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Introduction of Nanotechnology in Herbal Drugs and Nutraceutical: A Review

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Abstract

Nanotechnology is an opening up for new perspectives in all scientific and technological fields. Among these applications, herbal drugs and nutraceuticals are the fast growing fields in nanoresearch. A variety of new herbal formulations and nutraceuticals like polymeric nanoparticles, nanocapsules, nanoemulsions, transferosomes and ethosomes has been reported using bioactive, plant extracts and food materials. New herbal drugs and nutraceuticals are reported to have remarkable advantages over conventional formulations of plant actives and extracts which include enhancement of solubility, bioavailability, expansion of stability, sustained delivery, improved tissue macrophages distribution, protection from toxicity, enhancement of pharmacological activity and protection from physical and chemical degradation. This review provides an overview of the introduction of nanotechnology in the field of herbal drugs and nutraceuticals.

Keywords: Nanotechnology; Herbal drugs; Nutraceuticals; Phytomedicine

Introduction

Phytomedicines have been serving as a crucial source of drugs since ancient times, their usage has been increased due to their therapeutic activity and less side effects rather than the other medicines. Both developing and developed countries are focusing on the popularity of herbal drugs mainly due to their natural origin and low side effects. Fast-growing nanotechnologies have provided strong support for developing innovative novel herbal drugs. Nutraceuticals are foods and food constituents that provide health benefits beyond basic nutrition, but many nutraceuticals show poor bioavailability. Applications of nanotechnology have granted to overcome the challenges and technical barriers related to the solubility, bioavailability, stability and delivery of bioactives from foods. The rapid growth of nutraceutical nanotechnology carries great promise to provide new and effective functional foods as a tool for preventing and possible even bringing a cure to some non-communicable diseases. Numerous studies are already reported in different types of preparative methods of nanomaterials in the field of nanotechnology for herbal drug delivery and nutraceuticals (Figure 1) [1-5]. The current review focuses on the introduction of nanotechnology in herbal drugs and nutraceuticals for nanomedicine and functional foods. It is also highlights important and rapid developments in biomedical and food technology.

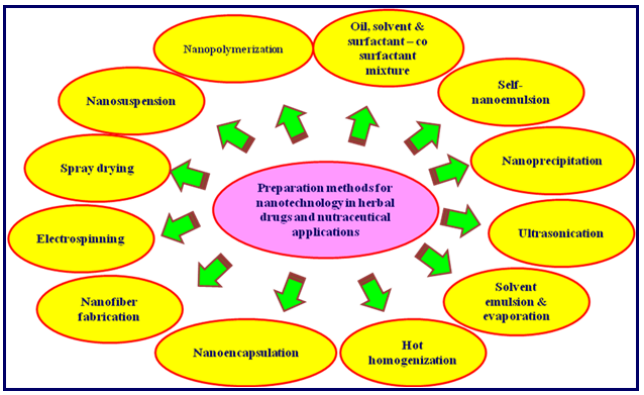

Figure 1: Schematic representation of various methods of preparation of nanotechnology in herbal drugs and nutraceuticals.

Nanotechnology in herbal drugs

Nanotechnology can be used to enhance delivery of poorly water soluble herbal drugs, targeted delivery in a cell or tissue, also a cross tight epithelial and endothelial barriers, release of large herbal molecules, co-delivery to two or more drugs and observation of sites of drug delivery by incorporating herbal drugs with imaging modalities [6-8]. Applications of nanotechnology formulated herbal drugs are schematically represented in Figure 2. Table 1 summarizes the various nanostructured herbal formulations, their different applications and biological activities.

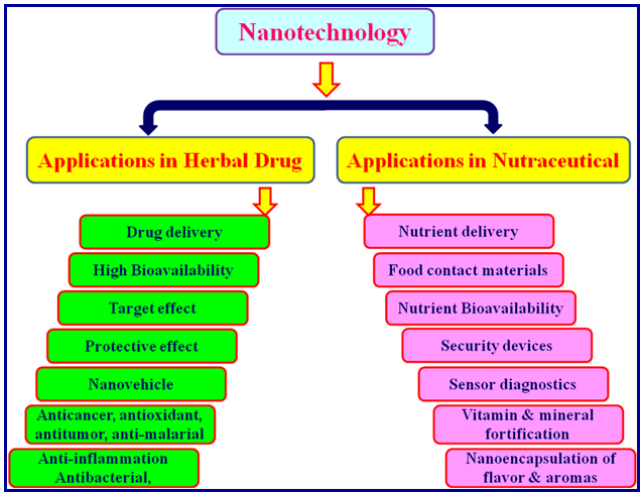

Figure 2: Schematic representation of applications of nanotechnology formulated herbal drugs and nutraceuticals.

Herbal and nanomedicine researchers have discovered that therapeutic nanoparticles (NPs) can provide as more effective drug delivery system than conventional forms of drugs. Nanocarriers transdermal gel (NCTG) was formulated from optimized nanotransfersomes of diclofenac diethylamine (DDEA) and curcumin (CRM) for providing a sustained and targeted effect. Due to nanoparticulate size of NCTG achieving higher absorption of the drug plus co-administration of lecithin; providing hydration gradient to the vesicles, increase permeability, decreased degradation and clearance by surfactant than that from marketed gel and plain curcumin gel was reported [9]. Formulated and optimized nanotransfersomes of DDEA and CRM provided a large surface area with high penetration potential and achieved high bioavailability [10]. pH-sensitive nanoparticles of curcumin-celecoxib combination were formulated as a potential therapy for uncreative colitis [11]. Curcumin solid lipid nanoparticles (CRM-SLN) were prepared with a high-loading capacity and chemical stability for the treatment of oral mucosal infection [12]. Curcumin-loaded hydrogel nanoparticles of hydroxyl propyl methyl cellulose (HPMC) and polyvinyl pyrrolidone (PVP) were successfully formulated and exhibited a significant improvement in anti-malarial action [13].

Biosynthesis of silver nanoparticles (AgNPs) were demonstrated by leaf extract of *Mukia scabrella*, it exhibited significant antimicrobial activity against MDR-GNB nosocomial pathogens [14].

Formulations	Active ingredients	Biological activity	Method of preparation	Applications of the formulations	References
Diclofenac diethylamine and curcumin nanocarrier transdermal gel	Curcumin	Anti-inflammatory activity	Encapsulation with sonication	Enriched biological activity Targeted effect	Chaudhary et al. [9]
Nanotransfersomes of diclofenac diethylamine and curcumin	Curcumin	Anti-inflammatory activity	Encapsulation with sonication	High bioavailability Enhanced permeation	Chaudhary et al. [10]
pH sensitive NPs loaded curcumin-celecoxib combination	Curcumin	Anti-inflammatory and antioxidant activity	Solvent emulsion evaporation	Enhanced efficacy for mitigating ulcerative colitis	Gugulothu et al. [11]
Curcumin-lipid NPs with Gelucire 39/01, Gelucire 50/13, percirol, compritol and polozamer 407	Curcumin	Anti-microbiological activity	Hot homogenization	Promising alternative for the manipulation of curcumin to overcome the clinical applications	Hazzah et al. [12]
Curcumin loaded NPs of HPMC and PVP	Curcumin	Anti-malarial activity	Solvent emulsion – evaporation technique	Beneficial for the prolonged utilization of the formulation as an adjuvant anti-malarial therapy to prevent the recrudescence and reduce the dose of the standard anti-malarial drugs	Dandekar et al. [13]
AgNPs of *Mukia scabrella*	Cysteine residues in protein	Anti-microbial activity	Nanosuspension	Antibacterial activity against MDR-GNB nosocomial pathogens	Prabakar et al. [14]
AgNPs of *Bauhinia tomentosa Linn*	Amines, carboxylic acids, aldehydes and ketone	Anticancer and antioxidant activity	Nanosuspension	Potential agent for cancer therapy	Mukundan et al. [15]
Fluorescent AgNPs of *Artemisia annua*	Amides and phenolics	Anticytotoxicity	Nanosuspension	Fluorescent properties can be exploited in	Khatoon et al. [16]

		and antibacterial activity		biomedical applications Biocompatible cytotoxicity against human erythrocytes	
AuNPs of *Pistacia integerrima* gall extract	Amines, amides, phenolic and alcoholic	Antifungal activity	Nanosuspension	Significant attenuation of pain and muscle relaxant effect	Islam et al. [17]
NiNPs of *Aegle marmelos correa*	Amines, amides, phenolic and alcoholic	Anti-inflammatory and mosquito larvicidal activity	Nanosuspension	Excellent anti-inflammatory agent Acts as a drug carrier for the control of Cx. quinquefasciatas	Angajala et al. [18]
Curcumin and temozolomide loaded magnetic NPs	Curcumin and temozolomide	Anticancer and antitumor activity	Nanosuspension with sonication	Dual drug delivery system (Cur + Temo) is provoking greater anticancer activity by stimulating cell death pathways	Dilnawaz et al. [19]
Polymeric NP formulation of *Syzygium cumini*	Gallic, chlorogenic caffeic and ellagic acids, catechin, epicatechin quarcetin etc	Antifungal activity	Emulsification/evaporative solvent technique	Significant attenuation against the chronic complications of diabetes mellitus	Bitencourt et al. [20]
Witepsol SLNPs and Carnauba SLNPs	Thujone, pinene, camphor	Antioxidant activity	Hot melt ultrasonication	Suitable vehicle for herbal extracts with high stability during digestion A significant release percentage of phenolic compounds at the small intestine	Campos et al. [21]
SNEDDS formulation of Persimmon (*Diospyros kaki*) leaf extract	Flavonoids (Quercetin and Kaempferol)	Antioxidant activity	Self nanoemulsion	Promising method for poorly aqueous soluble drugs including the extract of herbal medicine to achieve a significant improvement in bioavailability	Li et al. [22]
SNEDDS formulation of quercetin	Quercetin	Anti-liver toxicity	Self nanoemulsion	Protective effect against paracetamol induced hepatotoxicity Enhance the activity of antioxidant	Ahmed et al. [23]
SNEDDS formulation of Zedoary turmeric oil	Essential oil	Oral bioavailability	Self nanoemulsion	Increase drug loading Decrease the inert oil requirement	Zhao et al. [24]
MUDDS with four units	Realgar, frankincense and myrrh oil, musk, and bezoar	Antitumor activity	Ball milling followed by solvent evaporation	High antitumor activity High bioavailability	Shi et al. [5]
Incorporation of four prenylated flavanones from leaves of *Eysenhardtia platycarpa*	5,7-Dihydroxy-6-methyl-8-prenylflavanone; 5,7-dihydroxy-6-methyl-8-prenyl-4_-methoxy-flavanone; 5,7-dihydroxy-6-prenylflavanone; and 5-hydroxy-7-	Anti-inflammation activity	Oil, solvent and surfactant-cosurfactant mixture	Acts as potential topical anti-inflammatory agent	Domínguez-Villegas et al. [25]

	methoxy-6-prenylflavanone				
Oleanolic acid loaded PEGylated PLA and PLGA NPs	Oleanolic acid	Anti-cytotoxicity against cancer cells	Ring opening polymerization followed by nanoprecipitation method	High potentials to develop into an effective anticancer delivery platform for cancer chemotherapy	Man et al. [26]
Polycaprolactone/polyvinyl pyrrolidone nanofiber mat with bark extract of Tecomella undulate	Alcoholic, phenolic compounds carboxylic acids	Antibacterial activity	Nanofiber fabrication through electro spinning	Great potential in drug delivery, wound healing and treating against surface pathogenic microorganisms	Suganya et al. [27]
Electrospun gelatin nanofibres containing *Centella asiatica* extract	Alcoholic, phenolic compounds carboxylic acids	Anticytotoxicity and antibacterial activity	Electrospinning	Promising and potential material for use as wound dressing materials	Yao et al. [28]

Table 1: Nanostructured herbal formulations.

AgNPs have been synthesized by Mukundan et al. [15] using an aqueous leaves extract of *Bauhinia tomentosa Linn* and their *in vitro* anticancer activity has also been studied. Fluorescent AgNPs were synthesized using *Artemisia annua* leaf extract and these AgNPs were biocompatible, which was confirmed by checking the cytotoxicity against human erythrocytes and they showed significant fluorescence and antibacterial activity [16].

Gold nanoparticles (AuNPs) were synthesized by using a gall extract of *Pistacia integerrima* and they have potential for various biomedical and pharmaceutical applications particularly with significant antifungal and antinociceptive activity [17]. Phytofabrication of nickel nanoparticles (NiNPs) from *Aegle marmelos* Correa (AMC) aqueous leaf extract was investigated NiNPs can be used as excellent anti-inflammatory agents and drug carriers [18]. Magnetic nanoparticles (MNPs) based drug delivery approach for co-delivering of curcumin and temozolomide has been implemented and this system has been well efficient in provoking greater anti-cancerous activity [19].

In vitro efficacy against the complications of diabetes mellitus (DM) and the *in vivo* toxicity was evaluated by using an aqueous extract from *Syzygium cumini* seed (ASc) and of polymeric nanoparticles containing ASc (NPASc). NPASc demonstrated a high inhibitory activity against ox-LDL particles and showed high *in vitro* activity [20]. Solid lipid nanoparticles (SLNPs) can be used as vehicles for phenolic compounds rich extracts. Witepsol and carnauba were tested for the production of solid lipid nanoparticles (WSLNPs ad CSLNPs) loaded with medicinal herbs, sage and savory extracts. WSLNPs showed to be a more suitable vehicle for herbal extracts, with high stability during digestion and a significant release percentage of phenolic compounds in the small intestine [21].

The persimmon leaf extract was successfully formulated as a stable self-nanoemulsifying drug delivery system (SNEDDS) formulation that had significant improvement in solubility, *in vitro* release and bioavailability compared with Naoxinqing tablets [22]. SNEDDS formulation of the optimized quercetin (QT) formulae offered superior protective effect against liver damage, compared with QT against paracetamol-induced hepatotoxicity. Sefsol and linoleic-acid-optimized SNEDDS formulation showed no symptoms associated with toxicity and offered a protective effect against paracetamol-induced hepatotoxicity [23]. Potential utility of SNEDDS for formulating Zedoary turmeric oil (ZTO) extracted from rhizome of *Curcuma zedoaria* was demonstrated by improved aqueous dispersion activities, stability and oral bioavailability. The formulated ZTO-SNEDDS could serve as a partial lipid phase with double advantages of increasing drug loading as well as minimizing the amount of requirement of the inert oils [24]. Shi et al. were prepared a multi-unit drug delivery system (MUDDS) for a Chinese medicine Niuhuang Xingxiao Wan (NXW) to enhance the bioavailability and efficacy. NXW was formulated into four units, such as realgar, frankincense and myrrh oil (FMO), musk, and bezoar. The assay of *in vivo* antitumor activity shown that the efficacy of NXW-MUDDS was significantly higher than the NXW [5].

Incorporation of four prenylated flavanones isolated from *Eysenhardtia platycarpa* leaves into nanoemulsion and poly lactic-co-glycolic acid (PLGA) NPs as anti-inflammatory agents for topical administration was investigated. Among four prenylated flavanones, 5-hydroxy-7-methoxy-6-prenyl flavanone loaded nanoemulsion and polymeric nanoparticles could be proposed as potential topical anti-inflammatory formulations with the best properties for the treatment of inflammatory disorders [25]. Oleanolic acid (OA) was efficiently encapsulated in methoxy poly(ethylenglycol) (mPEG) with poly (lactic acid) [mPEG-PLA] and mPEG-poly(lactic-co-glycolic acid) (PLGA) NPs as nanoformulations for cancer therapy. All OA-loaded NPs system produced significant cytotoxic effects through apoptosis on cancer cell lines [26]. Polycaprolactone (PCL)/polyvinylpyrrolidone (PVP) nanofiber mat containing crude bark extract of *Tecomella undulate* were prepared and evaluated for their antibacterial properties. Extract loaded PCL/PVP nanofiber mat had inhibited the growth of bacterial strains which indicated that it could act in the treatment of wound healing or dermal bacterial infections [27]. *Centella asiatica* (CA) extract was successfully incorporated into electrospun membranes to improve wound healing in a rat model. The wound areas that were covered with electrospun gelatin membranes containing CA (EGC) membranes exhibited more collagen deposition and a higher number of capillaries than the wound areas to which the other treatments were applied. Hence EGC membranes can be used as a potential material for wound dressings [28].

Nanotechnology in nutraceuticals

Nanotechnology platforms are widely being used to create delivery systems for nutraceuticals and bioactive natural products with poor water solubility. Some of the extensively studied nutraceutical nanomaterials are discussed here. Figure 2 depicts the potential applications of nanotechnology in nutraceuticals. Table 2 summarizes the potential applications of nutraceuticals formulated as nanomaterials.

Hydrophobins (Hyd) used for nanoencapsulation of nutraceuticals for food enrichment is very much interesting they bid to hydrophobic materials like vitamin D_3 (VD_3). Hyd provided excellent protection to VD_3 against degradation. Moreover, Hyd were found to be promising nanovehicles of hydrophobic nutraceuticals for food and beverages enrichment [29]. Folic acid was encapsulated with two different matrices (whey protein concentrate (WPC) and a commercial resistant starch) and two different encapsulation techniques (spray drying and electro-spraying). Greater encapsulation efficiency was observed using WPC as encapsulating matrix. Electrospraying is a promising method in the food industry for encapsulation applications [30]. Emulsification-diffusion method (EDM) is an excellent alternative to prepare nanocapsules from food constituents. Formation of nanocapsules with DL-α-tocopheryl acetate and β-carotene has confirmed the versatility and reproducibility of the EDM when batches with different materials are prepared under optimal conditions [31].

Functional food components	Delivery system/ Experimental model/ Route	Major activities / Applications	Reference
Hydrophobins (Hyd)- Vitamin D_3	Nanoencapsulation	Hyd found to be promising nanovehicle of hydrophobic nutraceutical for food beverage enrichment Hyd provide excellent protection vitamin D_3 against degradation	Israeli-Lev et al. [29]
Folic acid with whey protein and commercial resistant starch	Nanoencapsulation	Greater encapsulation efficiency Improved folic acid stability Increase bioactive stabilization	Pérez-Masiá et al. [30]
DL-α-tocopheryl acetate and β-carotene	Pluronic-127 and poly-ε-caprolacotne envelop nanocapsule through emulsification-diffusion method (EDM)	EDM is a promising method to prepare nanoparticle for food materials	Zambrano-Zaragoza et al. [31]
Vitamin D_3 entrapped with whey protein NPs with different calcium concentration	Encapsulation	Great stability of Vitamin D_3 Can be used in clear and non-clear beverage as an enriching agent	Abbasi et al. [32]
Folic acid and calcium	Duel nutraceutical nanomaterial	To provide high content of essential nutrient in human health	Kim and Oh [33]
β-carotene, folic acid, curcumin and ergocalciferol	Protein-polysaccharide soluble nanocomplex	To increase the antioxidant activity	Hosseini et al. [34]
Carotenoids	Lipid nanocarriers	Great potential for clinical applications New delivery system for lipophilic plant extracts	Lacatusu et al. [35]
CoQ10	Lipid free nanoformulation	Effective vehicle for improving oral bioavailability of CoQ10	Zhou et al. [36]
Long chain fatty acids and CoQ10	Nanoemulsion	Nanoemulsion based delivery systems that increased oral bioavailability of lipophilic nutraceuticals	Cho et al. [37]
Omega-3-fatty acids and oil soluble vitamins	Biopolymeric nanogels	Encapsulate and protect bioactives Used only food grade ingredient Fabricated system improves the quality of food and beverages	Matalanis et al. [38]
Curcumin	Organogel based nanoemulsion	Digestion of nanoemulsion significantly fast and complete Oral bioavailability of curcumin increased Can be used in functional foods, dietary supplements and pharmaceutical industries	Yu et al. [39]
α-tocopherol	Supercritical assisted nanosuspension	Increases the dissolution rate Increases the bioavailability Increases the stability	Campardelli et al. [40]

(-)-epigalocatechin-3-gallate	Protein-polyphenol coassemblies: Lactoferrin based NPs	LF-EGCG-nano and submicrometer particles can be used as protective vehicles for EGCG for control release of other bioactive materials LF-EGCG have potential for the development of food formulation based on LF as a carrier of bioactive compounds	Yang et al. [41]
Clove oil and Eugenol	Oil titration–precipitation of COM and EM	Formulation in microemulsion provides a delivery system for oral administration of clove oil in homogenous, water based and thermodynamically stable dose	Al-Okbi et al. [42]
Dextran and isoflavone genistein	Enzymatic assisted inclusion complexation method	DMSO-water inclusion protocol has been found to be more suitable for the inclusion of genistein in the enzymatically dextran Increased the yield of inclusion of nutraceuticals by 11 to 141 folds due to formation of new H-bonds and Vander walls interaction	Semyonove et al. [43]

Table 2: List of nutraceuticals formulated as nanomaterials and their characteristics.

VD_3 was entrapped in whey protein isolate (WPI) nanoparticles prepared with different calcium concentration. Composition of nanoparticles with calcium can perform a compact structure providing reduction of VD_3 degradation during storage time. WPI nanoparticles containing VD_3 can be used for enriching of clear or non-clear drinks such as herbal beverages, fruit drinks or low fat food [32]. Dual nutraceutical nanohybrids consisting of folic acid (FA) and calcium were prepared based on layered double hydroxide (LDH) structure through exfoliation-reassembly hybridization method FA/LDH nanohybrids showed higher contents of essential nutrients in human health and they could be considered as dual nutraceutical nanomaterials [33]. Hosseini et al. [34] were explored the potential application of the protein-polysaccharide soluble nanocomplexes as delivery systems for nutraceuticals in liquid foods. The complexation between β-lactoglobulin (BLG) and four nutraceutical models including β-carotene, folic acid, curcumin and ergocalciferol was investigated under different conditions and the low water soluble nutraceuticals were successfully entrapped within electrostatically stable nanocomplexes [34]. Nanocarriers made with hempseed oil or a blend of amaranth and hempseed oils were investigated for a concomitant encapsulation and release of the carotenoids enriched plant extract. The nanocarriers have a great potential for clinical applications as a new delivery system for other lipophilic plant extracts enriched in bioactive compounds [35]. A novel lipid-free nano-CoQ10 system formulated and stabilized by various surfactants and the bioavailability of CoQ10 was evaluated by oral administration of CoQ10 formulation in Sprague-Dawley rats. The formulation can be an effective vehicle for improving oral bioavailability of CoQ10, it was confirmed by the observation of significant increase in the maximum plasma concentration and the area under the plasma concentration time curve [36]. The bioavailability of heptadecanoic acid and CoQ10 was investigated for the influence of droplet size and oil digestibility by a rat feeding study. The developed nanoemulsion based delivery system has increased oral bioavailability of lipophilic nutraceuticals [37]. Food grade biopolymers, proteins and polysaccharides can be used to create a diverse range of delivery systems suitable for encapsulating, protecting and delivering lipophilic functional components such as omega 3-fatty acids, conjugated linoleic acid, oil-soluble vitamins, flavors, colorants and nutraceuticals [38]. Novel organogel-based nanoemulsions were developed for oral delivery of curcumin and improvement of its bioavailability. *In vitro* lipolysis profiles revealed that the digestion of nanoemulsion was significantly faster and more complete than the organol. Organogel based nanoemulsion can be used for oral delivery of poorly soluble nutraceuticals with high loading capacity, which has significant impact in functional foods, dietary supplements and pharmaceutical industries [39].

Supercritical assisted injection in the liquid antisolvent process has been used for the production of α-tocopherol nanoparticles suspensions and produced NPs can be used as supplementation and as an antioxidant in food, cosmetics and pharmaceutical industries [40]. The potential of native and thermally modified lactoferrin (LF) to form co-assembled vehicles for the delivey of (-)-Epigallocatechin-3-gallate (EGCG) was investigated by Yang et al. LF-EGCG nano and submicrometer particles could act as protective vehicles for EGCG and a beneficial aid for the development of controlled release of other bioactive materials [41]. The effect of clove essential oil (CO) and its major constituents, eugenol, formulated in water-based microemulsion was studied on fatty liver and dyslipidemia in high-fractose-fed rats. CO and eugenol microemulsion (EM) produced significant improvement in fatty liver and dyslipidemia with consequent protection from cardiovascular disease and other complications of fatty liver [42]. Two nutraceutical induction methods, DMSO dilution in water and acidification were used for enzymatically synthesis of dextran NPs to entrap hydrophobic nutraceutical, the isoflavone genistein. The DMSO method was found to be more suitable for inclusion of genistein in dextran, resulted in a high genistein load and high percentage of nanosized particles [43].

Future perspective

Nanotechnology in drug delivery has been manifested into nanoformulations that can have unique properties both *in vivo* and *in vitro*, especially in targeted delivery. A few clinical studies have done to great effect in small animal models, but the translation of the small animal results to clinical successes has been limited [44]. Successful translation requires revisiting the meaning of nanotechnology in drug delivery, understanding the limitations of nanoparticles, identifying the myth persistent in the field, and facing inconvenient facts. For this approach to be successful, it may require fine-tuning of the procedure to maximize the usefulness of the nanoparticle to the drug delivery system. Nanoparticle researchers need to realize is that clinical application of any formulation requires approval by the Food and Drug

Administration (FDA) or its overseas equivalent. The safety and efficacy of new formulations must be proven through controlled clinical studies. Doxil® is the first FDA approved nanodrug in 1995 based on the three unrelated principles (i) prolonged drug circulation time and avoidance of the reticuloendothelial system due to the use of polyethylene glycolated nanoliposomes, (ii) high and stable remote loading of doxorubicin driven by a transmembrane ammonium sulfate gradient, which also allows for drug release at the tumor and (iii) having liposome lipid bilayer in a "liquid ordered" phase composed of the high temperature (53°C) phosphatidylcholine and cholesterol [45]. Even though, large reward, nearly two years after Doxil-related patents expired, there is still no FDA-approved generic "Doxil" available. The complexity of FDA approval of generic Doxil, the current situation is even more complex. Accordingly turning the potential of nanoformulations into clinically useful requires clear setting and reasonable goals. The challenges in drug delivery using nanoformulations can be overcome through understanding the limitations of nanoformulation approaches by FDA regulations and maximizing the existing capabilities of nanoformulations.

Conclusion

Overall, this review indicates that nanotechnology has great potential for delivering herbal drugs and nutraceuticals, and in light of the comprehensive health problems, its utilization for effective disease prevention and health promotion is necessary and to be anticipated. Even though nanotechnology offers promising approaches in herbal drug delivery and nutraceutical applications, additional innovative research is needed to address the cost effective and long-term safety of the nanomaterials.

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