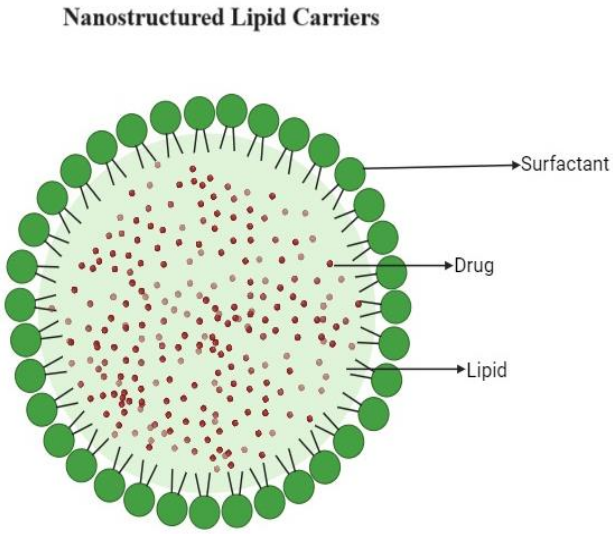

Fig. 5: Nanostructured lipid carriers [24, 25]

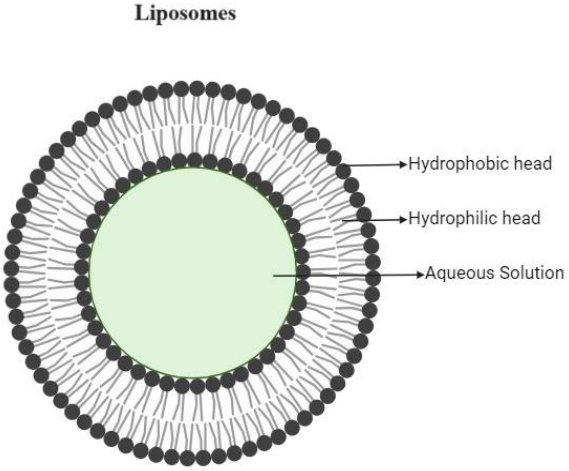

Fig. 6: Liposomes [26, 27]

Vesicular systems: liposomes

These are the nanocarriers which are the microscopic vesicles made of concentric layers of lipid bilayers. It is separated by an aqueous medium, where the hydrophilic drugs are loaded in the aqueous compartment and lipophilic drugs are inserted into the membrane [26]. It is made of biocompatible phospholipids and cholesterol. It can bypass the lipid membranes and, delivery of the drug to the site, specifically. Some of the liposome preparation methods are Thin-film hydration, Extrusion, Reverse-phase evaporation, and microfluidization methods.

Jagwani *et al.* argue that the conventional dosage form of resveratrol has several shortcomings, including low bioavailability and poor solubility. They propose a new liposomal formulation of resveratrol that addresses these shortcomings. The authors formulated liposomes using the thin-film hydration method and evaluated the liposomal formulation of resveratrol using a variety of methods, including *in vitro*, *in vivo*, and pharmacokinetic studies. The results of these studies showed that the liposomal formulation of resveratrol is more effective at killing cancer cells, is taken up by cancer cells more efficiently, results in higher levels of resveratrol in the blood and tissues, and is more effective at reducing tumor growth than the conventional dosage form [27]. Fig. 6 represents the structure of liposomes.

Phytosomes

Phytosomes are a type of drug delivery system that is made of phospholipids in which the phytochemicals are loaded and delivered [28]. They are comparatively smaller than liposomes and considered to be promising strategies for delivering phytoconstituents. Phospholipids are made from Soya Phosphatidylcholine (SPC). Egg Phospholipid is also used which contains lysophosphatidylcholine, phosphatidylethanolamine, and sphingomyelin [29].

Alhakamy *et al.* developed and optimized icariin Phytosomes to improve cytotoxicity and apoptosis-induced cell death in ovarian cancer cells. Since icariin is rapidly metabolized and has low oral bioavailability, it is formulated as phytosomes by solvent evaporation method and optimized using Box-Behnken design, and various evaluation tests were performed. MTT assay was performed to evaluate the cytotoxicity of the phytosomes in the ovarian tumor cells (A2780). This test proved that icariin-loaded phytosomes were more potent than free icariin [30]. Fig. 7 depicts the structure of Phytosomes.

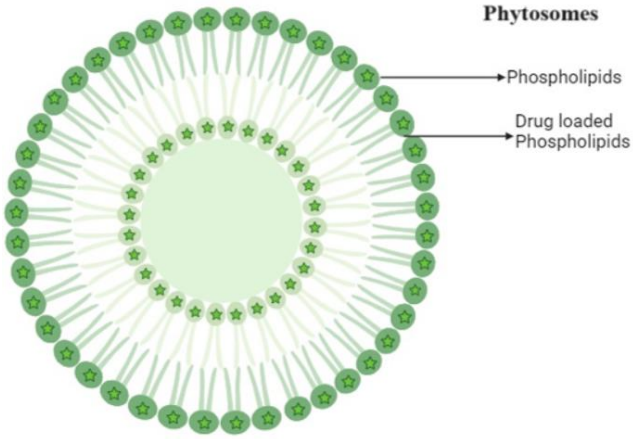

Fig. 7: Phytosomes [28, 29]

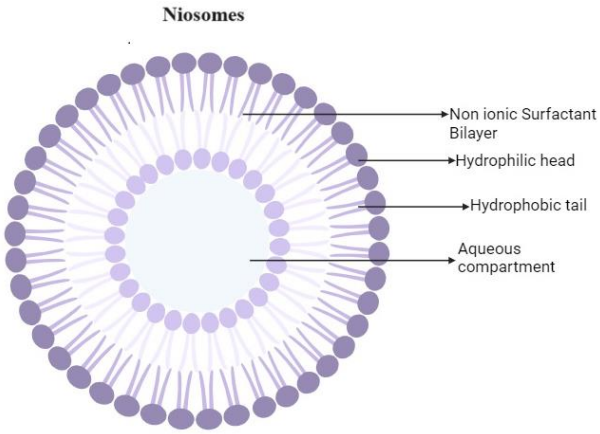

Fig. 8: Niosomes [31]

Niosomes

Niosomes are the non-ionic vesicular nanocarrier system made of non-ionic surfactants, with particle sizes ranging from 10-100 nm. It is made of lipids (Cholesterol), non-ionic surfactants, and hydrated medium [31]. Due to the high interfacial tension between water and the hydrophobic portion of the amphiphilic molecules when non-ionic surfactants are exposed to the aqueous environment, a closed bilayer vesicular structure forms. Due to steric and hydrophilic repulsion between the hydrophobic head groups of the non-ionic surfactant, the hydrophilic tail of the substance points towards an aqueous environment. For the development of such sealed bilayer structures, energy in the form of mechanical or heat is needed [32].

Barani *et al.* developed Niosomes with Carum which have a variety of pharmacological activities but are not used clinically due to their

low aqueous solubility and low bioavailability. They formulated the Niosomes using the thin film hydration method and it was characterized. The cytotoxicity of the Carum Niosomes was evaluated in breast cancer cells (MCF-7 cells) using the MTT assay. The results showed that the Carum Niosomes were significantly more cytotoxic to MCF-7 cells than free Carum essential oil. The Carum Niosomes also induced apoptosis in MCF-7 cells to a greater extent than free Carum essential oil. The effect of CNs on cell migration was evaluated using the scratch wound healing assay. The results showed that the Carum Niosomes significantly inhibited cell migration in MCF-7 cells [33]. Niosomes structure is represented in fig. 8.

Ethosomes

These are the type of vesicular drug delivery systems which is made of elastic lipids and alcohol [34]. It has gained popularity in recent decades due to its better drug loading of both hydrophilic and lipophilic phytoconstituents, and better transdermal absorption and delivery of drugs. Ethanol used in ethosomes can cause the skin to be disrupted easily. Hot method, cold method, Ultrasonication, and microfluidization are some of the methods by which the ethosomes are prepared [35].

Chen *et al.* (2023) investigated the preparation and evaluation of curcumin ethosomes. The authors found that the curcumin ethosomes exhibited significantly improved solubility and stability compared to free curcumin. The curcumin ethosomes were formulated using the thin-film hydration method. The curcumin ethosomes also showed better *in vitro* cytotoxicity against human lung tumor cells. The results showed that the ethosomes had a particle size of 211-320 nm, a zeta potential of-29.8 to-34.6 mV, and an entrapment efficiency of 87-91%. The ethosomes also have a sustained *in vitro* drug release, with 71.3% of the curcumin released after 24 h. The *in vitro* cytotoxicity of the curcumin ethosomes was evaluated in human lung cancer cells (A549 cells) using the MTT assay. The results showed that the curcumin ethosomes were significantly more cytotoxic to A549 cells than free curcumin [36].

Polymer-based: biopolymer-based

Pure biopolymer nanoparticles

Chitosan is a linear polysaccharide that is biocompatible and biodegradable, made of d-glucosamine and N-acetyl glucosamine units. It is extracted from the crustacean arthropods' exoskeletons, which include crabs, insects, lobsters, and prawns [37]. Fortunately, well-developed modified chitosan molecules, like those conjugated with dextran sulphate, biotinylated, and galactosylated chitosan, have more stable properties, can change the surface charge, and can enhance the delivery of the drug by specifically targeting the site of action [38].

Suksaeree *et al.* prepared Chitosan/Hydroxypropyl methylcellulose blended patches incorporated with Zingiber Cassumunar oil which is found to have analgesic and anti-inflammatory properties. Chitosan/HPMC blends can be used to formulate herbal blended patches with improved physicochemical properties and *in vitro* release characteristics. They found that the blended patches were more stable, had a higher drug loading capacity, and released the drug at a more controlled rate than conventional herbal patches. The drug content of the patches was determined by extracting the drug with a suitable solvent and analyzing the extract using a UV-Vis spectrophotometer. The drug content uniformity was found to be greater than 90%. The *in vitro* drug release of the patches was determined using the dialysis bag method. The blended patches were found to release the drug at a more controlled rate than conventional herbal patches [39].

Biopolymer-based hydrogels

In many therapeutic applications, hydrogels-cross-linked polymeric networks with hydrophilic functions are regarded as promising biocompatible materials that can provide niches for homing aqueous biological fluids [40]. Adorable hydrophilicity, high porosity, and regulated medication release are the characteristics of this formula. Inherently biodegradable BBH is constructed from naturally occurring biopolymers, including collagen, chitosan, hyaluronic acid (HA), alginate, and gelatin. These biopolymers are often pre-functionalized to integrin binding sites, enabling adhesion and integrated biological responses. The applicabilityis limited for these compounds, nevertheless, as there is notable batch-to-batch variability and possible immunogenicity in foreign model organisms [41].

Lustosa *et al.* formulated a hydrogel of carboxymethyl cellulose with phthalated cashew gum (CMC/PCG), which was used for the synthesis of silver nanoparticles (AgNPs) with anti-bacterial and wound healing activity. AgNPs were stabilized by the CMC/PCG hydrogel, and the CMC/PCG hydrogel was able to control the drug release and exhibited significant antibacterial activity against a wide spectrum of bacteria. The antibacterial activity was tested against various bacteria and wound-healing activity was checked in the rat model. The findings suggest that AgNP-loaded CMC/PCG hydrogel is a promising agent for treating bacterial infections and wounds [42].

Biopolymer drug conjugates

This can be accomplished by using a thermally sensitive biopolymer that can generate an insoluble, viscous co-acervate at body temperature very quickly [43]. Despite being licensed for clinical trials, several biomedical drug-polymer conjugates are not suitable for imaging-guided precision cancer therapy or total cancer arrest due to their lack of photothermal characteristics and multi-imaging capabilities. As a result, scientists developed a brand-new all-in-one biopolymer–drug conjugate nanotheranostics. For example, intracellular pH-sensitive polydopamine–doxorubicin conjugate nanoparticles under benign conditions are known for their superior photothermal properties, double stimuli-triggered drug kinetics, and somewhat longer blood circulation time compared to nonconjugated doxorubicin [44].

Yi et al. formulated a resveratrol-loaded whey protein–dextran colloidal complex (WPC-D-RES) that can be used to stabilize and deliver β-carotene emulsions. Since it is soluble in oil, it is difficult to formulate a conventional dosage form that is stable and bioavailable. It was found that stable emulsions are formed with WPC-D-RES with high encapsulation efficacy and sustained release of β-carotene. The dialysis method was used to assess the release profile. The emulsions were found to release β-carotene in a sustained manner over 24 h. The antioxidant activity of the emulsions was determined using a DPPH assay. The emulsions were found to have good antioxidant activity [45].

Nanocapsules

Nanocapsules are a core-shell form of nanosystem that protects the drug inside while also allowing for precise drug delivery to diverse body areas. The phytoconstituents present at the core position are released into the biological fluidics in a controlled manner [46]. The nanocapsules's cores can readily be filled with plant extracts. They are made up structurally of tiny droplets with liquid cores that are densely packed with polymeric shell walls. The polymeric shell regulates how the loaded bioactives are released. This method of using nanocarriers for controlled delivery of phytoactives allows nanocapsules to improve therapeutic efficacy while preventing degradation and lowering unintended toxicity. Particularly when administered orally, nanocapsules offer good stability against microenvironment variables such as light, enzyme, and pH [47].

Gaber et al. developed boronic-targeted albumin-shell oily-core nanocapsules (HSA-Oily-NCs) to deliver exemestane (aromatase inhibitor) and Hesperetin (citrus flavonoid) for the treatment of breast cancer. Both exemestane and hesperetin exhibit synergistic activity and since both are hydrophobic, in HSA-Oily-NCs the drugs can be loaded efficiently. These capsules are biocompatible, accumulate in tumor cells more when compared to free drugs, and have longer circulation time. The surface of the cancer cells has residues of sialic acid, the boronic acid moieties conjugated to the albumin shell interact with the sialic acid increasing the targeting of the tumor cells. The in vitro and in vivo evaluation has shown higher cytotoxicity against breast cancer cells in comparison to the free drugs. The in vivo evaluation was carried out with a xenograft mouse model which inhibited the tumor growth and prolonged the survival [48].

Emulsion based

Nanoemulsions

Nanoemulsions-biphasic dosage form made of two immiscible liquids in which one phase is dispersed as droplets in the continuous

phase with the help of surfactants or emulsifying agents. The particle size ranges from 100 to 600 nm [49]. Nanoemulsions are available in different dosage forms like creams, gels, liquids, sprays, foams, and aerosols. They have higher solubilization capacity and offer greater kinetic stability, which makes them the best candidate in the cosmetic and pesticide industry. Nanoemulsions are prepared by various methods like the Phase Inversion technique, Spontaneous technique, High-pressure homogenization, Ultrasound emulsification, Microfluidization, and High-shear homogenization [50]. Ganta *et al.* encapsulated paclitaxel and curcumin in nanoemulsion formulation using a high-pressure homogenization technique. Paclitaxel is a poorly water-soluble drug, which makes it difficult to formulate into conventional dosage forms, such as tablets and capsules. This can lead to low bioavailability and poor therapeutic efficacy. Additionally, Paclitaxel is a substrate for P-glycoprotein, a drug efflux pump that is often overexpressed in MDR cells. This can further reduce the efficacy of Paclitaxel in MDR patients. Curcumin administration inhibited NF-κB activity and downregulated P-glycoprotein expression in drug-resistant cells. The Combination of Paclitaxel and Curcumin therapy was effective in enhancing cytotoxicity in drug-resistant cells by aiding in apoptotic cell death [51].

Self-nano emulsifying drug delivery system

This a type of nano-emulsion where the mixture of surfactant, oil, and co-solvent forms a nano-emulsion spontaneously with the particle size<100 nm. It is a known fact that herbal extracts have issues related to solubility and permeability as they have phytoconstituents which are lipophilic. To overcome this, they can be developed as SNEDDS. This will improve their permeability, solubility, bioavailability, and their therapeutic activity [52, 53].

Khan *et al.* studied and formulated a Self-Nano Emulsifying Drug Delivery System for the grapefruit flavonoid Naringenin which is poorly water-insoluble. Naringenin had anti-inflammatory, anti-oxidant, and anti-cancer properties but had poor oral bioavailability, so the authors developed an SNEDDS formulation. Dialysis bad method was used to evaluate the *in vitro* drug release of Naringenin from SNEDDS formulation. The SNEDDS formulation showed a sustained release of Naringenin over 24 h. The *in vivo* pharmacokinetic studies of the SNEDDS formulation were conducted in rats. The SNEDDS formulation showed an increase in the oral bioavailability of Naringenin compared to the conventional dosage form. The results of the evaluation studies showed that the SNEDDS formulation was a stable and effective drug delivery system for Naringenin. The SNEDDS formulation significantly improved the dissolution and bioavailability of Naringenin [54].

Nanogels

Nanogels are three-dimensional swollen networks that are made of hydrophilic or amphiphilic polymers. They are 10-100 nm in diameter and are used for the transport of drugs by incorporating them through the formation of hydrogen bonds, salt bonds, or hydrophobic interactions [55]. They are characterized by high porosity, large surface area, encapsulation efficiency, and targeted delivery of a variety of molecules which includes drugs, proteins, and genes. Loading of molecules into the nanogels can be achieved these methods such as physical entrapment, covalent conjugation, and controlled self-assembly. Nanogels are prepared by 1) assembling interacting polymers physically; 2) the polymerization of monomers in a homogeneous phase or in a heterogeneous environment at the micro-or nanoscale; 3) the cross-linking of premade polymers; 4) Nanofabrication of nanogel particles with the aid of templates [56].

Wei *et al.* developed a targeted nanogel conjugate of curcumin (TNC-CUR) to improve the stability and cellular permeability of curcumin. They argue that the TNC-CUR can deliver curcumin to tumor cells more effectively than conventional curcumin formulations. The TNC-CUR was formulated using a self-assembly method. Curcumin was first conjugated to a targeting ligand (folic acid) and then incorporated into a nanogel matrix. The cellular uptake of the TNC-CUR was evaluated using a fluorescently labeled curcumin derivative. A mouse model was used to evaluate the anti-tumor activity of TNC-CUR. The formulated TNC-CUR was more readily taken up by the tumor cells than the conventional curcumin and *in vitro* study reports state that the cellular uptake was 2-fold more than the conventional curcumin. *In vivo*,thestudy states that TNC-CUR effectively inhibited tumor growth in mice and also significantly reduced the tumor weight and volume in mice. TNC-CUR was also stable in aqueous medium compared to conventional curcumin. Therefore, TNC-CUR was found to be a promising treatment strategy in treating breast cancer [57].

Nanosuspensions

Nanosuspensions are colloidal dispersions with solid drug particles and are biphasic. The particle size is not more than 1000 nm [58]. The solid drug particles are dispersed in the liquid phase. Reducing the particle size and increasing the cell permeability, enhances the bioavailability of the lipophilic drugs, which drastically increases the absorption. Media milling, High-pressure homogenization, Supercritical fluid technology, and Emulsion-solvent evaporation are the methods of preparing nanosuspensions [59]. Huang *et al.* developed high drug-loading celastrol nanosuspensions (CEL-NSs) using a high-pressure homogenization method. They argue that the CEL-NSs can improve the solubility and bioavailability of celastrol, a promising anticancer drug with poor solubility in water. The CEL-NSs were formulated using a high-pressure homogenization method. Celastrol was suspended in a solution of water and surfactant. The suspension was then homogenized at high pressure to reduce the particle size of the celastrol crystals. To reduce the particle size of the celastrol crystals, the suspension was homogenized. *In vivo*,thestudy reports about IC50 of CEL-NSs and celastrol, where CEL-NSs showed IC50 of 0.5 μM and celastrol alone showed 5 μM. *In vivo*, thestudy reports that CEL-NSs inhibited tumor growth in mice while celastrol did not. CEL-NSs were found to have high drug loading capacity and celastrol was stable in suspension for 6 mo. Overall, In the *in vitro* and *in vivo* studies, the inhibition of the breast cancer cells proved to be a better drug candidate for treating breast cancer [60].

Inorganic: metal based

Iron nanoparticles

Iron nanoparticles are nanocarriers that are known for their magnetic properties and can be used for both diagnosis and delivery of drugs. With the use of their magnetic properties, the drug can be directed to the target site by the external application of the magnetic field [61]. Microemulsion, sonochemical reactions, precursor hydrolysis, sol-gel synthesis, hydrothermal reactions, and thermolysis are some of the methods by which iron nanoparticles can be synthesized. Enhanced drug delivery and targeted action, controlled and sustained drug delivery, and fewer side effects are key advantages of iron nanoparticles. In cancer treatment, antibiotic delivery, and gene therapy iron nanoparticles are used [62].

Parmanik *et al.* formulated iron oxide nanoparticles (IONPs) containing Triphalachurna extract as a novel treatment strategy for TNBC (triple-negative breast cancer). Triphalachurnais atraditional herbal medicine to treat various ailments, but the oral bioavailability of Triphalachurna is low as it contains various complex molecules that are difficult for our body to digest. So TIONPs were synthesized by the green synthesis method. Triphalachurna extract reducedthe iron ions to iron nanoparticles and the latter was evaluated for anticancer activity using MTT assay. The authors found that the TIONPs were effective in inhibiting the growth of TNBC cells in a dose-dependent manner. They also found that the TIONPs were non-toxic to normal human cells. They argue that the IONPs are more bioavailable and have better anti-cancer activity than triphalachurna in its conventional dosage form [63].

Gold nanoparticles

Gold nanoparticles are nanoparticles made of gold, with sizes ranging from 1 to 100 nm in diameter [64]. They are now being used in the treatment of cancer, attributing to their easy preparation, nanostructure, flexibility, electronic structure, biocompatibility, and stability. By overcoming the difficulties of therapy resistance, limited solubility, great intrinsic characteristics release, short retention period of medications in the plasm, etc., AuNPs offer significant

antiviral therapeutic potential. The strategies for conjugation or modification must all be carefully considered [65]. Liu *et al.* synthesized gold nanoparticles using Curcuma wenyujin extract and evaluated their anticancer activity against *in vitro* renal tumor cells. The gold nanoparticles were synthesized using the green synthesis method. Gold nanoparticles induce apoptosis by upregulation of pro-apoptotic proteins and down-regulation of anti-apoptotic proteins. The evaluation was done using MTT assay, in the assay it inhibited the growth of renal cancer cells in a dose-dependent manner [66].

Silver nanoparticles

Silver nanoparticles are small silver particles in size ranging from 1 to 100 nanometers in diameter. The applications of silver nanoparticles in medicine include drug delivery, electronics, and catalysis. Silver nanoparticles are formulated either by the Top-down or Bottom-up synthetic approach and the Green synthesis approach. Physical methods include Laser ablation methods and Evaporation-condensation methods, Chemical methods include Chemical reduction, Microemulsion technique, and Microwave-assisted synthesis [67, 68].

Bhanumathi *et al.* formulated silver nanoparticles loaded with berberine and tested its anticancer activity against breast cancer. The berberine-loaded silver nanoparticles were formulated using a green synthesis method. The authors used plant extract as the reducing agent to synthesize silver nanoparticles. The berberine was then loaded onto the silver nanoparticles using electrostatic interaction. They found that the berberine-loaded silver nanoparticles complex exhibited a dose-dependent cytotoxicity against MCF-7 and MDA-MB-231 breast cancer cell lines. The berberine-loaded silver nanoparticles complex also induced apoptosis in breast cancer cells. The authors concluded that berberine-loaded silver nanoparticles are a promising agent for the treatmentof breast cancer [69].

Mesoporus silica

Mesoporous silica nanoparticles are particles with sizes ranging from 2-10 nanometers having 2D-Hexagonal and 3D-cubic structural characteristics [70]. The properties that make them promising candidates for, Diagnostic catalysis, Sensing and separation, and Drug carriers are porosity, controlled particle size, morphology, and high chemical stability. MCM-41 is the first reported mesoporous silica material as a drug carrier. Functionalization of the Silanol group can be used to control the drug diffusion kinetics [71].

Liu *et al.* formulated paclitaxel and quercetin co-loaded functional mesoporous silica nanoparticles (MSNs-PQ) to treat Multidrug resistance in breast cancer. It was formulated using the co-loading method and it was coated with Chondroitin sulfate to improve the tumortargeting. *In vitro* and *in vivo* studies were performed to evaluate its anticancer effects. *In vitro*, the formulation inhibited the growth of the breast cancer cells in a dose-dependent manner, down-regulated the P-gp receptors, and also increased the accumulation of paclitaxel in the tumor cells. *In vivo*, mice were used to evaluate the MSNs-PQ, which inhibited the growth of MDR breast cancer cells and also prolonged the survival of the mice. They argue that the MSNs-PQ nanoparticles can deliver both paclitaxel and quercetin to the tumor cells, where quercetin will inhibit P-glycoprotein (P-gp), a major MDR transporter. This will allow the paclitaxel to accumulate in the tumor cells and exert its cytotoxic effects [72].

Hybrid nanosystems

Hybrid nanosystems include lipid-metal, lipid-polymer or polymer-protein. It provides synergistic effects of different carriers used and overcomes the drawbacks associated with individual carriers. It provides better release of the loaded phytoconstituents with any degradation of the herbal and also protects the loaded phytoconstituents from the harsh environment of the GIT [73].

Drakalska *et al.* formulated hybrid liposomal PEGylated calix [4] arene systems that can be used to deliver curcumin at the target site. Curcumin is a natural compound with many potential health benefits, but it has poor solubility and bioavailability. This means that it is not easily absorbed by the body. The authors of the study found that curcumin could be encapsulated in hybrid liposomal PEGylated calixarene systems, which improved its solubility and bioavailability. The Curcumin BEC-X inclusion complexes were prepared using two methods heating method and Solvent evaporation methods and curcumin-loaded conventional and curcumin: BECX hybrid liposomes were prepared by modified thin film hydration method and the same subjected to various evaluation tests. The cell culture experiments were conducted using a variety of cancer cell lines, which makes the results more generalizable. The solubility studies were performed using various solvents to check the solubility in different environments. The study provides evidence that hybrid liposomal PEGylated calixarene systems will improve curcumin delivery [74].

Future perspectives and challenges

Any condition can be treated more effectively and safely by using current medications more effectively or by developing new ones. Several drug delivery strategies based on nanotechnology have caught the interest of researchers. Drug delivery techniques have evolved significantly, incorporating new materials and novel chemical or physical effects. Alternative delivery methods are required for modern therapeutic approaches that use proteins and nucleic acids to lessen their harmful effects and maximize their healing potential. Thus, it is possible to conclude that using a Novel Delivery System could be crucial when creating herbal formulations. Due to their capacity to penetrate the reticuloendothelial system, enhance stability, retention, and penetration, as well as their ability to target specific tissues and tumors, nanocarrier-based herbal drug delivery systems have demonstrated enormous promise in the treatment of numerous illnesses and disorders, particularly in the advancement of cancer therapeutics. Herbal formulations based on NPs have shown improved absorption, bioavailability, and precise distribution. NDS has demonstrated the capacity to stabilize pharmaceutical molecules that would otherwise rapidly disintegrate in physiological settings while maintaining efficient drug molecule delivery and negligible toxicity [75].

Nanotechnology-based drug delivery systems are promising carriers that will enhance pharmacological and therapeutic activity while overcoming the problems associated with plant-based medicines. Herbal nanomedicines have several advantages but there are challenges in terms of implementing them as treatment strategies for diseases. The interaction of nanomaterials with the biological system is a greater challenge in transferring these technologies to therapies. Other challenges include scaling up the process of nanoformulations from bench to bedside, fulfilling the biological and therapeutic requirements, improving the targeting efficacy, proper regulations for the herbal nanoformulations, and satisfying the toxicology and biocompatibility standards at international levels [76]. Table 2. Contains the list of marketed herbal nanoformulations.

Table 2: Marketed herbal nanoformulations

Formulations	Active constituents	Biological activity	Outcomes	Preparation method	Administration route	Reference
Cuscuta chinensis Nanocapsule	Flavonoids and lignans	Hepatoprotective and antioxidant effect	Improve water solubility	Nanosuspension	Oral	[77]
Berberine loaded nanoparticles	Berberine	Anti-cancer	Sustained drug release	Ionic gelation method	IV	[78]
Radix Salvia miltiorrhiza Nanocapsule	R. Salviamiltiorrhiza	Coronary heart disease, angina pectoris, and myocardial infarction	Improved bioavailability	Spray drying technique	Radix Salvia miltiorrhiza Nanocapsule	[79]
Artemisinin Nanocapsule	Artemisinin	Anti-cancer	Sustained drug release	Self-assembly procedure	Artemisinin Nanocapsule	[81]

Many desirable physiologic targets are inaccessible due to anatomical barriers including the BBB, the pulmonary system's branching channels, tight skin epithelial junctions, etc. The drug-loaded multi-layered nanocarrier assemblies, which break down within the biological system layer by layer as they pass through each barrier and ultimately deliver the medication at its intended spot, may be quite helpful in such situations. NDS has several notable benefits, including the ability to target therapeutic molecules to certain tissues or tumorous cells and the potential for cellular drug delivery.

CONCLUSION

Herbal treatments are increasingly popular worldwide, and combining them with nanocarriers could improve their effectiveness in treating chronic illnesses. Numerous biomedical research institutes are developing nanosized herbal treatments, aiming for key characteristics such as site-directed sustained delivery, improved patient compliance, therapeutic potential, and the absence of harmful side effects or hypersensitive reactions. Nanoformulations are suitable for different types of herbal extracts and phytoconstituents. Solid lipid nanoparticles can deliver phytoconstituents at a constant rate, improving their stability. Polymeric nanoparticles are suitable for poor bioavailability, while nanomicelles increase stability. Nanofibers are preferred for light and heat-sensitive extracts. Liposomes enhance oral bioavailability, while dendrimers address permeability issues. Ethosomes deliver drugs to deeper layers of the Stratum corneum, while nanoemulsions and nanosuspensions facilitate bioavailability, solubility, and stability. Novel-Drug Delivery System (NDS)--based herbal formulations address various health issues and provide significant health advantages. This multidisciplinary research combines modern drug delivery methods with traditional herbal therapeutics, leading to the development of visually appealing nanosized herbal drugs or phytopharmaceuticals that will be crucial for improving people's health in the future.

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CONFLICT OF INTERESTS

The authors report no conflicts of interest in this work

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