Review Article

Recent Advances in Herbal-Nano Formulation: A Systematic Review

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ABSTRACT

Plants have been used in the maintenance and protection of human health since ancient days and these medicinal plants play a dynamic role in preventing diseases. Natural compounds present in medicinal herbs were used to treat a bacterial infection, digestive disorders, respiratory illness, cardiac disorders, cancer, disorders in brain etc. Despite their outstanding therapeutic applications, the phytochemical components have limited solubility in water and thereby affecting bioavailability. In order to make effective use of this property and overcome limitations, novel strategies have been implemented in using medicinal herbs in health care. Nanotechnology has led to numerous scientific discoveries and invention of nano-medicine is tremendous. Nano-drug delivery is an attractive approach in the treatment of life-threatening diseases like cancer and neurological disorders as these nanoparticles could be linked with drugs to actively cross the blood-brain barrier. This review focusses on herbo-nano formulations and methods of delivering phytochemical drug to targeted cells. Nanoformulations have been implemented in research on delivering active herbal components, improving bioavailability and decrease toxic effects of diseases.

Keywords: Nanoformulation, Herbal drugs, Phytochemicals, Secondary metabolites.

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INTRODUCTION

Herbs are being used as therapeutics for over 4000 years with evidences being found in Indian, Perso-Arabic and European system of medicine. Among these, ancient civilization of India is well known as one of the richest repository of medically important herbs due to its highly diverse forest resources in India.[1] Though several indigenous medical systems like Ayurveda, Unani, Siddha and tribal medicines existed, Unani and Ayurveda were the most extensively used systems.[2] In monographs published by WHO lists nearly 21,000 species of herbs with effective therapeutic property and also says that around 80% of people rely on traditional medication for their primary health globally.[3]

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Phytochemical components possess low absorption qualities because of their high molecular weight and their inability to cross lipid membrane.[4] Also, it is reported that more than 40% of new bio-active principles are poorly water soluble with slow drug absorption.[5,6] Hence nanoformulations of herbal drugs were investigated to maximize bioavailability, solubility, retention time of the drug, drug delivery and to minimize the toxic effects of the drug. Bionanotechnology-based research in near future may invent more nanoformulation and their applications with more drugs delivered effectively.[7] This review discusses about use of herbal drugs in pharmaceutical purposes, herbo-nanoformulations synthesis and their applications in drug delivery, recent developments and future prospective.

NANOFORMULATION OF PHYTODRUGS

Nanoformulations are multifunctional systems engineered at nano-scale and possess unique physical

and chemical properties with diagnostic and therapeutic applications. They may be defined as carriers with particle size ranging between 10 to 100 nm, in which therapeutically active agent could be dissolved, encapsulated or attached to deliver.[8] Nanocarriers are in general made up of an outer polymer shell and a core inside to carry drugs. The particle circulation time and interaction of nanoparticle with the surface of cell are determined by the outer core. This also provides stability to the nanoformulation. The sizes of these carriers are normally 1 to 300 nm and are delivered to a specific target with a medicinal drug. The oral nanocarriers facilitate site-specific drug delivery and also controlled release. They are agents that could transport active principles to target tissues as they are smaller in size and have the ability to modify their shape and charge. Therefore, nanocarriers may be defined as objects with at least one dimension in 1 to 100 nm scale. Nanostrategies are followed in treatment of neural disorders, in particular, drug formulation because drugs cannot cross the blood brain barrier of their own. Different types of nanoformulations are used in the pharmaceutical field for drug delivery.

1. Inorganic Nanocarriers: Quantum dots, Metal Nanoparticles
2. Lipid Based Nanocarriers: Liposomes, Solid-Lipid Nanoparticles, Nanosuspensions, Nanoemulsions.
3. Polymeric Nanocarriers: Dendrimers, Nanogels, Polymer-drug conjugates, Micelles, Polymeric Nanoparticles etc.

Inorganic Nanocarriers

Inorganic nanocarriersare entities resulted from metallic complexes like iron-oxide NPs, gold NPs, Zinc NPs etc.[9] Metal and inorganic nanoparticles were synthesized by modifying different functional groups and used in conjugation with ligands, drugs and antibodies. They possess potential application in various fields of Biotechnology such as drug delivery to target cells, carrier of gene and drug, magnetic separation, etc.[10] Gold, silver and magnetic NPs were extensively used in diagnosis and therapeutics.[11] Quantum dots with sizes ranging from 2 to 20 nm were crystals with precise controlling ability were used as drug carriers for herbal active components. They were well known for their optical property, sharp density of states and also quality transport.

Lipid Based Nanocarriers

Lipid nanocarriers were preferred for their high-quality flexibility and biocompatibility. Pharma researchers defined these nanocarriers to deliver drugs for oral, pneumonic or parenteral ailments. Lipid nanoformulations were modified to suit disease conditions, administering routes, stability and toxicity of the product, viability of cells etc., thereby advancing with improved safety and efficacy in immunization, diagnostics and pharmaceuticals.[12,13] Such organic nanoformulations encompass lipid-based and polymeric frameworks such as nanoemulsions, liposomes, dendrimers and carbon-nanocarriers. Liposomes are spherical shaped vesicles with closed lipid bilayer made up of one or more phospholipids in an aqueous phase in which drugs get encapsulated in a closed spherical vesicle.[14] Their stability has made them one of the very important carriers to deliver vaccines, steroids and genetic materials.[15] The size of nanoemulsions ranges between 20 and 200 nm, more stable against sedimentation, increased stability against gravity driven effect of creaming of particles thereby facilitating improved drug delivery. An improvement to liposomes and emulsions in sustained release of drug with a solid matrix was introduced as solid-lipid NPs. The size of these carrier particles are small and have the ability to solubilize lipophilic compounds thereby increasing cellular absorption. Solid lipid nanoparticles occur as polymorphic complexes and this may lead to instability. But they are preferred as potential carriers for anti-cancer drugs for their property to reduce toxicity as they are composed of lipids of physiological importance.[16] Colloidal nanoparticles offer stability even in high temperatures along with larger surface area to volume ratio and high surface reactivity. They are nanometer sized particles and are distributed uniformly in a solution. Due to their unique physio-chemical properties they are used in drug delivery, cancer therapeutics, diagnostics and optical imaging.[17]

Polymeric Nanocarriers

Biodegradable natural and synthetic polymers are synthesized from polymeric nanoparticles. They are known to release drugs slowly based on the encapsulated molecule and are highly stable.[18,19] Dendrimers are connections of hyper branched blocks of polymeric molecules with a central-core of single atom or molecule and multivalent peripheral groups linked together to form a globular structure.[20] They are capable of carrying herbal drugs by encapsulation of the molecule in the core and forms a candidate structure in formulating a multi-functional drug. Micelles are amphiphilic molecules with a size of 10 to 100 nm. They possess two cores, inner hydrophobic and outer hydrophilic and form prominent drug carriers with prolonged circulation of the molecule in blood. Nanospheres and nanocapsules are polymeric

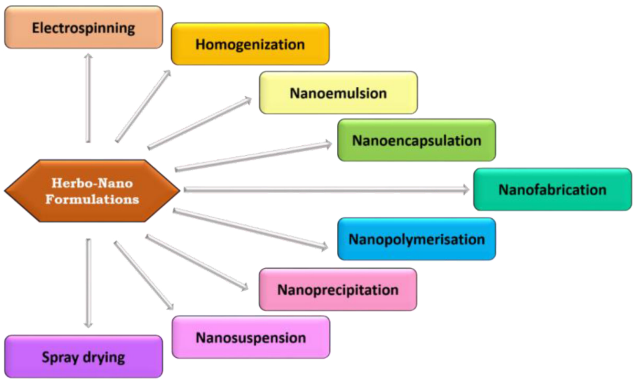

Figure 1: Schematic representation showing the methods for preparation of herbal nano-formulations.

nanoparticles used as effective drug carriers. They improve the solubility of herbal drugs in water and also control the rate of drug release.

METHODS OF PREPARATION OF HERBO-NANO FORMULATION

Nanosized materials are produced with the advent of nanotechnology and signifies the production, design and application of material at molecular level.[21] Nanoparticles used for therapeutic purposes are solid with sizes less than 100 nm diameter that may be biodegradable or non-biodegradable. Such nanoparticles may be in the form of two systems, nanocapsules and nanospheres. Nanocapsules have unique polymeric membrane in which the drug is encapsulated while the active components are uniformly distributed in a matrix system in nanospheres. Methods involved in herbo-nano formulations are briefed here and schematic representation showed in Figure 1.

Electrospinning

Electrofibres with diameter ranging between 10 nm to few micrometers are produced continuously with the use of electrostatic forces by this method. Several research investigations were carried out on electrospinning since 1999. Components namely high voltage power supply, syringe with metallic needle, collector are required to set up electrospinning. The high voltage power is supplied onto the active component and allowed to melt to form droplets. This droplet is converted into a conical droplet in the tip of the needle when electrostatic repulsion occurs in the fluid to manage surface tension. Charged polymer solution is released from the needle tip as a result of the electrostatic force and an interaction occurs between the electric field and surface tension of the fluid. The solvent gets evaporated and settles down in the grounded collector forming an uniform fiber.[22]

Nanoemulsification

Solvent Evaporation Method

Lipids and drug component are dissolved in an organic solvent. Volatile solvents such as chloroform and dichloromethane were used in the past whereas recent researchers use ethyl acetate as it is less toxic. Mixture of lipid, solvent and the drug are emulsified with stabilizers like poloxamer or polyvinyl alcohol.[23,24] The method was carried out in two steps; polymer solution is emulsified in an aqueous phase in the first step while the solvent evaporation and polymer precipitation occurs in the second step. This precipitate may be collectively termed as nanosphereswhich is collected after centrifugation and washing and stored after lyophilization.[25]

Solvent displacement method

Nanoparticles with size below 100 nm are produced using this emulsification technique. This method is formulated with slight modification of solvent evaporation method of emulsification. Partially hydro-miscible solvent is used to solubilize the drug and lipid, and then left for saturation. Due to thermodynamic equilibrium in the mixture, solvent diffuses into water and nanoparticles are precipitated out. The left-out solvent is removed later on by filtration or evaporation.

Homogenization

Homogenization or sonication is performed in the preparation of solid-lipid nanoparticles for drug delivery. Emulsion with small droplets is formed and solvents are removed by evaporation leading to lipid precipitation of nanoparticles. Hot and cold methods are incorporated in the preparation of nanoparticle. Hot homogenization is carried out in temperatures above the melting point and is preferred for lipophilic drugs. The drug is added after the lipid melts and this mixture is loaded with aqueous solvent. Congealing of the emulsion at room temperature results in formation of lipid nanoparticles. Disadvantages of this method are listed in Table 1. In order to overcome the issues, cold homogenization method was formulated.[26] In cold homogenization method, microparticles are prepared by melting lipid along with the drug and let to rapid solidification in the presence of liquid nitrogen. These microparticles are homogenized below room temperature and with vigorous stirring, nanoparticles are obtained.[27]

Nanoprecipitation

Polymers are precipitated by dissolving in organic solvents such as acetone and then diffusing into aqueous

Table 1: Advantages and disadvantages of nanoformulation.

Method	Advantages	Disadvantages	References
Electrospinning	Versatile, Efficient, and Cost effective method for fabrication of nanoformulations. High photoelectric conversion efficiency. Efficient charge separation and transport and the maximum light absorption. High specific surface areas and high porosity.	Inhibition of methanol permeation through PEM in Direct methanol fuel cell. Relatively low activity of photocatalysts.	[22]
Homogenization	Improved stability of the drug Enhanced drug loading. No use of organic solvents. Large-scale production.	Hot homogenization: Suitability for the thermostable drug. Infiltration of the drug into the aqueous phase. Complications of the crystallization process. Drug distribution and loss may occur into the aqueous medium during homogenization. Produced particles are of low size and narrow particle size distribution.	[32,27]
Nanoprecipitation	Appropriate for encapsulation of lipophilic drugs (water-miscible solvents) compared to hydrophilic drugs (water-immiscible solvents). Simple, quick processing, and reproducible results.	Instability when water-miscible solvents are mixed with an aqueous medium. Spontaneous emulsification is not observed due to “Marangoni effect”. Challenging in selecting appropriate drug, solvent, and non-solvent, inefficient encapsulation of hydrophilic drugs, and problem in mixing during nanoprecipitation.	[33-35]
Nanoemulsification- Solvent evaporation method.	Well-suited method for thermolabile drugs as it is devoid of thermal stress.	This method is limited to lipophilic drugs only and has some scale-up problems. More time consumption and particle coalescence during the solvent evaporation	[36]
Solvent displacement method.	High encapsulation efficiency. Better reproducibility, Homogenization not required. Ease of scale-up. Narrow size distribution.	Elimination of high volumes of water from suspension. Chances of leakage of the water-soluble drug during emulsification into aqueous external phase.	[37-39]
Nanoencapsulation	Coulombic interactions can be used for gene therapy and gene delivery as this provides a steady force which prevents undesired leaking. Hydrogen bonding for encapsulation as drug is out of the reach of water and hydrogen bonded drug can be stably encapsulated inside the carrier. Ability to protect active pharmaceutical ingredients from degradation. Nanoencapsulation has also improved the precision of drug delivery targets by utilizing surface coating or conjugating that ensures adequate cell entry Nanoencapsulated drugs can be labeled with fluorescent probes for imaging purposes, which is particularly useful for evaluating drug efficiency during preclinical and clinical studies. Targeted drug delivery. Increased shelf life and stability of drug, and nutrients like vitamins encapsulated.	Need of a large amount of solvent. Low product yield. Difficulty in scale-up. Adverse effects of residual surfactants.	[40,41]
Nanofabrication	Particles exhibit good biologic compatibility and can serve as drug carriers or nanoreactors. Ideally used because of the precision and resolution of the patterning. Used in designing nanobiosensors.	High-cost technique.	[42]

phase leading to formation of colloidal suspension. The method is devised by Nagavarma *et al*.[28] and may also be called as solvent displacement technique. The suspension is obtained in the presence or absence of surfactant and the aqueous medium used should be soluble with the solvent and non-soluble for the polymer.[29]

Nanoencapsulation

The method of packing of solid, liquid and gas nanoparticles are known as nanoencapsulation. The core within the drug material is known as a matrix and this forms nanocapsules. This method allows to encapsulate more than one drug molecule in an inert material and the molecule is secured from acid secretion of stomach and harsh environment. This also guides controlled delivery of drugs. Proteins and gene are encapsulated in nanocarrier as they are soft natured and less stable. Hence, their activity is retained by conjugation reaction with few structural changes

Proteins and gene are delicate in nature; therefore, they are capsulated inside the nanocarrier to maintain their stability and prevent them from metabolism. For attachment of proteins to delivery molecules, bioconjugate reactions are highly advisable to retain the activity of the protein as these reactions are very specific and there are fewer chances of structural changes in proteins.[30,31]

Nanofabrication

Elements with sizes ranging from 100 nm or less are generated by nanofabrication. This is a collection of methods and the etching process selectively removes the reacting agents thereby forming isotropic or anisotropic features that depends on the direction of the removed material. Hollow mesoporous silica nanoparticles are fabricated with sodium carbonate was reported with good biological compatibility and are well known as nanoreactors or nanocarrier of drugs.

DRUG DELIVERY AND MECHANISM OF ACTION OF NANOFORMULATIONS

Effective drug delivery of herbal components is achieved by various advantages in the field of nanoparticle drug encapsulation. Size, shape, charge of particle and the target cell are important entities that play an important role in drug delivery.

Distribution, efficiency and cellular uptake are affected by the particle size of the nanoparticle.[43] This is also important in degradation and elimination of nanocarriers. The charge of the nanoparticle is also critical in efficiency and mechanism of drug passage through the cell membrane.[44] The charges on the surface of the nanoparticle directly affect the stability of the drug-particle complexes.[45] A complex with high charge repels faster and is stabilized by the repulsive force thereby preventing aggregation of nanoparticle. Degree of absorption also varies based on charge of the particle as positive charges react with anionic mucus and helps in adhesion and retention of nanoparticles within the mucus layer. Numerous researches explain about the relevance of particle shape and biological properties of nanocomplexes.[46]

Polymer micelles were reported to facilitate effective blood circulation after intravenous injection.[47] A study by Patil showed reverse reaction of cellular adhesion and the length of nanoparticle.[48] Mechanism of drug action begins with interaction between within cellular receptors and their ligands. The receptors are the targets for nanodrugs which are complex molecules and in this case dendrimers and polymer-based nanoparticles were used for polyanionic receptor mediated targeting.[49]

Transport of Nanoparticles

The nano-drug complex crosses plasma membrane of cells through two methods; passive diffusion or endocytosis. The lipophilic nanoparticles could bypass the lipid membrane slowly and this process is known as passive diffusion. In endocytosis, various steps are involved where initially the components present in the external region of the cell membrane interact with the nanomedicine resulting in the formation of invaginations. The invaginations later on converts as phagosomes and then are delivered targeting specific region of the cell.[50] The process involved in nanoformulations and drug delivery is depicted in Figure 2.

TOXICITY ISSUES ASSOCIATED WITH NANO-HERBAL MEDICINES

Though nanobased herbal drug delivery is rapidly growing with improved drug delivering potential, they are also reported to possess cell toxicity, genotoxicity and immunotoxicity. Several assays like MTS, MTT and WST-1 are widely applied in order to find the count of viable cells. The cell viability is usually assessed by reduction assays with tetrazolium, immune histochemistry biomarkers and comet assay. The inflammatory response by the cell after delivering nanoparticles are measured by biomarkers like interleukin 8, interleukin 6 and TNF-α. These are carried out using assays like ELISA and Lactate Dehydrogenase (LDH)

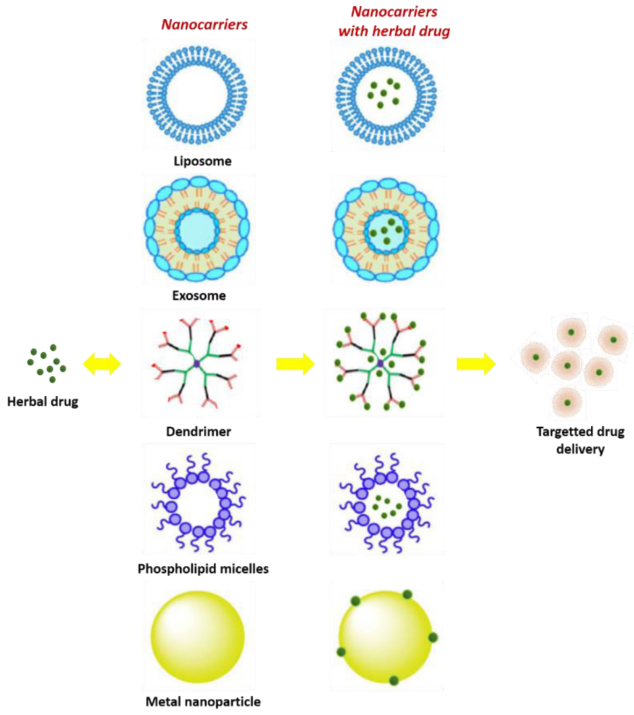

Figure 2: Mechanism of delivery of herbal drugs to cellular targets using nanocarriers.

tests. Several *in vitro* toxic experiments are also employed with cancer cell lines.

Silver nanoparticles and toxic effects

Silver nanoparticles are widely used from long since for the preparation of anti-bacterial products. They are also used to dress wounds and also in the manufacture of surgical instruments and prostheses.[51] They cross the blood brain barrier to reach brain and accumulate in various organs of human body. Deposition of Ag NPs was reported in organs like kidney, liver, lungs, spleen and brain in experimentation with rats exposed to silver nanoparticles by subcutaneous injection.[52] Weak cell viability, formation of ROS and LDH leakage were also associated with these nanoparticles.[53]

Polymeric Nanoparticles and toxicity

Cancer chemotherapy is been done widely with the use of biodegradable polymeric nanoparticles. They are also used in nanomedicine preparation by encapsulation for targeted release of drugs to specific tissues.[54] A report proposes toxicity of surface coating with poly -(D,L-lactide-co-glycolide)-based nanosystem towards human-like macrophages.[55]

Considering numerous application of nano-herbo formulations in medical industry, researchers are interested in developing particles with less toxicity by carrying out several *in vivo* assessments. FDA has reported that the problems associated with toxicity of nanoparticles were considered for approval and has reported that nano derived drugs are either totally safe or harmful for human health. It has also said that every nano-formed products are subjected to toxicity testing and regulation.[56]

ADVANTAGES OF NANO-HERBAL FORMULATIONS

Numerous critical issues such as poor specificity, sensitivity, toxicity and drug resistance issues are associated with conventional method of delivering therapeutic agents. These problems reduce the therapeutic efficiency of herbal drugs.[57] Several biologically active entities like tannins, terpenoids and flavonoids are highly water soluble with low absorption quality. They also face difficulty in crossing the lipid membrane due to high molecule size thereby decreasing the bioavailability, absorption of drug and efficacy. There are studies to prove presence of herbal compounds with higher *in-vitro* bioactivity which is lost during *in-vivo* experimentation. Incompatibility of herbal components with other compounds also results in rare preference in using those formulations. The Table 2 provides a list of the applications of herbonano formulation.

Various nano strategies have been discovered to overcome this difficulty. Nanoparticles are known to allow materials with diverse properties to be formulated together. Nanocarriers are submicron sized compounds used to transport therapeutic active components with high surface area to volume ratio. Such nanostructures were able to deliver components including anti-cancer drugs effectively and specifically to the affected tissue. They were also able to treat the infection of the tissue with minimal side effects. The novel drug delivery system with the use of nanotechnology has increases the effectiveness of herbal active components by protecting them against thermal degradation, phytodegradation, reducing toxicity and side effects and also controlled delivery of active principle.

FUTURE PROSPECTS OR DEVELOPMENTS OF NANOFORMULATION

Deliveries of herbal active components potentially improve their activity in biological systems and also help to tackle the issues associated with herbal medicines. Though there are immense advancements in the nanoformulations of herbal active components, challenges still remain in the implementation of nanoformulations in therapeutics. Methods to detect and control the interactions of nano-herbal complexes with the cellular components face clinical challenges.

Table 2: Applications of herbo-nanoformulation.

Herbal drug and therapeutic applications	Nanoparticle used as carrier	Advantages/Recent Developments	References
Colchicine from *Autumn crocus* used to prevent attacks of pain in the abdomen, chest, or joints caused by a certain inherited disease.	Liposome-NPs (Rotary evaporation sonication method)	Enhance skin accumulation, prolong drug release and improve site specificity, increased permeation through skin.	[58]
Curcumin from Rhizome of turmeric for cancer therapy, potent anti-inflammatory and antioxidant and may also help improve symptoms of depression and arthritis.	cancer therapy, potent anti-inflammatory and antioxidant and may also help improve symptoms of depression and arthritis.	Curcumin overcomes solubility issues of herbal drugs, nanocurcumin acts on pancreatic cancer cells, induces cellular apoptosis, blockade of nuclear factor kappa B (NF-kB) activation, and downregulation of steady state levels of multiple pro-inflammatory cytokines.	[59]
Asiaticoside, aglyconeasiatic acid from *Centella asiatica* used to repair nervous tissue due to spinal injury, euromuscular disorders, and to increase general brain function and memory.	Chitosan- alginate (Ionic gelation method).	Nano encapsulation of CAE provided physical stability compared to its extract alone.	[60]
Tanshinone IIA, salvianolic acid B from Danshen for the treatment of stroke, chest pain, and other diseases of the heart and blood vessels. It is also used for menstrual disorders, and chronic liver disease.	Phospholipids complex loaded nanoparticles.	Nano-coated *S. miltiorrhiaza* that exhibited stronger antioxidant bioactivities and also the polar active constituent in nanotechnology samples were released faster than the traditionally powdered samples. Phospholipids complex loaded nanoparticles also enhanced oral bioavailability of salvianolic acid.	[61]
Lipophilic molecule from Paclitaxel used in cancer medication that interferes with the growth and spread of cancer cells in the body. Taxol is used to treat breast cancer, ovarian cancer, and lung cancer. It is also used to treat AIDS-related Kaposi's sarcoma.	Chitosan (Emulsion-solvent evaporation).	Aqueous solubility of PX is greatly enhanced, preferential delivery of PX into the tumor site due to the enhanced permeability and retention (EPR) effect and the pharmacokinetic profiles of the drug from NPs is improved.	[62]
Asiaticoside, Madecassoside, Asiatic acid, Madecassic acid from *Centella asiatica* in treatment of skin problems, to heal wounds, for revitalizing the nerves and brain cells.	Gelatin (Nanoencapsulation method).	Skin-protective activities of *C. asiatica* were significantly improved through the nano-encapsulation and indicates that crude extract can be used and have the same efficacy as purified compounds, which should reduce the purification process and production costs.	[63]
Triterpenes, Saponins and Tannins from *Phytolacca decandra* used in homeopathy for the treatment of various ailments like chronic rheumatism, regular conjunctivitis, psoriasis, and in some skin diseases was tested for its possible anticancer potential.	PLGA-NPs (Encapsulation).	Nano-encapsulation of PD increases drug bioavailability and thereby has a better chemo-preventive action against lung cancer *in vivo* and on A549 cells *in vitro* than that of PD.	[64]
Flavonoid glycosides Quercetin used as anti-oxidant and anticancer agents.	PLA Nanoparticles (Solvent Evaporation Method).	Improves therapeutic efficacy and bioavailability of the herbal molecule.	[65]
Ursolic acid from *Ocimum sanctum.* For the treatment of bronchitis, bronchial asthma, malaria, diarrhea, dysentery, skin diseases.	Sodium alginate chitosan NPs. (Gelation method/ cation-induced).	Better and long-lasting antimicrobial activity than the unloaded formulation, producing cotton fabrics with excellent antimicrobial activity.	[66]
Artemisinin from *Artemissia annua* treated for fevers and malaria.	Au, Ag	*A. annua* - reducing and capping agent for Au and Ag nanoparticle production. Au, Ag NPs - significant Tyrosinase inhibitory and antibacterial effects.	[67]

Continued...

Table 2: Cont'd.

Herbal drug and therapeutic applications	Nanoparticle used as carrier	Advantages/Recent Developments	References
Catechin, a phenolic compound from white tea rich in antioxidants. Reduce the risk of heart disease, weight loss, Help to Protect Teeth from Bacteria, anti-cancer property, Lower the Risk of Insulin Resistance.	PCL, Alginate, Pluronic F-127 (Nanoprecipitation method).	White tea extract retained antioxidant activity and NPs protected tea polyphenols from degradation, thus opening new perspectives for the exploitation of white tea extract-loaded NPs for nutraceutical applications.	[68]
Naringenin with anti-dyslipidemic, anti-obesity and anti-diabetic and antifibrotic activity.	Polyvinylpyrrolidone (PVP). (Nano-precipitation technique).	NAR NPs are used to reduce the dosage of NAR, improve its bioavailability and merits further investigation for therapeutic applications.	[69]
Penta- cyclic triterpenoid – Silymarins.	Eudragit nanoparticles (cold homogenization technique and nanoprecipitation technique).	SNPs were safe and potentially offered enhancement in the pharmacological hepatoprotective properties of silymarin. SLN was a good carrier for improving the oral bioavailability of poorly soluble drugs.	[70]
Paeonol from *Paeonia fruticosa* used as an analgesic, antipyretic, anti-inflammatory agent.	Polymeric nanoparticles-Gelatin (Nanoprecipitation).	Pae-NPs could exert much stronger antitumor effects than free Pae and represent a promising delivery system.	[71]
Isoquinoline alkaloid from Berberine used to treat liver disorders, including acute and chronic viral hepatitis, toxin/drug-induced hepatitis, and cirrhosis and alcoholic liver diseases. It has also been reported to be effective in certain cancers.	Chitosan NPs (Emulsification and Ionic gelation methods).	BH/FA-CTS NPs promoted apoptosis and necrosis of CNE-1 cells. And BH/FA-CTS NPs displayed distinguished higher tumor inhibition than control group, free BH and BH/CTS NPs *in vivo*. Therefore, as a nanocomposite, BH/FA-CTS NPs provide a new method and option for the treatment of nasopharyngeal carcinoma patients.	[72]
Triterpenoids and Alkaloids from *Murva* used in treatment of skin diseases, fractures, convulsions, hemiplegia, facial paralysis, and cephalalgia. For fungal infections of the skin.	Chitosan (Ionic gelation technique).	Newly developed formulation with potential and effective agent to enhance the bioavailability and stability.	[73]
Rutin from green tea enhances the action of vitamin C, to support blood circulation, as an antioxidant, and to treat allergies, viruses, or arthritis and other inflammatory conditions.	Solid–lipid nanoparticles (Complex-coacervation method).	Targeting into cardiovascular and cerebrovascular region. Nano-system of ISR against hypertension is achieved with consequent dose reduction with enhanced systemic bioavailability.	[74]
Ginkgolic acid from *Ginkgo biloba* L. that protects against Aβ-Induced Synaptic Dysfunction in the Hippocampus. supplement for cognitive ailments and allergic reactions.	Silver nanoparticles (AgNPs) (gas-phase grinding techniques and liquid-phase grinding techniques).	*G. biloba* containing nanoparticles increase acetylcholine releasing activity from cerebral cortical synapses and the improvement of stimulation response of hippocampal pyramidal cell. Thus, the nanosized *G. biloba* extract is expected to activate the brain cell and work on the treatment of Alzheimer's dementia.	[75]
Triptolide from *Tripterygium wilfordii* effective in the treatment of variety of inflammatory and autoimmune diseases, especially rheumatoid arthritis and anti-inflammatory effect.	Galactosylated-chitosan-TP-Nanoparticles (GC-TP-NPs). (Tripolyphosphate cross-linking method).	GC-TP-NPs retained the anti-cancer activities of the free TP, exerting the same pro-apoptotic and anti-proliferative effects on HCC cells *in vitro*, and displayed higher efficacies in reducing tumor sizes *in vivo*. induced cancer cell apoptosis via blocking TNF/NF-κB/BCL2 signaling. Promising candidate in halting liver cancer progression while minimizing systemic toxicity.	[76]
Breviscapine for treating hypertension, cerebral embolism, and paralysis, cerebral infarction and diabetic nephropathy.	Mesoporous Silica Nanoparticles (MSNs). (Ultrasound-assisted solution-enhanced dispersion.	Nanocoated breviscapine increases plasma concentration and pharmacological activity of breviscapine hence, enhances blood circulation.	[77]

Some of such challenges are fulfilment of therapeutic requirements, feasibility in developing and introducing novel therapeutic methods in market, avoiding toxicity and compatibility to international standards and probing of targeting efficiency of the nanomedicine.[78]

CONCLUSION

The discovery of herbal drug and its development towards marketing involves tedious efforts in accomplishing several factors like solubility, bioavailability, efficiency and toxicity. Nanoparticle based drug delivery system has been introduced to overcome the problems associated with discovery to commercial production of a drug. Since last few decades nano-herbal medicines has played a major role in academic research with benefit to clinical and marketing of improved therapeutics thereby improving human health.

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CONFLICT OF INTEREST

The author declares no conflict of interest.

ABBREVIATIONS

Ag-NPs: Silver nanoparticles; **AIDS:** Acquired immunodeficiency syndrome; **Au-NPs:** Gold nanoparticles; **BH/FA-CTS NPs:** Folate acid modified chitosan nanoparticles loaded berberine hydrochloride; **ELISA:** Enzyme linked immunosorbent assay; **FDA:** Food and drug administration; **GC-TP-NPs:** Galactosylated-chitosan-Triptolide-nanoparticles; **LDH:** Lactate dehydrogenase; **NAR:** Naringenin; **NF-kB:** Nuclear factor kappa B; **NPs:** Nanoparticles; **PAE:** Paeonol; **PCL:** Poly(ε-caprolactone); **PEM:** Proton electrolyte membrane; **PLA-NPs:** Poly-lactic acid nanoparticles; **PLGA-NPs:** Poly (lactic-co-glycolic acid) nanoparticles; **PVP:** Polyvinylpyrrolidone; **PX:** Paclitaxel; **ROS:** Reactive oxygen species; **TNF-α:** Tumor necrosis factor-α; **WHO:** World health organization.

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