Phytochemicals and Nano-Phytopharmaceuticals

Subjects: Integrative & Complementary Medicine

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Nanomedicines emerged from nanotechnology and have been introduced to bring advancements in treating multiple diseases. Nano-phytomedicines are synthesized from active phytoconstituents or plant extracts. Advancements in nanotechnology also help in the diagnosis, monitoring, control, and prevention of various diseases. The field of nanomedicine and the improvements of nanoparticles has been of keen interest in multiple industries, including pharmaceutics, diagnostics, electronics, communications, and cosmetics. In herbal medicines, these nanoparticles have several attractive properties that have brought them to the forefront in searching for novel drug delivery systems by enhancing efficacy, bioavailability, and target specificity.

nanomaterials locomotor disorder dermal disorder urogenital disorder phytopharmaceuticals

1. Introduction

Physicians and patients have recognized the use of herbal medicine since ancient times [1]. For instance, the first-ever plant-derived painkiller, morphine which belongs to the benzylisoquinoline class of alkaloid, was isolated from *Papaver somniferum* L. (Papaveraceae) and authorized to be used in 1827 [2]. Herbal medicines are well known for their better therapeutic performance as well as lesser side effects compared to modern medicines. The demand for phytochemicals and plant products has been increasing rapidly in many areas of medicine, as in the treatment of dermal, urogenital, and locomotor disorders. Advanced phytopharmaceutical research especially with novel drug delivery systems by applying nanotechnology plays an important role in troubleshooting scientific needs with the determination of the pharmacokinetics, mechanism of action, site of action, accurate dosage, improved bioavailability, and reduced toxicity of various herbal medicines [3][4]. Several safety concerns related to biocompatibility, possible toxicity (of unknown natural compounds), and lack of enough clinical trials on medicinal plants and herbal medicines can be resolved by the implementation of nano-based drug delivery systems [5][6][7]. Thus, herbal medicines can be used for the treatment of a wide range of ailments, including dermal, urogenital, and locomotor disorders.

Nanoparticles are often classified as particles of less than 100 nm in diameter. They occur extensively in nature as products of photochemical, plant, and algae activity and have also been created as by-products of combustion and food cooking for thousands of years [8]. There are various kinds of nanosystems available, such as niosomes, liposomes, nanostructured lipid carriers (NLCs), and nanoemulsions. Niosomes are defined as microscopic vesicles composed of non-ionic surfactants, liposomes as microscopic spherical vesicles having one or more phospholipid bilayer membrane, NLCs as novel nano-sized pharmaceutical formulations composed of solid and liquid lipids, surfactants, and co-surfactants. Nanoemulsions as nano-sized emulsions have droplet sizes between 20 and 500 nm, respectively. Nanomedicine is the application of nanoscale materials such as nanoparticles for the diagnosis, monitoring, control, prevention, and treatment of disease [9]. The field of nanomedicine and the application of nanoparticles has been of keen interest in several industries, such as electronics, communications, cosmetics, biology, and medicine [10]. In medicine, these nanoparticles have various attractive properties that have brought them to the forefront in the search for novel drug delivery systems with most advances in the utilization of nanoparticle drug delivery for the treatment of cancer with several nanotherapies being used clinically after approval by the FDA in the United States of America [11][12]. The properties exhibited by nanoparticles include a high surface-to-volume ratio, high surface energy, unique mechanical, thermal, electrical, magnetic, and optical behaviors [13].

The term “nanotechnology” is derived from a Greek word that means dwarf, which employs the concepts of engineering and manufacturing at the molecular level [14]. The advantages generated by the use of nanotechnology can assure the revolutionary changes in herbal medicines along with several other multidisciplinary emerging applications in chemistry and physics. The reason behind the achievements of nanotechnology in medicine includes the possibility of working at the same scale of many biological processes, cellular mechanisms, and organic molecules. For this reason, medicine has looked at nanotechnology for the ideal solution in the treatments of several diseases. Furthermore, the methodology has drawn attention toward providing treatments in a safe and effective form [15].

From the existing literature, the increasing trend in nanoformulation using phytochemicals studies has been remarkable, particularly from the last 5 years (from 2018 to date) and it is commonly investigated against cancer-related disorders. This entry therefore focuses on the potential of herbal medicines highlighting the successful application of nanotechnology to treat some diseases, specifically dermal, urogenital, and locomotor activities. In addition, this entry aims to understand the justification and significance of using nanotechnology-derived phytochemicals or herbal formulations (i.e., nano-phytopharmaceuticals) in the three specific disorders based on locomotion, skin, and urogenital conditions (**Figure 1**).

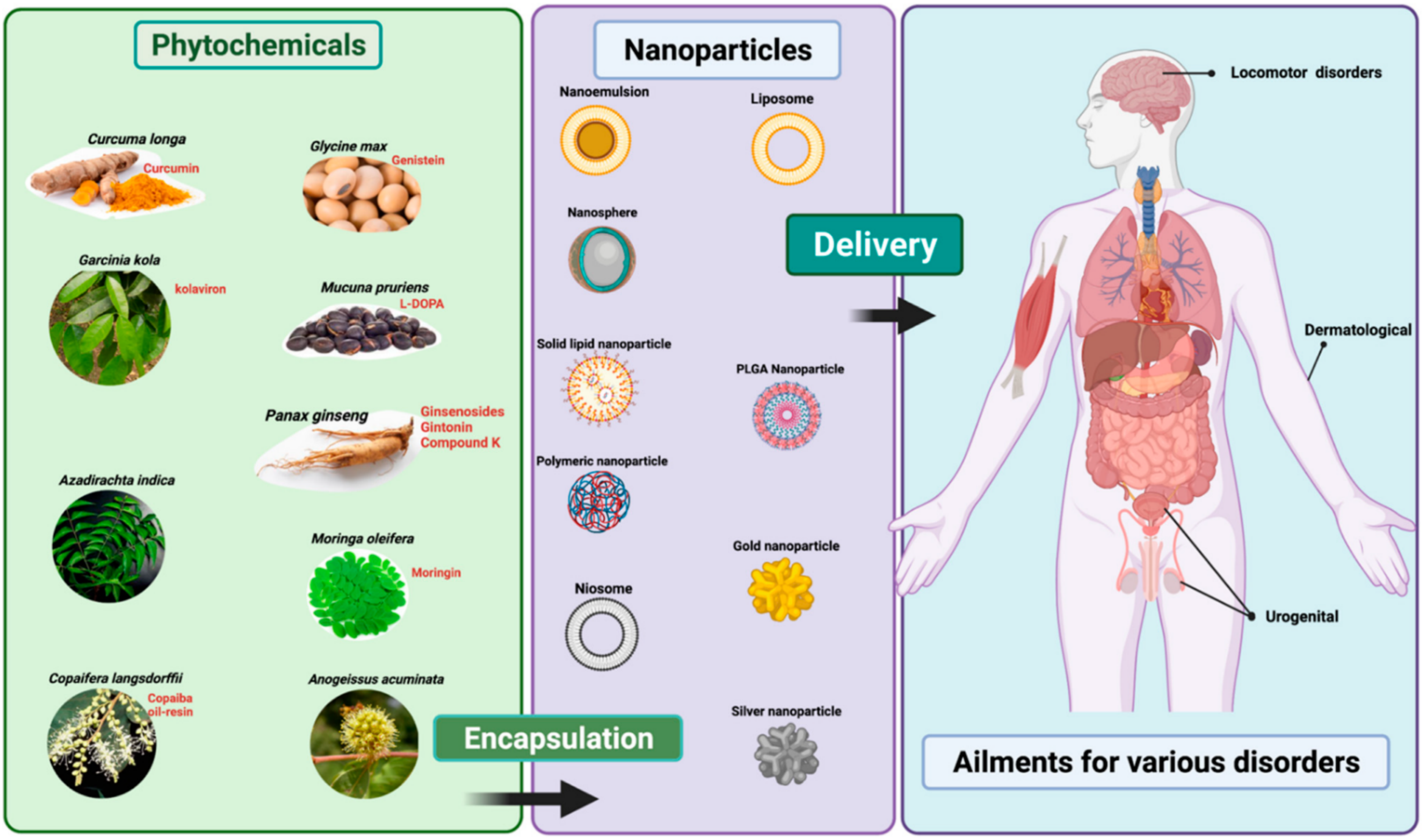

Figure 1. Representation of delivery of phytopharmaceutical using nanotechnology. The figure was made with www.biorender.com (access date: 15 March 2022).

2. Therapeutic Applications of Nano-Phytopharmaceuticals

2.1. Nano-Phytopharmaceuticals in Dermal Disorders

Dermatological disorders are prevalent worldwide and regarded as one of the major global burdens among various diseases [16]. Severe skin damage from burns or wounds as well as acne (i.e., often causes erythematous papulopustular lesions such as rash consisting of papules and pustules) can also lead to trauma and further psychosocial stresses besides possible pain or other aggravations caused by the disorder itself [17][18]. Dermatological disorders can be atopic dermatitis, alopecia (androgenic alopecia and alopecia areata, both indicating hair loss), hirsutism (growth of excess coarse body hair usually in women in places where hair is not supposed to grow), hyperhidrosis (excessive sweating), hidradenitis suppurativa (chronic and progressive inflammatory skin condition affecting groin, buttocks, and perineal and perianal regions), vitiligo, psoriasis, and melanoma [19].

Most dermatological disorders affect the outermost layer of the skin (horny layer), which is typically water repellent and dense, the latter characteristic acting as an effective barrier against rapid passage of any outward items, which may be chemicals or infectious agents. Topical therapeutic agents usually contain in combination the agent and a base-formulation, which facilitates the absorption of the agent. Drugs for dermatological disorders must cross the horny layer to get to the root of skin infection to produce their therapeutic effects. A low molecular weight of the therapeutic agent (20-300 kDa) enhances penetration of the horny layer or stratum corneum [20], which is further enhanced if the agent is applied as an oleaginous ointment, emulsified ointment, cream, or gel. Nanotechnology can be an important tool for the delivery of therapeutic agents for both topical and transdermal applications through engineered nanoparticles of drugs and enabling them to better reach their target sites. Various types of nanoformulations are available such as solid nanoparticles, liposomes, secosomes, transferosomes, ethosomes, niosomes, nanoemulsions (NE), nanostructured lipid carriers (NLCs), solid lipid nanoparticles (SLNPs), and flexible nanovesicles [21].

Solid nanoparticles, such as zinc oxide and titanium dioxide nanoparticles (NPs) are mainly used in sunscreens to filter out UVA and UVB radiations. Studies on keratinocytes suggest that titanium dioxide nanoparticles are safer than zinc oxide, as zinc oxide NPs can generate reactive oxygen species within cells. Both NPs have been found to produce adverse effects in human keratinocytes in vitro following long-term exposure [22]. Liposomes are usually composed of cholesterol and phospholipids that show higher biocompatibility, improved solubility, and efficacy of lipophilic and amphiphilic drugs and thus facilitate the application of topical drugs [23].

Nanomaterials such as NLCs are prepared from a combination of solid lipid (SL) and liquid lipid (LL) ingredients. The use of LL in the manufacture of NLCs permits a greater drug load. The SLs include compounds such as glyceryl monostearate and glyceryl tripalmitate; the LLs include a more diverse variety of compounds such as oleic acid and squalene. Surfactants used in the preparation of NLCs include lecithin and Tween 80 [24]. Flexible or deformable nanovesicles have greater penetrability through biological barriers but thus far have seen limited use because of their physical and chemical instabilities. However, a recent study reported that flexible nanovesicles at a low density and containing 8% lactose and trehalose at a ratio of 1:4 have a spherical shape, smooth surface morphology in the lyophilized state, a whorl-like structure, high entrapment efficiency, and deformability after reconstitution; thus confirming their stability. Importantly, the secondary structure of insulin was well protected in the insulin-phospholipid complex deformable nanovesicles [25], which further confirmed their functional ability.

From the above section(s), it is apparent that nanovesicles and nanoparticles can play an important role in the delivery of drugs to target organs especially on skin. It is important because many drugs have poor aqueous solubility; thus limiting their bio-absorption. These lipophilic drugs can be encapsulated within nanovesicles as nanoparticles and then administered through suitable routes. Various nanotechnological approaches have been and still are experimented with towards a more efficacious treatment of skin disorders. The therapeutic nanoparticles comprise conventional drugs, crude extract of plants, and phytochemicals. For example, the ethanolic extract of *Ocimum sanctum* L. (Lamiaceae) reportedly has anti-aging properties on skin, as demonstrated by its anti-oxidant and anti-inflammatory properties, as well as its inhibitory features against hyaluronic acid and collagen fiber degradation inhibition [26]. The encapsulation of the ethanolic extract was completed in several types of nanodelivery systems, including NLCs, NEs, liposomes, and niosomes. Among the various delivery systems containing *Ocimum sanctum* L. (Lamiaceae) extract nanoparticles, NLC and NE were the most stable, with NLC delivering the highest amount of extract to the skin layer [27]. The ethosome gel was reported to deliver quercetin to treat inflammation, and amphotericin B to treat fungal infections [28][29]. Quercetin-loaded phospholipid vesicles containing, in addition, 5% polyethylene glycol demonstrated effectiveness in amelioration of skin inflammation induced by TPA (12-*O*-tetradecanoylphorbol-13-acetate). The nanoethosomal formulation exhibited a 3.5-fold higher skin deposition of amphotericin B, leading to a significant increase in anti-fungal activity against *Candida albicans*.

Application of various forms of nanodelivery systems for the treatment of skin disorders have been reviewed by Roberts et al. [21]. These include liposome, ethosome, and deformable liposome-based delivery of ketoconazole to treat dermatological fungal infections from *Candida albican*; the use of nanostructured lipid carrier-based gel to deliver clobetasol propionate to treat eczema; the use of solid lipid nanoparticles for delivery of artemisone and doxorubicin for the treatment of melanoma and squamous cell carcinoma, respectively. Silver nanoparticles have been used to treat scalp-based fungal infections caused by *Malassezia furfur*; and gold nanoparticles are used for the treatment of psoriasis. The use of tyrospheres (tyrosine-derived nanospheres) as a delivery medium for vitamin D_3 has also proved to be effective for psoriasis treatment. It appears that there is enhanced absorption of vitamin D_3 through this nano-treatment method [30]. In fact, as reviewed by Petit et al., the use of biodegradable nanocarriers for delivery of vitamin D_3 or other therapeutics for psoriasis treatment includes nanospheres, nanocapsules, liposomes, ethosomes, solid lipid nanoparticles, and nanostructured lipid carriers [31].

Curcumin, which is derived from rhizomes of *Curcuma longa* L. (Zingiberaceae), containing nanomaterials, including lipid-based nanoparticles such as liposomes, niosomes, solid lipid nanoparticles, and nanostructured lipid carriers are used in various dermatological disorders such as psoriasis, dermatitis, bacterial, viral and fungal infections, burns, acne, vitiligo, arthritis, and skin cancer [32][33][34]. Lipid-based nanoparticles (NLCs and SLNPs) of curcumin have higher biocompatibility with skin layers, can increase their penetration into this organ and thus increase their solubility, stability, and therapeutic efficiencies [33] (**Table 1**). NLCs and SLNPs can also increase patient compliance by maintaining delayed and regulated release and improving their pharmacological activities [35][36].

Table 1. Role of nano-phytopharmaceutical formulations against various locomotor, skin, and urogenital disorders.

Plant Source	Formulation	Study Type	Action	Reference
Citrus fruits, onions, apples, parsley, sage, tea, and berries.	Nanoencapsulated quercetin in zein nanoparticles (NPQ)	Preclinical (rats)	NPQ improved memory and cognitive ability in rats (but no effects on locomotor activity test)	[37][38]
Citrus fruits, onions, apples, parsley, sage, tea, and berries.	Quercetin nanoparticles	Preclinical (rats)	Quercetin nanoparticles improved memory and pathological damage induced by scopolamine	[39][40]
Berries, currants, grapes, red to purplish blue colored leafy vegetables, grains, roots, and tubers.	Anthocyanin-loaded poly (ethylene glycol)-	Preclinical (mice)	PEG-AuNPs improved amyloid-beta ($A\beta_{1-42}$) induced neuronal damage and neuroinflammation	[41][42]

Plant Source	Formulation	Study Type	Action	Reference
	gold nanoparticles (PEG-AuNPs)			
Curcuma longa **L. (Zingiberaceae)**	Nano-curcumin particles	Preclinical (mice)	Enhanced memory, motor function, contextual fear	[43]
***Anamirtacocculus* (L.) Wight and Arn. (Menispermaceae)**	*A.cocculus* NPs in cocc 30c, in a homeopathic formulation	Preclinical	Improved attention and motor functions in sleep-deprived rats	[44]
Solanum tuberosum **L. (Solanaceae)**	*S.tuberosum* Lectin NPs	Preclinical	Helped improved drug delivery enhanced memory and motor function	[45]
***Azadirachta indica* A.Juss. (Meliaceae)**	Neem oil incorporated in argan-liposomes and argan-hyalurosomes by sonicating with argan oil, soy lecithin, and water	In vitro	Protected skin cells by reducing oxidative stress	[46].
***Curcuma longa* L. (Zingiberaceae)**	Curcumin formulated with lipid-based nanoparticles such as liposomes, niosomes, solid lipid nanoparticles, and nanostructured lipid carriers	Review	Improved its penetration into skin and thus increased the solubility, stability, and therapeutic efficiencies of curcumin against various dermatological disorders such as psoriasis, dermatitis, bacterial, viral and fungal infections, burns, acne, arthritis, and skin cancer	[33][34]
Curcuma longa **L. (Zingiberaceae)**	*C. longa* leaves extract Silver nanoparticles (CL-AgNPs) loaded cotton fabric	In vitro	Enhanced wound healing and antimicrobial activity on skin	[47]
Curcuma longa **L. (Zingiberaceae)**	Solid lipid nanoparticles (SLN-curcuminoids)	Ex vivo (Sheep ear skin)	Showed good spreadability and stability on skin	[48]
Curcuma longa **L. (Zingiberaceae)**	Curcumin nanoparticles	Preclinical (rats)	Improved erectile response in diabetic male	[49][50]

Plant Source	Formulation	Study Type	Action	Reference
	(curc-NPs)		rats	
Panax ginseng **C.A.Mey (Araliaceae)**	*P.ginseng* nanoparticles	Preclinical (rats)	Improved serum testosterone secretion and decrease sperm abnormalities in male rats	[51]
Oxaliscorniculata **L. (Oxalidaceae)**	Aqueous extract of *O. corniculata* and its biofabricated silver nanoparticles (AgNPs)	In vitro	Effective against urinary tract infection (UTI) causing microorganisms	[52]
Anogeissusacuminata Wall. (Combretaceae)	Aqueous leaf extract of *A. acuminata* and its AgNPs	In vitro	Effective against multidrug resistant UTI causing bacteria	[53]
Passiflora caerulea **L. (Passifloraceae)**	Zinc oxide nanoparticles (ZnO NPs) using *P. caerulea* extract	In vitro	Effective against multidrug resistant UTI causing bacteria	[54]
Catharanthus roseus ***(L.)*** **G. Don (Apocynaceae)**	Sulphur nanoparticles (SNPs) produced from *C. roseus* leaf extract	In vitro	Effective against multidrug resistant UTI causing bacteria	[55]
Mimosa pudica **L. (Fabaceae)**	Sulphur nanoparticles (SNPs) produced from *M. pudica* alcoholic extracts	In vitro	Antibacterial effects on uropathogenic *E. coli* (UPEC) and *S. aureus* and other UTI pathogens	[56]
Nigella sativa **L. (Ranunculaceae)**	Sulphur nanoparticles (SNPs) produced from seeds of *N. sativa* L. alcoholic extracts	In vitro	Antibacterial effects on UPEC and *S. aureus* and other UTI pathogens	[57]
Rauwolfia serpentina **L. (Apocynaceae)**	Biologically synthe-sized gold nanopar-ticles with aqueous leaf extract of *R. serpentina* L.	In vitro	Antibacterial effects on *E. coli* and *S. aureus*	[58]

eliaceae), nin in the [46] 40 nm in [46]

eted site mize the side effects of the herbal product, which contains hormone-like activity. Hormone replacement therapy (HRT) is the primary management strategy for menopause. Although the benefits of using HRT (estrogen and progesterone) for the management of moderate-to-severe menopausal symptoms outweigh the risk, the non-selective delivery of the hormones may cause increased risks of cerebrovascular diseases, such as stroke [59]. Herbal medicines are promising alternatives for the management of menopause. Phytoestrogen is a plant-derived compound that is structurally and/or functionally similar to estrogen. Plant compounds such as soy, red clover, hop, and other botanicals contain naturally occurring phytoestrogens [60]. Genistein is a primary phytoestrogen compound of soybean which is poorly soluble in an aqueous medium. Its poor aqueous solubility and low serum concentration after administration warrant the development of a novel drug delivery system [61]. Encapsulation of genistein in Fe_3O_4-carboxymethylated chitosan nanoparticles and EudragitR E cationic copolymers improves water solubility, leading to better absorption from the gastrointestinal tract [61][62]. A low dose of phytoestrogen is associated with the development and progression of breast cancer in vitro and in vivo [63]. Activation of estrogen receptors in the breast by phytoestrogen promotes the growth of breast cancer. These limitations can be overcome with the incorporation of a nanotechnology-based drug delivery system. Encapsulating phytoestrogen in nanoparticles may help delivery of the bioactive compounds to the estrogen receptors in endothelium and vascular smooth muscle specifically. The agonist effect of estrogen receptors on vascular smooth muscle helps to relieve vasomotor symptoms (hot flash, night sweat) in menopausal women. The extended-release activity of the herbal preparation can be achieved through encapsulation into nanocarriers, such as multivesicular liposomes. This approach is valuable in delivering bioactive compounds which are intended to produce long-lasting action. Genistein nanoparticle preparation has been widely used for anticancer therapy [64]. However, its potential as a phytoestrogen to treat menopause is not yet fully elucidated.

Herbal products such as rhizome extract of wild yam (*Dioscorea villosa* L. (Dioscoreaceae), root extract of Dong Quai (*Angelica sinensis* (Oliv.) Diels (Apiaceae)), evening primrose oil (*Oenothera biennis* L. (Onagraceae)), dried root of Maca (*Lepidium meyenii* Walp. (Brassicaceae)) are commonly used among menopausal women to relieve menopausal symptoms [65]. Black cohosh (*Cimicifuga racemosa* L.) Nutt. (Ranunculaceae) is one of the common herbal products that has been used among indigenous people for the management of menopausal symptoms. Several mechanisms of action of black cohosh have been proposed: selective estrogen receptor modulation, serotoninergic pathway, anti-oxidation, and anti-inflammation [66]. The blood-brain barrier is a challenge for the delivery of bioactive compounds, which act centrally. Formulating black cohosh in nanoparticles may help enhance the crossing of the bioactive compound through the blood-brain barrier. This novel formulation increases the selectivity of black cohosh bioactive compounds towards the central serotoninergic pathway in the brain [67].

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