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COMPREHENSIVE REVIEW ON USE OF NOVEL NANO AND MICROPARTICLES FOR DELIVERY OF HERBAL ACTIVES

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ABSTRACT

The active phytoconstituents isolated from plants are well recognized for their therapeutic potentials. The various therapeutic properties of plants like hepatoprotective, antimicrobial, neuroprotective, antitumor, antioxidant, skin protectives were well demonstrated by numerous experts. However, clinical use of these active constituents is limited due to their poor bioavailability, stability in biological fluids and authentication issues. These continue to be an open problem that affects application of these valuable ancient herbal herbs in effective treatment and management of various disease conditions. A potential solution to these difficult problems could be encapsulation of phytoactives in novel colloidal particulate systems. Novel colloidal carriers like nanoparticles, microspheres, lipid microparticles, were effectively utilized recently to solve drawbacks and for effective delivery of phytoactives. Several landmark studies observed better therapeutic efficacy of phytoactive loaded colloidal carrier compared to conventional drug delivery. Thus colloidal carrier based phytoactive delivery is recently developed promising and attractive strategy for better therapeutic control on disease conditions. The present exhaustive review highlights recent advances in herbal bioactives loaded colloidal carrier based drug delivery systems.

Keywords: Colloidal carriers, Herbal medicines, Herbal novel drug delivery systems, Nanoparticles, Microparticles

1. INTRODUCTION

Plant extract or isolated therapeutically active phytoconstituents have long been used worldwide for treatment of various diseases as well as accepted by physicians and patients because of their fewer side effects [1]. Therapeutic efficacy of herbs is widely reported and extensively explored in the literature by ancient Indians. Plant derived phytoactives based drug delivery systems are becoming more popular in the modern world for treating various diseases with lesser toxic impressions and better therapeutic potential. Modern herbal medicines developed on the basis of traditional ayurvedic knowledge. Nearly, 50% of modern herbal medicines are developed using isolated active phytoconstituents from various parts of herbs. In addition to this, most of the novel therapeutic molecules discover nowadays are developed using plant based lead molecules [2]. However therapeutic effects of some herb based products are limited due to various constraints like limited solubility as well as stability in gastrointestinal tract (GIT), poor absorption across GIT linings, considerable first pass metabolism and limited oral bioavailability. These issues are well documented in the scientific literatures. In order to tackle limitations associated with conventional herb based products various scientific experts have utilized nanotechnology based approaches [3].

Nanotechnology is an interdisciplinary area of research and development associated with production, processing, and utilization of materials having nanometer size range [4]. Furthermore, nanotechnology in the herbal drug domain is investigated to understand how bioavailability of phytoconstituents improved by nanomaterials. In recent decades, noble attention has been paid to use of nanotechnology based looms for the development of herbal novel drug delivery systems (NDDS) [5]. Clear, strong and well documented evidence supports the concept of herbal actives loaded NDDS [6]. Extensive research and investigations in the field of herbal NDDS came up with successful designs of herbal actives encapsulated NDDS [7]. Numerous novel colloidal carriers like liposomes, phytosomes, polymeric nanoparticles [8], lipid nanoparticles [8], microspheres, microsponges, microemulsion, nanoemulsion, ethosomes [9] and transfersomes were successfully utilized for effective delivery of plant extracts/ isolated phytoconstituents [10].

Use of colloidal carriers is considered as promising strategy because they offer various advantages like enhance solubility, stability, bioavailability as well as pharmacology activity and controlled release kinetic of herbal actives [11].

Additionally it is feasible to alter features of colloidal carriers like composition (polymer, lipid, phospholipid, non-ionic surfactant), size (small, large), shape (spherical, cube, rod) and surface functionalities (functional group, charge, targeting ligand, polymer) which makes suitability of these systems to encapsulate almost all phytoactives [12]. In addition to this, it is possible to improve circulation time and targeting potential of phytoactive loaded colloidal carriers by conjugating polymer like polyethylene glycol and targeting ligand on its surface.

Essential oils are natural, volatile secondary metabolites of aromatic

plants. Essential oils are well known phytoactives for their antifungal, antibacterial and antioxidant potentials. In addition to this few essential oil also revealed anti-inflammatory and antitumor potentials. Inspite of their good therapeutic potential these are suffer with certain limitations like instability in presence of light, temperature and atmospheric oxygen. Several authors have shown these are often limiting factor in therapeutic use of essential oils. Numerous studies have shown improvement in stability of essential oil by its encapsulation in colloidal carriers [13]. Many colloidal carriers have been used to encapsulate essential oil such as lipid nanoparticles, nanoemulsions, microspheres, nanospheres, niosomes, phytosomes, polymeric nanoparticles, liposomes, ethosomes and transfersomes. Extensive literatures showed improved therapeutic efficacy of essential oils on its loading in colloidal carriers [14].

Although novel colloidal carrier based phytoactive delivery is promising and effective strategy its use is limited in developing countries like India due to various drawbacks like requirement of costlier production equipment, costlier ingredients, standardization as well as quality related issue [15]. The concentration of phytoactive in crude drug varies with changing geographical source thus critical standardization is required. Standardization covers all aspects from cultivation of medicinal plants to its clinical application. Thus standardization is tedious task required in herbal drug development [16]. Therefore present exhaustive review written with aim to highlight outcomes of herbal actives loaded colloidal nano and microparticles.

2. NANOPARTICLES

NPs have a particle size between 1 and 100 nm. NPs are synthetic or semi-synthetic polymers with nanometer or sub nano-sized structures [17]. In nanotechnology, a small object used as a whole transport unit is defined as a particle. NPs can easily achieve efficient localization because the formulation is encapsulated in it easily [18]. Microencapsulation of the extracted herb in the NPs is an effective way to protect food or medication components from volatile loss, spoilage, or interactions with other components [19]. NPs offers several advantages, such as better dissolution, bioavailability and enhance absorption of herbal bioactives [20]. There have been multiple previous attempts to use polymeric NPs for encapsulation of herbal therapeutic agents like anticancer, antioxidant and hepatoprotective. The examples of some herbal nanoparticulate drug delivery systems are highlighted in Table 1.

Chen et al. [21] have formulated artemisinin loaded chitosan NPs. The drug loaded NPs were found to exhibit sustained drug release behavior than free drug solution. NPs offers great advantages in antitumor drug delivery because of their nano size rage they can easily filter through leaky tumor vasculature and enter at tumor site which could possibly improve antitumor efficacy of loaded drug. Various researchers and scientific workers have reported significantly better antitumor efficiency of phytoactives on its encapsulation in NPs. Tang et al. [22] have engineered star shaped paclitaxel

loaded copolymeric NPs using nanoprecipitation technique. The designed NPs evaluated for antitumor potential in tumor bearing mice. Drug loaded copolymeric NPs significantly reduce growth of tumor compared to free drug. In addition to these copolymeric NPs exhibited improved uptake in MCF-7 tumor cells compared to PLGA NPs.

Berberine is alkaloid having anti-inflammatory and antihypertensive potentials. However poor oral bioavailability due to limited aqueous solubility is major hurdle oral administration of berberine. The most promising strategy to improve dissolution rate of phytoconstituent is use of nanosuspension approach. Nanosized particles of drug offer significantly better surface area for dissolution which could possibly enhance dissolution rate of drug. Khayam et al. [23] have formulated berberine nanosuspension using antisolvent precipitation technique. Nanosuspension formation resulted in significantly enhancement in solubility and dissolution rate of berberine. In addition to this berberine nanosuspension showed improved antimicrobial potential than free drug against both Gram negative and Gram positive bacterial strains. Thus nanosuspension is attractive strategy to improve aqueous solubility and consequently oral bioavailability of phytoactives.

Curcumin is natural antioxidant and hepatoprotective phytoconstituent obtained from rhizomes of *Curcuma longa* L. Mukerjee et al. [24] have fabricated curcumin loaded polymeric NPs. The intracellular uptake of drug loaded NPs in prostate cancer cells was significantly more than free drug. These results can prove suitability of NPs for delivery of anticancer phytoconstituents. Hyun et al. [25] have successfully formulated camptothecin loaded chitosan NPs. Camptothecin is anticancer alkaloid extracted from plant *Camptotheca acuminate*. This anticancer alkaloid has great utility in treatment of various cancers like ovarian cancer, breast cancer, stomach cancer and pancreatic cancer. However its use is limited due to its poor solubility and instability. The encapsulation of alkaloid in chitosan NPs significantly improved its stability in biological fluid. The *in-vivo* antitumor efficacy in mice bearing MDA-MB231 human breast tumors revealed significantly greater antitumor efficacy of drug loaded NPs than drug alone. The drug loaded NPs suppressed tumor size by 77.2% in 32 days while free drug decreased tumor size by 48.8%. Thus NPs can improve biodistribution, stability and bioavailability of phytoconstituents. NPs retains the encapsulated drugs while distribution, thereby preventing drug release before accumulation of NPs in the tumor.

Yen et al. [26] have designed naringenin loaded Eudragit® E nanosized particles to improve oral bioavailability and anti-oxidant potential of naringenin. The naringenin encapsulated polymeric NPs were found to exhibit better antioxidant and hepatoprotective activity in hepatoxic rat. The nanoparticle improved oral bioavailability of naringenin which increase its antioxidant potential. Que et al. [27] have formulated tetrandrine loaded polymeric NPs. Tetrandrine is alkaloid in the extracted from roots of *Stephania tetrandra*. It is clinically proven herbal

anticancer agent used in treatment of various cancers. However major limitations of tetrandrine are its poor aqueous solubility, limited bioavailability and short biological half-life. Encapsulation of drug in polymeric NPs resulted in improve bioavailability in animal model and sustained drug release behavior.

Glycyrrhizic acid is anti-inflammatory phytoconstituent found in *Glycyrrhiza glabra*. It has ability exert anti-inflammatory effect by inhibition of pro-inflammatory mediator production. The major drawbacks of glycyrrhizic acid are poor solubility in biological fluids and consequently limited oral bioavailability. Bernela et al. [28] have attempted solve these limitations by encapsulation of glycyrrhizic acid in chitosan-katira gum NPs using ionic complexation technique. Carrageenan induced hind paw model was used to prove anti-inflammatory potential of phytoconstituent loaded NPs. Phytoactive loaded NPs exhibited improved anti-inflammatory activity in rats by reduction of paw edema volume compared to free glycyrrhizic acid. *Cuscuta chinensis* extract is traditionally accepted herbal medicine for management of liver injury and disease related to kidney. The antioxidant and hepatoprotective potentials of extract make it ideal remedy to treat liver injury. Yen et al. [29] engineered *Cuscuta chinensis* extract nanosuspension by nanosuspension technique and assessed its hepatoprotective potential using acetaminophen induced hepatotoxicity in rats. Nanosuspension revealed better hepatoprotective activity in animal model with significant reduction of serum liver injury markers compared to control. The significantly better outcomes in present study was due enhancement in dissolution and absorption of phytoactives by nanosized formulation. Sesamol is well known antioxidant and liver protective phytoactive. However poor oral bioavailability limits its therapeutic use. Gupta et al. [30] formulated sesamol loaded polymeric NPs. The sesamol loaded PLGA NPs revealed significantly better hepatoprotective activity in animal model.

Solid lipid nanoparticles (SLNs) are colloidal nanocarriers successfully developed in the early 1990s. SLNs made up of solid lipids with particle size ranges from 50 to 1000 nm [31]. The solvent injection, high-pressure homogenization (HPH) and microemulsification are commonly used techniques for fabrication of SLNs. These lipid NPs provides lipophilic matrix for dispersion and encapsulation of natural bioactives. The essential oils are safe and biocompatible bioactives having great therapeutic potential due to presence of constituents like fatty acids, terpenes, triterpenes and many other lipophilic constituents. Whole essential oil or its individual phytoconstituents are effectively entrapped in SLNs matrix owing to its lipophilic nature. Mei et al. [32] have successfully encapsulated triptolide an anti-inflammatory and immunosuppressive diterpenoid in SLNs. NPs with biocompatible and biodegradable polymers of uniform size, spherical shape and smooth surface were developed to avoid poor solubility and permeability hurdles of triptolide. Triptolide loaded SLNs exhibited significantly greater anti-acute

inflammatory activity than free triptolide in carrageenan induced rat paw edema. The better anti-inflammatory activity of drug loaded SLNs was due to increase in skin permeation of drug. Breviscapine is phytoconstituents extracted from the herb *Erigeron breviscapus*. It is clinical used for treatment of acute cerebral infarction and paralysis. The major hurdles in conventional delivery drug are limited bioavailability and poor chemical stability *in vivo*. Liu et al. [33] attempted to improve brain bioavailability of breviscapine by its encapsulation in SLNs. The encapsulation of drug in SLNs resulted significant increase in brain uptake of drug as well as its chemical stability.

Essential oil extracted from *Zataria multiflora* plant is well known as green insect repellant due to its potent mosquito repellant potential. However use of free essential oil is limited due to its volatility and poor stability. Various attempts have been investigated to reduce volatility of essential oils. The use of lipid NPs is most promising strategy due to their ability to encapsulate oil with optimum extent. Kelidari et al. [34] engineered *Zataria multiflora* essential oil loaded SLNs and its insect repellant potential against *Anopheles stephensi*. Encapsulation of oil resulted in significant increase in insect repellant potential with minimum toxicity to skin. Sesamol loaded SLNs revealed significantly better hepatoprotective and antioxidant potential compared to free sesamol in CCl_4 induced hepatotoxicity animal model [35]. Curcumin encapsulated SLNs showed better antimalarial efficacy compared to curcumin alone in *P. berghei* infected mice [36]. The major drawbacks of these two phytoconstituents are poor aqueous solubility and consequently poor oral bioavailability [37]. SLNs promote encapsulation of these phytoconstituents and subsequently improve their bioavailability. The outcomes of SLNs in essential oil deliver are highlighted in Figure 1.

Nanostructured Lipid Carriers (NLCs) are second-generation lipid nanoparticle made from combination of solid and liquid lipids. These novel particles were originally investigated to overcome drawbacks associated with SLNs [31]. Solid lipid and liquid lipid being different molecules forms imperfect/ less-ordered crystalline structure of NLC compared to SLN which provides a higher phytoconstituent entrapment (Figure 2). These novel particles better than SLNs with respect to controlling of the drug release behavior, stabilization of phytoconstituent, drug encapsulation efficiency and lesser chances of drug leakage during storage. Thus, various plant bioactives have been successfully encapsulated into NLC in previous studies focused on improving aqueous solubility, maximizing gastrointestinal absorption, systemic bioavailability and increasing circulation time by reducing reticuloendothelial system (RES) uptake. Multiple numbers of authors have reported stabilization, controlled release and better therapeutic potentials of phytoconstituents on its encapsulation in NLCs.

Essential oil extracted from leaves of *Eucalyptus globulus* is reported to exhibit antiseptic, antibacterial and antifungal potentials. The major phytoconstituent responsible for these pharmacological actions is eucalyptol. However limited

stability due to its volatile nature restricts its topical use. Bonferoni et al. [38] designed *Eucalyptus globulus* essential oil loaded NLCs and assessed it for wound healing potential. Essential oil loaded NLCs exhibited better proliferation of fibroblasts cells with minimum cytotoxicity. In addition to this, NLCs loaded with oil showed improved bioadhesion and wound healing in animal model compared to free oil. Essential oil extracted from *Rosmarinus officinalis* oil is commonly known as rosemary oil. Bonferoni et al. [38] designed rosemary oil loaded NLCs and assessed it for bioadhesion, biocompatibility as well as wound healing potentials. Oil loaded NLCs exhibited better proliferation of fibroblasts cells with good bioadhesion potential. In addition to this, oil loaded NLCs showed enhanced wound healing in animal model compared to free oil.

Cardamom essential oil is pale yellow aromatic liquid extracted from dried fruits of *Elettaria cardamomum*. Antimicrobial and anti-inflammatory activities are major therapeutic potentials of this oil. However oxidative degradation of terpene component oil thus loss of pharmacological activity and aroma in presence of heat are major constraints in use of essential oil. Encapsulation of cardamom essential oil in colloidal carrier can minimize oxidative degradation of oil and improve therapeutic efficacy. Nahr et al. [39] have reported successful loading of cardamom essential oil in NLCs. Cardamom essential oil loaded NLCs was fabricated using olive oil and cocoa butter by nano-emulsification method. Essential oil loaded NLCs exhibited improve storage stability and antioxidant activity than free oil. Thus NLCs can be utilized for stabilization of essential oil against oxidative degradation. Essential oil of sucupira is extracted from plants of the genus *Pterodon*. It is traditionally accepted herbal medicine exhibiting anti-inflammatory, antimicrobial and anticancer potentials. However poor stability in presence of heat and atmospheric air due to oxidative degradation of oil components is major limitation. Vieira et al. [40] attempted to solve limitations associated with conventional delivery of oil by formulating NLCs. The oil loaded NLCs exhibited very less toxicity to human intestinal Caco-2 cell line which confer its biocompatibility.

Ferulic acid is antioxidant phenolic phytoconstituent isolated from various plant tissues. Carbone et al. [41] engineered ferulic acid loaded NLCs using *Lavandula* essential oil as liquid lipid and assessed it for wound healing potential. *Lavandula* essential oil is known for its wound healing potential. Ferulic acid NLCs prepared using *Lavandula* essential oil showed significantly better wound healing potential by promoting fibroblast proliferation and migration. β-Elemene well known natural anticancer phytoactive having ability to inhibit tumor growth and induce tumor cell death. Shi et al. [42] successfully formulated β-Elemene loaded NLCs using glyceryl monostearate as well as Maisine 35-1 and evaluated for antitumor potential in tumor bearing mice. Phytoactive loaded NLCs significantly reduce weight of tumor in mice compared to free phytoactive on ten days treatment. In addition to this, loading of phytoactive into NLCs matrix resulted in reduction of venous irritation and thereby venous toxicities. The results

of present study quite successful to demonstrate the potential outcomes of NLCs based anti-cancer phytoactives delivery. Sansare et al. [43] fabricated curcumin loaded mannosylated NLCs for hepatocyte targeting. The curcumin loaded NLCs exhibited enhanced hepatoprotective potential in CCl_4 induced heptatoxic rats with significantly better reduction of serum liver injury markers and oxidative stress parameters.

Based on strong evidences reported in various literatures NLCs and SLNs are viable alternatives for stabilization and controlled delivery of essential oil.

Advantages of the plant-based NPs delivery system

i) NPs are more effective because they increase the solubility of phytoconstituents and help to transport encapsulated drug at specific target site. Administration of the drug in small particles dissolves more rapidly in the blood as the total surface area of the drug increases [44]

3. MICROSPHERES MICROPARTICLES AND MICROSPONGES

The successful targeted controlled drug delivery systems deliver encapsulated drug at target site with controlled manner. Targeted controlled drug delivery system facilitates distribution of drug at target site and minimize off target distribution of drug which can minimize adverse drug reactions. In addition to this, controlled drug release prevent need of frequent dosing which can minimize dosing frequency and improve patient compliance [45]. Polymeric microspheres considered as safe and convenient option for targeted controlled drug delivery. These are spherical particles having size in the range of 1 to 300 µm. Polymeric microspheres offer polymeric matrix for encapsulation and adsorption of drug. The encapsulated drug releases in controlled manner by either diffusion or polymer erosion. Both natural as well as synthetic polymers can be utilized for fabrication of microspheres. Natural polymers are commonly employed due to their biodegradability, biocompatibility and cost effectiveness. Effective use of microspheres for delivery of therapeutically active phytoconstituents is recently explored area [46]. The phytoconstituent/ plant extract loaded microspheres can administered by oral as well as topical route depending on its utility.

Extract of *Ocimum sanctum, Morus alba, Musa acuminata, Mangifera indica, Zingiber officinalis* and *Piper nigrum* have potential to cure gastric ulcer lesions [47]. The extract of such plants/ their isolated phytoconstituent can be encapsulated in floating microsphere to improve their pharmacological action by prolonging their gastric retention. In addition to this, such phytoconstituents can be load in microspheres fabricated using mucoadhesive polymers like chitosan [48].

Essential oil of *Syzygium aromaticum* and *Eucalyptus globulus* has anti-inflammatory analgesic potential. Such oils can encapsulate in lipid microparticles and effective utilized for topical applications. The microparticles made up of solid lipid offers lipophilic matrix for encapsulation essential oil bioactives [49]. Essential oil being its hydrophobic characteristics can effectively load in lipid microparticles with better encapsulation efficiency. The advantages of microparticles for delivery of curcumin is represented in Figure 3.

Advantages of microsphere formulations

Polymeric microspheres can be successfully utilized to improve solubility, stability and bioavailability of phytoconstituents. Some herbal microspheres, microparticles and microsponge found in literatures are highlighted in Table 2.

Donato et al. [50] have fabricated rutin loaded chitosan microparticles. Rutin is a glycoside found in many plants. It is well known phytoconstituents for its anti-inflammatory and anti-oxidant potential. Rutin encapsulated chitosan microspheres exhibited improved best anti-inflammatory responses in carrageenan induce rats paw edema with effective reduction in paw volume and inflammatory marker like interleukin. The mucoadhesive properties of chitosan favored a localization of the rutin in the paw which significantly improved anti-inflammatory than free rutin. You et al. [51] have encapsulated zedoary turmeric oil (ZTO) in polymeric microspheres. ZTO mainly contains hepatoprotective and it is extracted from the dry rhizome of *Curcuma zedoaria*. The oil loaded microsphere exhibited better bioavailability in rabbit model than unloaded oil. Machida et al. [52] have fabricated camptothecin loaded polymeric microspheres. Camptothecin is topoisomerase inhibitor anticancer constituent isolated from the bark and stem of *Camptotheca acuminate*. Drug loaded microspheres exhibited better anticancer activity in animal model as compare to free drug. Quercetin is well known anti-inflammatory phytoactive reported to inhibit nuclear factors involved in various autoimmune diseases like rheumatoid arthritis. However poor oral bioavailability and susceptibility to photooxidantion are major constraints in delivery of such potential phytoactive. Natarajan et al. [53] have loaded quercetin in polymeric microspheres with high entrapment efficiency. Furthermore the phytoactive loaded microspheres showed non-toxicity to HIG-82 synovial cell which confer biocompatibility of carrier. Thus polymeric microspheres could be viable and biocompatible carrier for delivery of phytoconstituents.

Caulis sinomenii is traditionally accepted remedy to manage arthritic pain. Zhang et al. [54] have encapsulated total alkaloids of *Caulis sinomenii* in polymeric microspheres using emulsion solvent evaporation technique. The better encapsulation of phytoactive in polymeric matrix of microspheres was major outcome of present study. In addition to this the sustained release of encapsulated phytoactive for polymeric microspheres could be useful for long term therapeutic benefit. Polymeric microspheres or microparticles made with biodegradable polymer confer biocompatibility which could be desirable for controlled administration of number of phytoactives. *Calendula officinalis* flower extract is traditionally accepted remedy to heal skin wounds due to its anti-inflammatory and antioxidant potentials. Jimenez et al. [55] attempted to formulate collagen I scaffolds loaded with *C. officinalis* flower extract encapsulated gelatin-collagen microparticles. Collagen I scaffolds has great role in wound healing thus dual therapeutic effect can be expected on combination it's with extract. In addition to this, microparticles can release extract in sustained manner which has added

advantage in wound healing where sustained concentration of antioxidant is necessary. The formulated system was found to exhibit minimum toxicity to fibroblast cells which confer its actual utility in wound healing. The conclusions quoted in literature showed applicability of extract collagen I scaffolds in efficient wound healing.

Piperine is active phytoconstituent extracted from dried fruits of *Piper nigram* reported to exhibit hepatoprotective and gastric ulcer protective potentials. This phytoactive reduces lipid peroxidation which is beneficial to protective liver against injury. Boddupalli et al. [56] have encapsulated piperine in floating polymeric microspheres and assessed hepatoprotective as well as gastric ulcer healing potentials in animal models. Phytoactive loaded microspheres significantly reduce hepatotoxicity in rats induce by paracetamol. In addition to this microsphere based system was proved to be successful in reduction of gastric ulcer in rat induce by ethanol (80%). Silymarin is well known phytoactive having hepatoprotective activity due to its antioxidant and radical scavenging potentials. The major constraints in oral delivery of this phytoactive are poor bioavailability, short biological half-life and significant first pass metabolism. Garg et al. [57] had attempted to solve constraints associated with oral delivery of silymarin by formulating polymeric hollow microspheres for gastroretentive drug delivery. Hollow polymeric microspheres for encapsulation of silymarin were fabricated using various polymers like hydroxypropyl methyl cellulose, ethyl cellulose and Eudragit. The drug loaded microspheres were showed zero order drug release profile and prolonged gastric retention. Thus polymeric microspheres could be best alternative for oral delivery of phytoactives.

The well-known antimicrobial constituent in essential oil is thymol. Essential oils rich in thymol were reported to inhibit growth of both bacterial as well as fungi. Thymol specifically inhibits both Gram-positive and Gram-negative bacterial than eugenol. However susceptibility to oxidation and poor aqueous solubility are major limitations encounter in thymol use. Rassu et al. [58] engineered spray dried polymeric microspheres to improve stabilization and bioavailability of thymol. Enhanced bioavailability of thymol on its encapsulation in microspheres is major fruitful outcome of present study. Polymeric microsphere facilitates encapsulation of phytoactive in matrix and thereby prevent oxidative its degradation. Quercetin is antioxidant and anti-inflammatory flavonoid reported to reduce skin damage induce by harmful UV radiations. Topically applied quercetin is beneficial to reduce skin damage and inflammations induce by UV light. However photodegradation of this valuable phytoactive is major hurdle in its therapeutic use. Scalia et al. [59] utilized lipid matrix for photostabilzation by encapsulation of quercetin in lipid microparticles. Quercetin was successfully encapsulated in tristearin lipid matrix and assessed for photodegradation in presence of UV light. Lipid microparticles successfully improved photostabilzation of quercetin with retention of 88.7 % potency at the end of 90 days. Thus use of lipid based micro or nanoparticle is promising strategy to enhance chemical

stabilization of phytoconstituents. Yang et al. [49] have attempted to improve stabilization of peppermint oil by its encapsulation in SLMs. Peppermint oil encapsulated SLMs were fabricated using hydrogenated soybean oil. Solid lipid provided highly lipophilic matrix for encapsulation of essential oil. The oil loaded in lipid matrix was found to be stable even at high temperature and humidity. Thus lipid colloidal particle could be promising strategy for preservation of antimicrobial properties of active essential oil.

Curcumin is polyphenolic phytoactive well known for its anticancer, antimalarial, hepatoprotective and antimicrobial properties. The major limitations encounter while therapeutic use of curcumin are its poor aqueous solubility and limited oral bioavailability. Bhatiya et al. [60] successfully utilized ethyl cellulose porous microsponges for effective oral as well as topical delivery of curcumin. Curcumin loaded microsponge revealed sustained drug release profile in addition to this permeation of curcumin across rat abdominal skin significantly improved. Thus ethyl cellulose based polymeric microsponge could be viable way for sustained delivery of curcumin both by oral and topical route. Tang et al. [61] have loaded *Eucalyptus globules* oil encapsulated liposomes in chitosan microsponge in order to improve antimicrobial efficacy of both essential oil as well as chitosan. Microsponge loaded with essential oil liposomes showed enhance antimicrobial potential against both Gram-positive and Gram-negative bacteria as well as fungi. The improved antimicrobial activity of microsponges could be due to additive microbial killing action of essential oil and chitosan.

Essential oil obtained from *Psoralea coryfolia* found to exhibit various therapeutic effects like antimicrobial, anti-inflammatory, antitumor and antioxidant. Wadhwa et al. [62] have attempted to improve antimicrobial potential of oil by its encapsulation in ethyl cellulose based polymeric microsponges. Essential oil loaded microsponge revealed better antimicrobial potential against *Pseudomonas aeruginosa, Escherichia coli,* and *Staphylococcus aureus* than free oil. In addition to this, improved cell viability of HaCaT cells revealed non-toxicity of oil loaded microsponge. The strong fruitful evidences of above studies prove suitability of microspheres, microparticles and microsponges for effective delivery of active phytoconstituent.

Table 1. Herbal nanoparticulate drug delivery systems

Sr. No.	Plants/constituents	Therapeutic category	Type of nanoparticle	Major outcome
1	Artemisinin	Anticancer	Chitosan nanocapsules	Sustained drug release
2	Paclitaxel	Anticancer	Cholic acid-polylactide copolymeric	Superior antitumor potential of drug loaded NPs compared to free

			NPs	drug
3	Berberine	Anticancer and antimicrobial	Nanosuspension of berberine	Sustained drug release behavior with better antibacterial activity
4	Curcuminoids	Anticancer and Antioxidant	PLGA NPs	Prolonged release of the curcuminoids with inhibition of inhibition of activated NF-κB in prostate cancer cell line
5	Camptothecin	Anticancer	Chitosan NPs	Prolonged blood circulation and high accumulation in tumors
6	Naringenin	Hepatoprotective	Eudragit® E NPs	Improved oral bioavailability and antioxidant potential
7	Tetrandrine	Anticancer	PLGA NPs	Improve bioavailability and sustained drug release
8	Glycyrrhizic acid	Anti-inflammatory and antihypertensive	chitosan-katira gum NPs	Improved bioavailability
9	*Cuscuta chinensis* extract	Hepatoprotective	Nanosuspension	Better hepatoprotective potential of extract loaded nanoparticles
10	Sesamol	Hepatoprotective	PLGA NPs	Enhanced hepatoprotective potential
11	Triptolide	Anti-inflammatory	Solid lipid nanoparticles (SLNs)	Enhance the penetration of drugs through the stratum corneum and greater anti-acute inflammatory activity
12	Breviscapine	Cardiovascular and cerebrovascular	SLNs	Improve chemical stability and brain uptake of drug
13	*Zataria multiflora* essential oil	Insect repellant	SLNs	Oil loaded SLNs exhibited better mosquito repellant potential in human and non-toxicity to HFFF2 cells.
14	*Eucalyptus globulus* essential oil	Analgesic and antibacterial	NLCs	Improved wound healing property in animal model and

				bioadhesion behavior
15	*Rosmarinus officinalis* oil	Antibacterial, antioxidant and antifungal	NLCs	Improved antibacterial activity and wound healing property in animal model
16	Cardamom (*Elettaria cardamomum*) oil	Antioxidant	NLCs	Sustained release with improved antioxidant property
17	Sucupira essential oil	Anti-inflammatory, antioxidant and anticancer	NLCs	Sustained release behavior with minimum cytotoxicity against Caco-2 cell line
18	Ferulic Acid	Antioxidant	NLCs	Improved antioxidant and wound healing potential of ferulic acid
19	β-elemene	Anti-neoplastic	NLCs	Drug loaded NLCs significantly reduce tumor weight of tumor bearing mice than free drug
20	Curcumin	Hepatoprotective	NLCs	Better hepatoprotective potential

Table 2. Major findings of microspheres, microparticles and microsponge based phytoactive delivery.

Sr. No.	Plants/constituents	Therapeutic category	Type of particulate system	Major outcome of formulations
1	Rutin	Anti-inflammatory and antioxidant potential.	Chitosan microparticles	Best anti-inflammatory response in carrageenan induce rats paw edema
2	Zedoary oil	Hepatoprotective	Polymeric microspheres	Sustained release and Higher bioavailability
3	Camptothecin	Anticancer	Polymeric microspheres	Significantly better anticancer activity of camptothecin
4	Quercetin	Anti-inflammatory and antioxidant	Polycaprolactone Microspheres	Non-toxicity to HIG-82 synovial cell
5	Alkaloids of *Caulis sinomenii*	Anti-inflammatory	poly(lactic acid) microspheres	Better encapsulation of phytoconstituents in polymeric matrix. Sustained release of encapsulated phytoconstituents
6	*Calendula*	Anti-inflammatory	gelatin-collagen	Sustained release of extract.

	officinalis Flowers extract	and antioxidant with wound healing potential	microparticles	Minimum toxic potential to fibroblast cells
7	Piperine	Anti-inflammatory, antioxidant and hepatoprotective	Polymeric microspheres	Piperine loaded microspheres exhibited significantly better hepatoprotective and gastric ulcer healing potential in animal model
8	Silymarin	hepatoprotective	HPMC and ethyl cellulose microspheres	Increase in gastric retention time of silymarin
9	Thymol	Antibacterial and antifungal	Spray dried HPMC phthalate microspheres	Improved bioavailability of thymol on encapsulation in microparticles.
10	Quercetin	Anti-inflammatory and antioxidant	Solid lipid microparticles (SLMs)	Improved stabilization of oil at elevated temperature
11	Peppermint oil	Antimicrobial	SLMs	Improved stabilization and encapsulation of oil in SLMs
12	Curcumin	Antimicrobial	Microsponge	Microsponge exhibited sustained drug permeation across skin with improved drug deposition in skin strata.
13	*Eucalyptus globules* oil	Antimicrobial	Microsponge	Oil loaded microsponge exhibited better antimicrobial activity against *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Candida albicans*
14	Babchi (*Psoralea coryfolia*) oil	Anti-microbial and anti-inflammatory	Microsponge	Enhance encapsulation and photostability of oil with improved antimicrobial potential.

3. CONCLUSION

Today, medicinal plants are at the forefront of the pharmaceutical industry, as their effects are well known and their side effects are very low. Moreover, herbal medicine has an interesting symmetrical way of making nanoparticles compared to synthetic drugs. Herbal drugs/plant actives have great therapeutic potential to be found by applying new technologies for the administration of medicines. High molecular size, lipid solubility, and gastric acid degradation are some of the problems that limit the in vivo therapeutic activity of these extracts, although they have excellent in vitro biological activity. The use of Novel drug delivery systems

has improved the bioavailability of herbal active ingredients by increasing permeability and solubility and reducing side effects. Nanomaterials have made great strides in nanotechnology due to their adjustable physico-chemical and biological performance compared to their counterparts. In recent years, there has been received a lot of attention and excitement about herbal remedies with nanoparticles for their potential and unique properties in the future, as these materials become essential in many areas of human activity. So herbal nanosystems have high hopes for overcoming the dilemmas of herbal medicine and increasing activity. Therefore, there is great potential for the development of a novel medicinal system to obtain valuable herbal medicines, as it provides effective trends and cost-effective trends for the implementation and integration of new medicinal systems. It has also been used on an industrial scale for herbal medicines. New research can also help you gain and maintain your market. However, some medicinal problems need to be overcome, such as difficulties in conducting clinical research on medicinal plants, the development of simple standardized biological tests, the development of methods for the evaluation of drugs, and the toxicological examination of drugs. Various animal models have been found to evaluate the toxicity, toxicity and safety of the herbs used the legal and regulatory aspects of herbal medicines, etc.

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Author contribution

Manish Kumar Gupta: Methodology, Data Curation, Writing - Original Draft preparation, Writing - Reviewing and Editing, Visualization. **Sujit Nagare:** Conceptualization, Writing - Reviewing and Editing, Supervision. **Birendra Shrivastava:** Supervision. **Supriya Hyam:** Investigation. **Vipul Sansare:** Writing - Reviewing and Editing

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Conflict of interest (If any)

The authors declare that they have no competing interests.

Ethics approval

"None to declare".

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