



## Review paper

## Nanophytomedicine in Clinical Management: An Introductory Evidence-based Review

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## ABSTRACT

**Introduction:** Herbal medicines are an important ingredient of traditional and alternative medicinal system and thus being used since ancient times. Owing to their characteristic of having lesser side effects and potential therapeutic effect they have drawn attention of pharmaceutical scientists from across the globe. Herbal medicines have now strongly captured a whopping US \$62 billion market globally. Herbal medicines have been widely accepted of their potential to treat chronic diseases, low toxicity profile, cheap and wide availability etc.

**Methods:** The Safety and efficacy of herbal drugs have played an important part in their successful commercialization. With the emergence and application of nanotechnology the bioavailability and bioactivity of herbal medicines have improved drastically.

**Results:** Development of nano-phytomedicines by reducing their size to nano scale range, attaching it with polymers and by modifying their surface properties, solubility, permeability, eventually enhances the bioavailability of herbal formulations.

**Conclusion:** Novel formulations like niosomes, liposomes, nanospheres, phytosomes etc. can be exploited in this area. However, novel nano-phytomedicines comes with its own pros and cons. This article extensively reviews herbal nano-medicines with its reported success and failures.

**Keywords:** Nano-Phytomedicine; Liposomes; Nanospheres; Toxicity; Bioavailability

### Introduction

In recent years, herbal medicines are being extensively studied and prescribed for possessing comparatively low adverse drug reactions and side effects to their synthetic alternates. Restorative application of herbal medicine has increased drastically owing to increased body of clinical evidence [1,2].

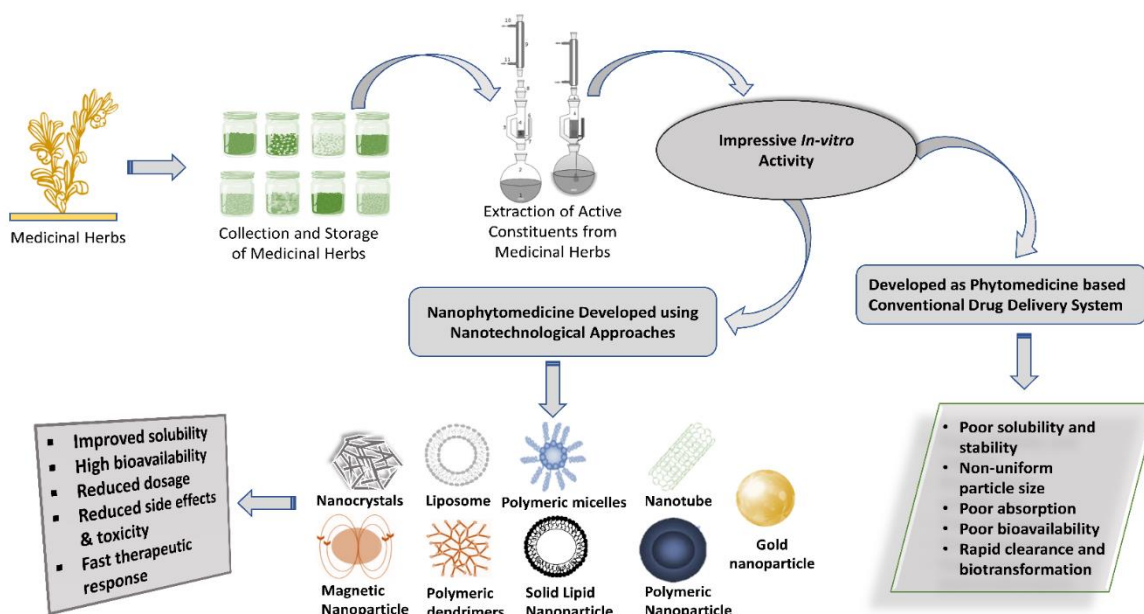
The use of herbal medicine has certain limitations, due to a lack of proper guidelines detailing about the risk

factors associated with their self-medication, toxicity due to overdose, and poisoning due to incorrect identification or improper selection of parts of plant or their associated method of preparation [3,4]. Any error in quality control may increase the risk of adulteration in botanical materials.

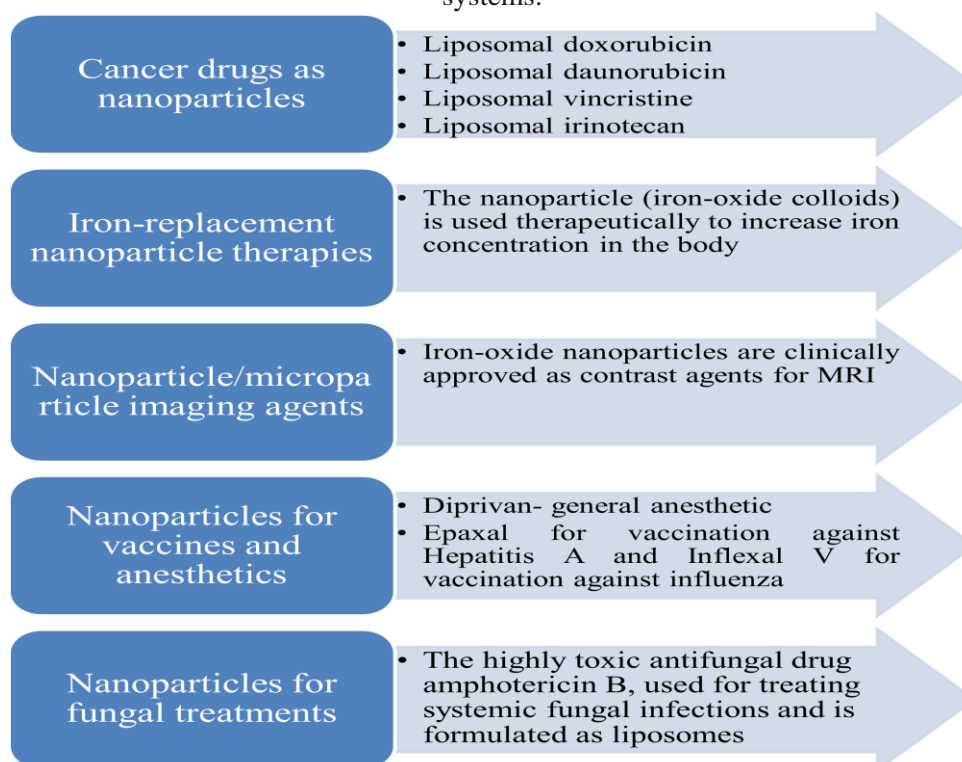
A major issue with herbal medicines is poor or uncertain bioavailability and thus there is always a space for the

improvement of effective and efficient delivery of herbal drugs to specific targets. The *in vitro* bioavailability results of active phytoconstituents usually do not translate into effective *in vivo* therapeutic applications. Novel drug delivery system provides a

better platform to overcome such limitations (**Figure 1**). Drugs can be effectively controlled by incorporating into carrier systems or by amending the structure of the same [5].



**Figure 1:** Systematic representation of advantages of nanophytomedicines over conventional herbal based delivery systems.



**Figure 2:** Clinically approved nanoparticles.

Phytomedicines must be extensively studied for its biopharmaceutical and pharmacokinetic parameters for designing rational dosage regimens [6].

Nano-formulations of phytomedicines are being studied by researchers throughout the globe. The development of herbal theranostic nano-formulation is very useful for the treatment of different diseases [7-8]. Herbal formulation developed by exploiting nanotechnology provides numerous advantages over conventional phytomedicines.

The solubility and systemic bioavailability of curcumin have been improved by developing into a nano-formulation and was found to be effective in colorectal cancer [9-11]. Many nanotechnologies based herbal formulation has already published with improved efficacy. Thymoquinone nano-formulation [12], a

natural polyphenol has remarkable anticancer effects but have limited bioavailability, which was overcome by developing it into a nano-formulation [13]. A high dissolution rate and better stability of quercetin was achieved with nano-formulation [14].

### Clinically approved nanoparticles and nanoparticles undergoing clinical trials

Currently, there are several nanoparticles approved for clinical use as therapeutic agents, imaging agents, or technologies by the U.S. FDA or the European medicines agency. We hereby enlist the recent clinical trials which are based on phytomedicines, their indication and study status (**Table 1**) [15].

**Table 1:** Enlists the recent clinical trials which are based on phytomedicines, their indication and study status.

ClinicalTrials.gov Identifier	Intervention/Treatment	Indication	Study Phase
NCT01861496	Liposomal Cisplatin Formulation	Advanced or Refractory Solid Tumours, Metastatic Breast Cancer, Prostate Cancer and Skin Cancer	Phase I/II
NCT00441376	Thermally Sensitive Liposomal Doxorubicin (ThermoDox™) in combination with radiofrequency ablation	Hepatocellular Carcinoma Liver Neoplasms	Phase I
NCT00826085	Thermally Sensitive Liposomal Doxorubicin (ThermoDox™) in combination with Microwave Hyperthermia	Breast Cancer	Phase I/II
NCT02112656	Thermally Sensitive Liposomal Doxorubicin (ThermoDox™) with standardized radiofrequency ablation	Hepatocellular Carcinoma	Phase III
NCT02536183	Lyso-thermosensitive Liposomal Doxorubicin and MR-HIFU	Pediatric Refractory Solid Tumors	Phase I
NCT00093444	Heat Activated Liposomal Doxorubicin and Radiofrequency Ablation	Primary or Metastatic Liver Tumors	Phase I
NCT00355888	Liposomal oxaliplatin suspension for injection (MBP-426)	Cancer	Phase I
NCT00964080	Liposomal oxaliplatin suspension for injection (MBP-426) in combination with Leucovorin/5-FU	Second Line Gastric, Gastroesophageal, or Esophageal Adenocarcinoma	Phase I/II
NCT00448305	EndoTAG-1 + paclitaxel	Breast Neoplasms	Phase II
NCT03002103	EndoTAG®-1 in Combination with Paclitaxel	Triple-Negative Breast Cancer	Phase III
NCT01151384	Liposome Encapsulated Docetaxel (LE-DT)	Solid Tumors	Phase I
NCT01188408	Liposome Entrapped Docetaxel (LE-DT)	Prostate Cancer	Phase II
NCT00765973	Topotecan Liposomes Injection (TLI)	Small Cell Lung Cancer, Ovarian Cancer, Solid Tumors	Phase I

NCT01770353	MM-398 (Nanoliposomal Irinotecan, Nal-IRI)	Solid Tumors, ER/PR Positive Breast Cancer, Triple Negative Breast Cancer, Metastatic Breast Cancer with Active Brain Metastasis	Phase I
NCT02640365	MM-398 Plus Irinotecan	Unresectable Advanced Cancer	Phase I
NCT03088813	Irinotecan Liposome Injection (ONIVYDE®)	Small Cell Lung Cancer	Phase I/III
NCT02013336	MM-398 (Irinotecan Sucrosfate Liposome Injection) plus cyclophosphamide	Recurrent or Refractory Solid Tumors, Ewing Sarcoma, Rhabdomyosarcoma, Neuroblastoma, Osteosarcoma	Phase I
NCT03810742	Nano-liposomal Irinotecan	Refractory Solid Tumors	Phase I
NCT03483038	Liposomal Irinotecan in Combination With the 5-FU and Oxaliplatin	Pancreatic Adenocarcinoma	Phase II

### Biological barriers to effective drug delivery

Novel drug delivery systems are designed to minimize pharmacokinetic issues. Biological barriers are hindrance in the proper delivery of drug which may be connective tissues or sheaths surrounding the nerves. Sometimes the outer skin layer may act as a living barrier that could make the drug difficult to pass. They act similarly like the blood brain barrier.

### Reticuloendothelial system

Mononuclear phagocyte system (MPS) commonly known as reticuloendothelial system (RES), it may be either cellular or noncellular components. The reticuloendothelial system performs phagocytosis of foreign materials and particles. The location of RES in the body is the liver [16]. Apart from phagocytosis the functions of RES are cytotoxicity against tumor cells and have a function in the regulation of the immune system. An important task of RES is to capture and clear unwanted particulate material from blood and lymph [17]. Nanoparticles bind with phagocytic cells, release cytokines and enhance its clearance from the bloodstream and local inflammation of the tissue [18]. In the RES, macrophages catch the particle-bound with serum proteins and, surface modification of liposomes by polyethylene glycol (PEG) decreases the opsonization which lessens the clearance by the RES, leading to enhanced pharmacokinetic characteristics [19]. The modified liposome was found to be capable of avoiding reticuloendothelial system thus prolonging their circulation time assisting in reaching them to targeted tissues. Further coating of nanoparticles with membranes derived from erythrocytes and leukocytes was suggested to improve their self-recognition [18]. Phagocytic clearance prevented by using ligands such as CD47-SIRP $\alpha$  [20].

Nanoparticles of spherical shape may gather in the middle of the blood vessels and so are less prone to come out upon interaction with endothelial cells [21].

### Renal system

Filtration of blood takes place in the kidney becoming one of the key factors to be kept under consideration while designing of nanoparticles. The filtration process depends upon the size of particle and pore size. Nanoparticles can cross the perforated endothelium having 70 to 100 nm pores and also through the glomerular complex sitting between the podocytes and capillary endothelium thus allowing clearance to particles in the size range of 2–8 nm [18]. The clearance of nanoparticles through the kidney is associated with the size, shape, and charge of the particle. Spherical shape particle has more renal clearance. In glomerular apparatus, the slit diaphragms opening, and closing is controlled by tCD2-associated protein and nephrin which usually allows passage of small molecules and water [22]. The clearance of nanoparticles having a positive charge is more because the glomerular membrane has a negative charge and develops an attractive force. The smaller size of nanoparticles the more easily it gets filtered, and thus the efficacy may be compromised [23]. Drugs are released from the nano-encapsulated system in a sustained manner to show chemotherapeutic activity [24], and safely gets eliminated from the bloodstream thus limiting any unexpected long-term adverse actions [25].

### The blood-brain barrier (BBB)

For the treatment of brain cancer, BBB causes a challenge for molecules to pass through it. This strong barrier allows only 2% of molecules which includes specific proteins and peptides, nutrients, ions,

leukocytes and certain nutrients [26]. The structure of endothelial cells bonded by tight junctions and is enclosed by astrocytes cells, basal lamina, pericytes, and microglia [18]. Nanoparticles enter through the BBB by receptor-mediated endocytosis mechanism and depending upon the binding capacity of peptides or ligands to receptors, nanoparticles get attached to the endothelial surface [18,27]. Nanoparticles as carrier can cross the blood brain barrier by exploiting surfactants like poloxamer 188 or polysorbate 80 [28-29]. Nanoparticles, with diameters of 20-70 nm and neutral to anionic charge easily penetrate through BBB [30-31].

### Types of nanoparticles

Protein-drug conjugated nanoparticle is a novel approach where the protein is directly conjugated with drug molecules [32]. However, such conjugation is biodegradable, the drug sometimes gets released before the target site, the presence of protease and redox-altering substance in the blood destroys the protein-drug linkage [33]. Different techniques are exploited for the successful development of nanophytomedicines (**Figure 2**). Presence of antibody proteins in the drug-protein conjugated nanoparticles increases the targeting potential of the drug. Another challenge is the sensitivity of protein-drug based nanoparticles towards the base part of the protein; consequently, making certain drugs unsuitable for being developed as nanoparticle-based delivery system. The enzymatic agents which are readily available in blood plasma degrade the protein-drug linkage, leading to premature activation and thus reducing the circulation time and increasing the bioavailability [34].

### Liposomal nanoparticles

Liposomal nanoparticles are prepared by using lipid bilayers. They are commonly of spherical shape [35]. Liposomal nanoparticles are formed instantly when the amphiphilic lipid is added to aqueous or other hydrophilic liquid thus producing spheres of 50-500 nm size range. Hydrophilic drugs are encapsulated by dissolving in the liquid used for developing nanoparticles, leading to the formation of a layer of drug molecules in between the lipid bilayer system [33]. Extrusion, solvent injection, reverse phase evaporation, sonication etc. are some of the most common techniques of developing liposomal nanoparticulated system [36]. The liposome nanoparticles release the encapsulated drug at a specific temperature are called thermosensitive nanoparticles, such a mechanism allows targeted delivery of drugs under the influence of high-intensity ultrasound, microwaves, or radio

frequencies. This technique has been a success in clinical application to enhance drug delivery [33, 37]. The quality of the polymer used with an object to easily fuse with the target cell. The other advantage of polymeric coating is to increase the circulation time, improving the bioavailability of the encapsulated drug, enhancing targeting efficiency, and altering the surface charge of the liposome [33]. Synthesis of polymeric nanoparticles depends upon the molecular weight, biodegradability, and hydrophobicity of the polymer. Several methods like nanoprecipitation, electrospray, and emulsification are adopted in lab to efficiently encapsulate drug molecules.

### Dendrimer nanoparticles

They are spherical macromolecular structure having branches of dendrimers which originates from a central point. It is formed in layers in which the first core of the dendrimer engulfs on to the pre-layer before allowing the branches to form. Modification of dendrimer in respect of degree of branching and size favor the polydispersity of the nanoparticles [33].

### Hydrogels

This nanoparticle formed by water-soluble polymers, it has a three-dimensional structure and is capable of retaining large amount of fluids. Most of the synthetic hydrogels are non-biodegradable in nature but addition of components like enzymatic agents, hydrolytic agents, and stimuli-responsive agents added to the hydrogel's matrix makes them biodegradable under certain conditions. The water contained in the hydrogel is very similar to tissues that make it unique. The drug load and release are controlled by modulating the quality and quantity of porosity and cross-linking in the hydrogel matrix [38].

### Other nanoparticle platforms

Gold is a well-known example of metallic nanoparticles and it has been frequently used as a theranostic agent for cancer therapy for which it is either used as a lone drug or loaded with certain imaging and therapeutic agent. The detection properties of it are due to the optical absorbance behavior and its photothermal activity makes it suitable for cancer treatment. A layer of thermo-responsive polymers makes it possible for controlled drug release [33].

For cancer treatment carbon nanotubes are used, it binds to different biological systems and enters cellular system through endocytosis. Single-walled carbon nanotubes are highly suitable in biological environments because these suspensions are stable in

physiological buffers [39]. These nanoparticles have properties to treat photo-chemically damage tumor cells through photo-dynamic and photo-thermal therapy [40]. Silver nanoparticles are another example for the treatment of cancer; however, the exact mechanism is not known, it is postulated that in the acidic environment of cancer cells they produce ROS which induces damage to cellular materials and triggers apoptosis [41].

### Successful nanophytomedicine

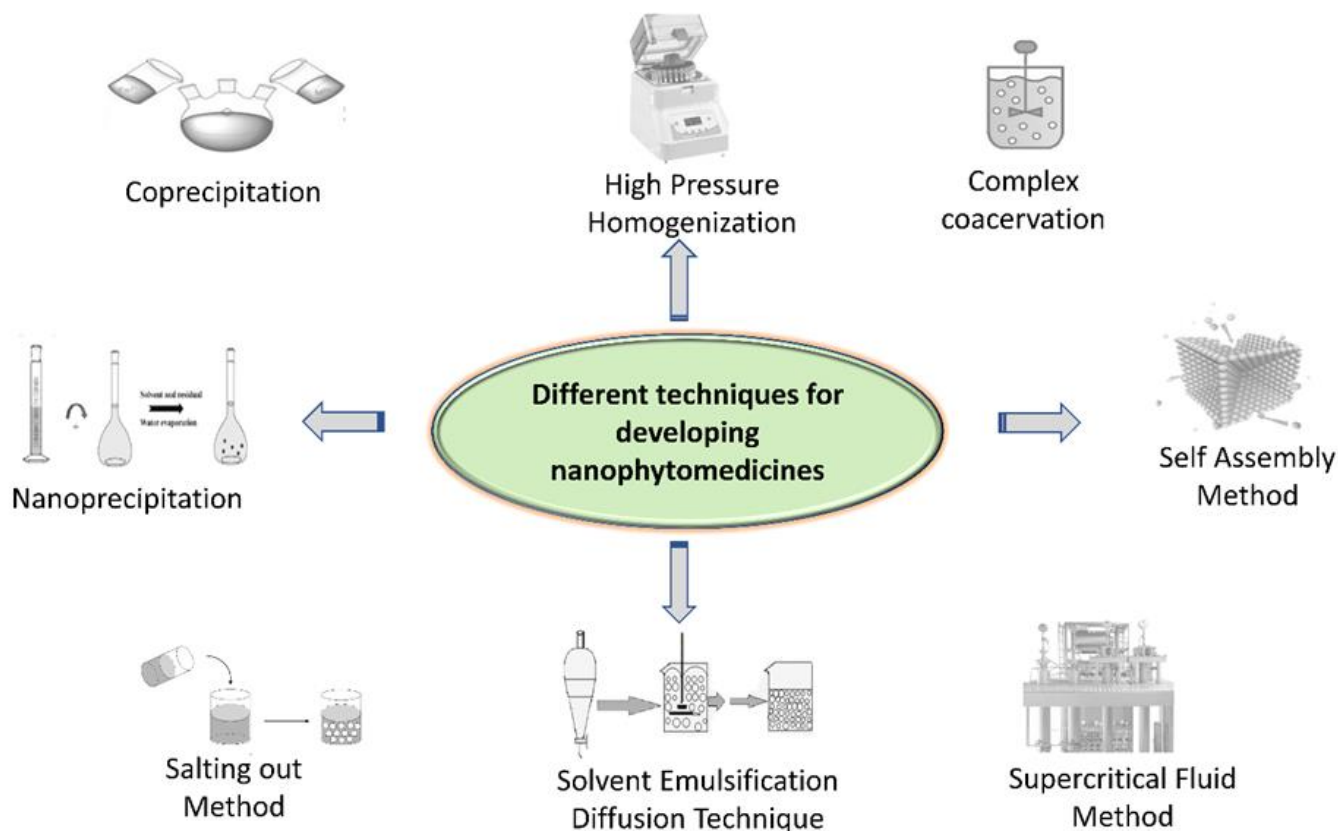
The phytoconstituents curcumin has been widely used for several therapeutic applications like anti-microbial activities, anti-inflammatory, and anti-hyperlipidemic [42]. Animal studies do not produce reproductive toxicity at certain doses. Curcumin at the dose of 500 mg two times in a day for 30 days was safe but more studies on the human at nano-formulation level must be considered [43]. Paclitaxel (TXL) is an anti-cancer agent extracted from the bark of Pacific yew tree. They can cause toxicity to normal tissues, which can be overcome by designing chemo drug-loaded nano-formulations. Poly (l-glutamic acid)-paclitaxel (PG-TXL) is one of the few formulations that reached phase III clinical trials [44]. Different formulations of nanophytomedicine such as nano-capsules, nanogels, herbal nanoparticles, nano-tablets, nano-paste, nano-powder, and nano-emulsions provide advantage for ayurvedic drugs which are high solubility, better bioavailability, lesser toxicity, good pharmacological activity and high stability [45,46]. Many reports have successfully reported the treatment of cancer by nanophytomedicines. Grape seed extract (GSE) encapsulated in Poly (lactide-co-glycolide) (PLGA) nanoparticles having particle size in the range of 100 nm which were found to be highly stable at physiological pH. Nano-precipitation technique is exploited for its preparation. In vitro studies confirm its anticancer potential. A flow cytometric and fluorescence microscopic study revealed enhanced targeted cellular uptake of Nano-GSE conjugated folic acid on folate receptor-positive tumor cells. The studies to determine the efficacy of the developed formulation in terms of IC<sub>50</sub> values were reported to be decreased for the developed complex by a factor of 3 in comparison to the free drug, thus enhancing the bioavailability of the developed formulation at the tumor site with the potential of targeting cancerous cells one eventually improving the apoptotic index [47]. Curcuminoids-loaded lipid nanoparticles formulation has been reported with two times more antimalarial activity when compared to conventional formulation. The bioavailability concern was overcome by the controlled

delivery of curcuminoids for an extended period of time. Parenteral administration overcomes the low bioavailability issues. Lipid based nanoparticles are capable of increasing the concentration of drug at the targeted site and could potentially help in cerebral malaria. Nanoparticles of trimyristin, glyceryl monostearate and tristerin, as solid lipid nanoparticles and medium-chain triglyceride (MCT) as liquid lipid nanoparticles having a mean particle size of 100–250 nm has been reported [48]. Triptolide (TP) is an herbal medicine obtained from traditional Chinese medicine *Tripterygium wilfordii* Hook F. It has potent immunosuppressive effects, anti-inflammatory. Nano-formulation- TP-loaded poly (D, L-lactic acid) (PLA) nanoparticles has been formulated by spontaneous emulsification solvent diffusion method. Absorption of poorly water-soluble drugs (Triptolide) was found to be increased because of the bio-adhesive properties of nanoparticles. Upon toxicity study no deaths of rats were reported up to the study termination on day 30. The release of TP from nanoparticles was biphasic in nature with initial burst release followed by release of the drug in a sustained manner. Established arthritic therapeutic effects, significantly inhibits adjuvant-induced arthritis and had been reported with anti-inflammatory effect upon long time administration [49]. Catechin a polyphenolic compound has antioxidant effects, which shows controlled release with chitosan-based nano-formulated system. The formulation was prepared by using sodium tripolyphosphate ionic cross-linking technique. Nanoparticles are developed by the crosslinking technique. In vitro studies confirm catechin release in enzyme-free simulated gastric and intestinal fluids and in simulated intestinal and gastric fluids between 40% and 15% which is dependent on the structural interaction between chitosan matrix and the catechin [50]. Cryptotanshinone (CTS) found in the roots of *Salvia miltiorrhiza* Bunge has anti-inflammatory, cytotoxic, anti-bacterial, anti-parasitic, anti-angiogenic activity. The oral bioavailability of the drug was found to be enhanced in nano-formulation. The solid lipid nanoparticles are prepared by exploiting high pressure homogenization technique and ultrasonication method. The pharmacokinetic studies on rats demonstrated that upon oral administration of CTS in different solid lipid nanoparticles was found to increase the bioavailability of CTS compared to conventional CTS suspension. SLN distinctly changes the metabolism behavior of CTS to tanshinone IIA. CTS-SLNs formulation was found to be increasing the oral absorption of poorly soluble drugs [51]. All-trans-retinoic acid (ATRA) is a derivative of vitamin A, has low bioavailability due to poor solubility. Solid lipid nanoparticles (SLNs) encapsulated with TRA was

reported to be prepared successfully by high-pressure homogenization method. The developed formulation was found to enhance the solubility of the drug. The oral pharmacokinetic study in rats showed that solid lipid nanoparticles demonstrated significantly enhanced bioavailability profile of ATRA compared with ATRA solution. The report suggested their anti-cancer activity against human malignant gliomas [52].

Docetaxel an anticancer drug belonging to the class of alkaloid, the bioavailability of the drug-enhanced was found to be enhanced by three-fold by formulating a nano-formulation of the same. The phytonanomedicine was developed as solid-liquid nanoparticles (SLNs). Oral deliveries of many drugs are hampered by chemical and enzymatic barriers in the gastrointestinal (GI) tract. SLNs used to increase the efficacy over conventional formulation by protecting the drug from enzymatic degradation. Natural compound is encapsulated suitably and used for the treatment of many diseases like cancers, central nervous system-related disorders, cardiovascular related diseases, infection, diabetes [53,54] and osteoporosis [55]. Hypocrellins, a natural substance found in Chinese herbal medicine have two exceptional constituents namely hypocrellin A (HA) and

hypocrellin B (HB). Both are used as photosensitizers, having a very good antiviral and antitumor property. It is found to inhibit the growth of the human immunodeficiency virus. The efficacy of the drug in the natural form is reported to be very less. Their development as nano-formulation using silica nanoparticle (SN) has been reported better efficacy. The developed formulation has been characterized by different analytical techniques. Encapsulated drugs exhibit better stability and hydrophilicity than natural hypocrellin-A [56]. Frankincense and myrrh essential oils (FMO) are natural oil obtained from the *Boswellia* and *Commiphora* trees respectively [57]. It has several medicinal properties like antiseptic, astringent, carminative, digestive, diuretic and sedative effect. However, the hydrophobic properties of drugs reduce the therapeutic effects in traditional medicine. Solid lipid nanoparticles (SLNs) are exploited to develop nanophytomedicines. Aqueous SLNs are prepared by high-pressure homogenization technique where Compritol 888 ATO acts as the solid lipid and Tween 80 and soybean lecithin as the surfactants. SLNs as a drug carrier for hydrophobic compounds overall enhances the efficacy of the drug as antitumor agent [58].



**Figure 3:** Different techniques for developing nanophytomedicines.

### **Limitation of nanophytomedicines (NPMs) in clinical trials**

Developing herbal medicine as nanophytomedicine is a complex task compared to conventional formulation technology in different dosage form [59-61]. Various factors impose hurdles in the development of NPMs during large-scale manufacturing. It possesses challenges of safety, biocompatibility and cost effectiveness. Strict government regulations related to intellectual property (IP) challenges them against current therapeutic techniques [62, 63].

### **Large scale manufacturing**

NPMs face structural and physicochemical complexity during its formulation. Thus, large scale manufacturing is quite problematic [59-61]. Large scale manufacturing of NPMs with high batch to batch reproducibility is obtained by avoiding organic solvents in its preparation [64,65]. Encapsulating more than one therapeutic agent is a complex method and requires surface modification with coatings and/or addition of ligands (**Figure 3**).

### **Biocompatibility and safety**

NPMs may develop toxicity which can be confirmed with *in vivo* studies. The preliminary knowledge of free drugs activity and its toxicities makes it difficult to translate into clinical application. The bioavailability of the drug depends on the rate of release from the formulation in the biological environment [66]. Developing a nanomedicine using different synthetic compositions, coatings, and ligand creates hurdles in its translation into clinical application [60-63]. Novel strategies which are capable of specifically evaluating nanomedicines are being developed since the conventional techniques are inefficient toxicological evaluation of these nanomedicines for their potential clinical application. Novel techniques include high-throughput screening methods, alternative test strategies and computational modelling [67]. These techniques are capable of analyzing and comparing different nanophytomedicines simultaneously.

### **Intellectual property (IP)**

The involvement of nanotechnology in the development nanophytomedicines (NPMs) creates complexities in biomedical and clinical application, thus requires more precise definition for the same [68]. The phytonanomedicines have several components and very components must have IP [69,70]. General approaches to control the NNMs/NPMs products require IP which includes the drugs being encapsulated, the technology

of the carrier system and the characteristic properties of carrier and drug together.

### **Biological challenges**

The development of nanophytomedicines is done with an object of targeted delivery, However, there are limitation in clinical translation of the system into pathological application as a nanotherapeutic agent [71]. To improve the clinical translation, it is necessary to focus on a disease-driven approach for the development of NPMs which can exploit pathophysiological changes in disease biology. Several nanomedicines are not succeeding in clinical trials because of the NPMs behavior with patient biology as well as disease heterogeneity in patients [66]. Such challenges are problematic for the development of NPMs in pharmaceutical industry.

### **Government regulations**

In every country there is a regulatory body (e.g., FDA, TGA, and EMA) which regulate the manufacturing of nanomedicines. From last two to three decades NPMs are available in the market. These nanomedicines products require passing the regulatory approval and meeting the general standards which are applicable to the medicinal compound. Because of the complexity of nanophytomedicines, their interaction at tissue and cellular level with the body is not exactly known, which eventually increases complexity in their clinical application and the multifunctionality of some formulation (e.g., theranostic property) makes it an even more difficult task [60, 61,72-78].

### **Conclusion and Future Prospects**

Current research on nano-phytomedicine represents a novel approach in the treatment of different types of diseases. Numerous phytochemicals have been found to show promising result in this regard. Tailoring phytomedicines into nano-formulations potentially increases their effectiveness and decreases their toxicity profile. It also assists them in targeting specific sites. However, developing nano-formulation is a complex task and comes with its own demerits. Moreover, it is a relatively unsearched area of science where both herbal medicines and nanotechnology are combined and studied together. Fusions of herbal medicines with nano-technological method are being studied at different basic and clinical trial levels. It is the need of the hour to develop active delivery systems capable of delivering herbal drugs at a specific target with eventually decreasing their side effects. As a future prospect the development of phytomedicines for the



treatment of proposes vast area that needs special consideration by researchers. Herbal drugs in conjugation with nanotechnology are proving to be a productive therapeutic approach for pharmaceutical industry to enhance the health care system. It can be anticipated that the valuable and effective relevance of herbal medicines fused with nanotechnology will enhance the significance of existing system of drug delivery.

#### **Consent for Publication**

Not applicable.

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#### **Conflict of Interest**

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

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