REVIEW ARTICLE

RECENT ADVANCES IN NANOTECHNOLOGY - BASED DRUG DELIVERY SYSTEMS FOR DELIVERY OF PHYTOCONSTITUENTS WITH SPECIAL EMPHASIS ON PSORIASIS MANAGEMENT

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ABSTRACT

Psoriasis is an inflammatory, autoimmune disorder characterized by thick and silvery lesions of the skin. Beyond its physical dimension, this disease has a significant adverse effect on quality of life and represents a huge social health burden. Based on symptoms, psoriasis may be characterized from mild to severe. A range of therapeutic agents are available to treat the disease, but none is able to provide permanent cure of the disease. The most commonly used medicines for treatment of psoriasis include anti-inflammatory drugs, steroids, biological and immunosuppressants. Though these drugs cure the disease to an extent, they are associated with many contra-indicative manifestations. Hence, an alternative system of medicine could be an excellent approach in the management of this disease, and numerous studies proved that bio-actives derived from natural sources have potential anti-psoriatic activity. Further, the therapeutic actions of these natural products can be enhanced by incorporating them in nano-formulations. The present era of medicine is focusing on implementation of natural product based nanotechnology to overcome the drawbacks of conventional treatment. This review primarily aims to focus on the recent advances in the field of natural product based nanomedicines for the effective management of psoriasis.

Keywords: Psoriasis, nanotechnology, phytoconstituents, drug delivery, topical application

INTRODUCTION

Psoriasis is common inflammatory autoimmune disorder, which primarily affects the skin and joints[1,2]. The disease is characterized by the sub corneal lesions of the skin with irregular distribution and severity[3,4]. Depending upon the type of disease, the lesions are distributed on the different areas of skin such as scalp, body folds, nails, etc[5,6] and sometimes it may also be followed by systemic symptoms including, but not restricted to, hypertension, hyperlipidemia, diabetes mellitus and obesity[7,8]. Psoriasis affects populations of different ages and regions all over the world. According to the report of World Health organization (WHO), the incidence rate of psoriasis in the world varies from 0.09% and 11.43%[9,10]. In India, the estimated prevalence of psoriasis ranges from 0.44 to 2.8%. Plenty of therapeutic agents are available to treat the disease, but none can effectively treat the disease without affecting the patient's safety and compliance[11,12]. Most commonly used medicines for treatment of psoriasis are anti-inflammatory drugs, steroids, biological and immunosuppressants. Though these drugs may cure the disease, they are associated with many contraindicative effects[13,14], such as mutagenicity, organ toxicity and a high degree of immunosuppression, which limit their use. However, psoriasis affects only a particular area of the body, like skin, joints and most commonly nails. So, the systematic treatment with conventional formulations may increase health as well as economic burdens as they decrease the therapeutic effects and adverse effect ratio. Consequently, there is an urgent requirement to explore

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new natural product based nanotechnology to manage the disease, effectively[15]. Various studies demonstrated that phytoconstituents such as curcumin, resveratrol, ellagic acid and many more have the advantages of lower risk of adverse effects over conventional treatment. Phytoconstituents work by multiple mechanisms of actions, which enable synergistic activity to mitigate psoriasis.

PATHOGENESIS OF PSORIASIS

Psoriasis is a complex skin disorder with intricate of pathogenesis. Initially, koebnerization is triggered by various environmental and genetic factors such as obesity, drugs, infection, stress etc[16,17]. After the initiation of koebnerization, neutrophils in damaged skin release an antimicrobial peptide LL-32, self-complex of DNA and pro-inflammatory chemokines, like CXCL1, CXCL2, CXCL8, and CCL20[18,19]. The production of these antimicrobial peptides is increased by the interleukin Il-17A[20, 21] which enhances the proliferation of keratinocytes. The released antimicrobial peptide activates the plasmacytoid predendritic cells (PDCs) and dermis dendritic cells (DCs), which release a mass of pro-inflammatory cytokines such as IL-12, IL-23, TNF-α and type 1 interferon[22]. PDCs cells are considered as the primary source of type-I interferon (INF-α) in skin. Hence, their activation leads to abundant production of INF-α, which initializes the activation of T-cell and maturation of myeloid dendritic cell (mDC). Matured DC cells release a pool of cytokines, which leads to the activation of T helper cell- type 1 (TH1) and T helper cell- type 17 (TH17). These activated T-cells initialize the auto-inflammation and hyperproliferation of keratinocytes and psoriatic plaque formation[23], as shown in Fig. 1.

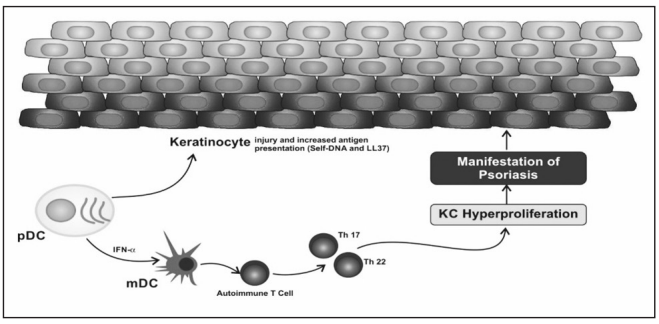

Fig. 1: Pathogenesis of psoriasis [17]

Management of psoriasis via implementation of natural product based nanotechnology

Novel nano-sized natural product based formulations can be a promising area to target the disease by enhancing the permeability of therapeutic agents through skin, drug retention time, and increasing patient compliance by reducing the frequency of dose with high efficacy and safety[24,25]. The larger particle size of drug hinders the permeability of drug via different layers of the skin, which decreases the bioavailability as mentioned in Fig. 2. Being nano-sized, nano-formulations can improve permeation of drugs and their accumulation in the skin[26]. These advanced nano-formulations consist of nanoparticles, dendrimers, polymeric micelles, nanoemulsions, vesicular drug delivery systems and others.

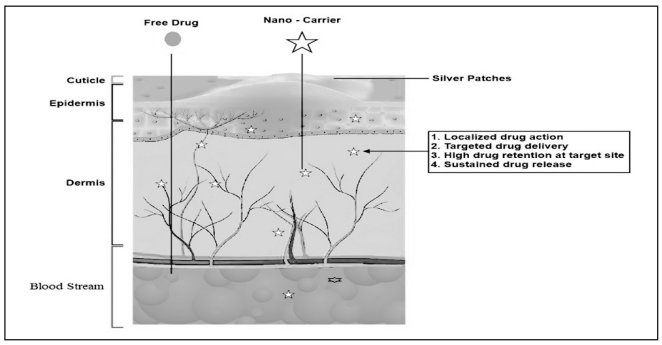

Fig. 2: Nanotechnology mediated management of psoriasis[24]

How natural products deal with psoriasis

Primarily, all the natural products work by some common mechanism, however, some variations may occur.

They normally work by down regulating the concentration of TH17 cell mediated release of pro-inflammatory cytokines like TNF-α, IL-6 IL-12, IL-23, IL-22, CRP type 1 interferon, and activation of CD4+ cell by blocking the activity of T-lymphocytes. By this mechanism, natural product attains a high degree of immune-suppression, by controlling the differentiation and hyperproliferation of keratinocytes[27], by inducing apoptosis, and by obstructing the keratinocytes cell cycle[28].

In addition, natural products counteract the inflammation inducing the enzyme nitric oxide synthase, which increases the release of nitric oxide. The release of nitric oxides stimulates the dilation of blood vessels and enhances the blood supply to the skin, which promotes the regeneration of affected tissue and skin[29].

Inhibition of the enzyme phosphorylase kinase increases the phosphorylation events of both serine/threonine and tyrosine amino acids to activate the inflammatory transcription factors NF-κB. NF-kB is responsible for the activation of 200 genes responsible for inflammation including 5-lipoxygenase and cyclooxygenase-2[30] and hyper-proliferation of keratinocytes[31].

Table I: Metallic nanoparticles for management of psoriasis[41-43]

Sr. no.	Metal	Plant	Bio-actives	Findings
1.	Gold, Silver	*Cornus mas*	Iridoid and phenolic components i.e cyanidin 3-galactoside	Metal complex may provide an efficient tool for modulating inflammatory effects of psoriasis[41].
2.	Gold	*Woodfordia fruticosa*	Myricetin, quercetin and ellagic acid	Topical application of gold nano-particle decreases the hyper-proliferation of keratinocytes, level of cytokines and the quench of skin lesions, hence could be used as efficient alternative to treat psoriasis[42].
3.	Titanium dioxide	*Curcuma longa*	Curcumin	Metal drug complex have better anti-psoriatic potential along with its no toxicity to normal cells[43].

Table II: Vesicular drug delivery systems for the management of psoriasis[49-55]

Sr. No.	VDDs	Plant	Bio-actives	Findings
1.	Ethosomes	*Piper nigrum*	Piperine	Ethosomes reduced thickness of skin and cytokine levels[49].
2.	Liposomes	*Andrographis paniculata*	Andrographolide	Liposomal formulation enhances the topical delivery of andrographolide [50].
3.	Glycethosomes	*Mangifera indica L.*	Mangiferin	Glycethosomes provide synergistic treatment of psoriasis[51].
4.	Spanlastics	*Vitis vinifera*	Resveratrol	Resveratrol loaded spanlastics involves in the improvement of skin lesions and erythema[52].
5.	Transethosomes	*Rosmarinus officinalis*	Rosmarinic Acid (RA)	RA loaded vesicles are found to be effective in the reduction of TNF-α, interleukins level and in punch edema[53].
6.	Ethosomes	*Curcuma longa*	Curcumin, glycyrrhetinic acid	Topical application of ethosomal formulation exhibits synergistic effects in imiquimod-induced psoriatic mice[54].
7.	Niosomes	*Tripterygium wilfordii*	Celastrol	Highly reduction in serum cytokines was observed which leads to the high effectiveness of niosomes in psoriasis[55].

Table III: Nano-structured lipid carriers for management of psoriasis[61-63]

Sr. No.	Plant	Bio-actives	Findings
1.	*Capsicum annuum*	Capsaicin	Developed formulation was found to enhance *in vitro* drug release, loading capacity and localized action with minimum of skin irritation[61].
2.	*Nigella sativa L.*	Thymoquine	NLCs enhanced the bioavailability of thymoquine thus can be considered as highly effective carriers in management of psoriasis[62].
3.	---------	Propolis flavonoids	After topical targeting, SNS reduce the edema volume up to three-fold, thus concluded that propolis flavonoid loaded SLN could be an excellent option for psoriasis[63].

Treatment of psoriasis is also carried out by inducing regulatory T-cells, also called as Tregs[32]. Tregs suppress the excessive immunity of immune systems against, a wide range of antigens, including self-antigens and thereby block the hyper-proliferation of keratinocytes[33]. In psoriasis, Tregs are unable to give their suppressive action, which leads to alterations in T-helper 17/Treg balance[34].

Nanotechnology based carriers for the delivery of natural anti-psoriatic drugs

Plasmonic nanoparticles: They are also called metallic nanoparticles (MNs)[35,36]. These are basically a colloidal dispersion of pure metal particles in the sub-micron range. MNs can themselves be used as anti-inflammatory, antimicrobial, anti-cancer and anti-

Table IV: Polymeric nanoparticles in management of psoriasis[68-70]

Sr. No.	Type of polymer	Plant	Bio-actives	Findings
1.	Chitosan	---------	Combination of gallic acid and rutin	The chitosan nano-particles reduced keratinocyte hyper-proliferation[68].
2.	Chitosan	----------	α-Tocopherol	PNs entrapped in silk fibroin hydrogel showed a high therapeutic efficiency with a highly effective anti-proliferative effect on keratinocytes[69].
3.	Chitosan	*Coffea arabica*	Caffeine	Results indicated a high anti-inflammatory value of *Coffea arabica* loaded nanoparticles[70].

Table V: Micellar nano-particles in management of psoriasis[76-78]

Sr. No.	Plant	Bio-actives	Findings
1.	*Centella asiatica*	Madecassic acid, asiaticoside, and madecassoside	Nanocarriers increase the entrapment efficiency, stability with high bioavailability[76].
2.	*Vitis vinifera*	Resveratrol	Resveratrol loaded polymeric micelles exhibit a remarkable reduction in inflammatory cytokines levels and in skin lesions, which indicated high utility of this formulation in psoriasis[77].
3.	*Silybum marianum*	Silibinin	Silibinin loaded polymeric micelles improve its deposition in skin when compared with control. It also reduced the psoriasis area index (PAI) by more than 78% after 14 days[78].

Table VI: Cyclodextrin based nanoparticles in management of psoriasis[84-87]

Sr. No.	Plant	Bio-actives	Findings
1.	*Gynura pseudochina* (L.)	p-Coumaric acid (PCA)	The findings revealed that incorporation of PCA in nanoparticles led to an enhancement in efficacy and safety[84].
2.	-------	Ellagic acid (EA)	A remarkable enhancement in the photostability, solubility and antioxidant potential of EA was observed after its inclusion[85].
3.	*Psoralea corylifolia*	Babchi oil	The results revealed that prepared cyclodextrin-based nanogels played an important role in the management of reactive oxygen species (ROS) associated in psoriasis pathogenesis[86].
4.	*Curcuma longa & Coffea arabica*	Combination of curcumin and caffeine	Combination of drugs was found to be more effective than the individual drugs[87].

psoriatic agents, which synergize the therapeutic effects of medicines[37,38]. In addition to this, MNs can be easily synthesized by green synthesis, which is a reliable, and eco-friendly protocol for their synthesis. There are blends of metals, which are used in the fabrication of MNs such as selenium, gold, silver, iron, platinum and zinc[39,40]. A wide range of plant derived bioactives (PDB) has been incorporated in metallic nano-particles for the management of psoriasis, and are listed in Table I.

Vesicular drug delivery systems (VDDs): In the current scenario, vesicular drug delivery systems appear as a powerful tool in the topical delivery of various therapeutics agents. Vesicles are highly ordered self-assembly of amphiphilic building block[44]. These lipid vesicles provide sustained drug delivery with advantages of high efficacy, permeability, bioavailability, and improved retention ability of therapeutics[45, 46]. The structure of bilayer of vesicles mimic the cell membrane, hence they can be used to study the behavior of the cell membrane[47, 48]. A wide range of anti-psoriatic drugs has been incorporated in different VDDs like liposomes, niosomes, pharmacosomes, glycerosomes, ethosomes etc. and some of them are listed in Table II.

Nano-structured lipid carriers (NLCs): These are novel nano-formulations, having emerged recently as an alternative to first generation lipid particulate carriers like liposomes, emulsions polymeric nanocarriers etc. NLCs are composed of biocompatible and biodegradable solid lipid, liquid lipid, counter ions and surface-active agents[56, 57]. They were primarily developed to deliver lipophilic drug, but now they can be used to deliver hydrophilic drug as well[58, 59]. Due to the proper ratio of solid and liquid lipid in their composition, they remain solid at room temperature, which overcomes the problem of stability as seen in micro/nano-emulsion. The solid state of NLCs at room temperature controls the mobility of particles and prevents their coagulation, hence increasing the stability[60]. A wide range of natural products has been incorporated in NLCs for the management of psoriasis, and are listed in Table III.

Polymeric nanoparticles (PNs): These are colloidal vesicular particles of nanosize range, in which pharmacological active compound is dissolved, incorporated and/or adsorbed/conjugated on the surface of particles[64, 65]. Nano/microcapsules and nano/microspheres are also recognized as reservoir type PNs and matrix type PNs. In the matrix type, PNs bio-actives are loaded in between the network of polymers, and in reservoir type PNs, bio-actives are loaded in core of polymeric shell[66]. PNs are composed of an oily core, which is surrounded by polymeric wall balanced by steric charge. Polymeric nano-particles offer a wide range of advantages in the management of dermatological disorder like dermatitis, acne, alopecia and psoriasis. PNs have ability to maintain their structure for long period on topical application of formulation in management of psoriasis[67]. The use of thermosensitive PNs is the most explored approach in psoriasis when applied at the site of inflammation and this will serve as a basis of psoriasis management. Some plant derived bio-actives incorporated in PNs are mentioned in Table IV.

Micellar nanocarriers: Micelles are self-assembled spherical, colloidal particle of size 10 to 200 nm having both hydrophilic and lipophilic compartments in same molecule, which makes them an attractive carrier for a wide range of therapeutic agents. Among all of the presently available micelles, polymeric micelles are widely used in dermatology to treat acne, dermatitis, psoriasis and many more dermatological disorders[71, 72]. Polymeric micelles have the property to encapsulate both hydrophilic and lipophilic agents, high *in vitro* and *in vivo* stability, better retention ability of drug in different layers of skin, high permeability via *stratum corneum*[73, 74]. These mentioned advantages make them a perfect carrier for management of psoriasis[75]. Various therapeutic agents have been incorporated into polymeric micelles, such as silibinin, resveratrol and D-α-tocopherol for the transdermal targeting of psoriasis as mentioned in Table V. All research studies support the fact that polymeric micelles enhance the efficacy of treatment.

Cyclodextrin based nano-particles: Cyclodextrins are amphipathic cyclic polysaccharides, which contain a minimum of six D-(+) glucopyranose units joined by α-(1, 4) glycosidic bond[79, 80]. They are also known as cyclomaltodextrins. They can be easily obtained from the enzymatic decomposition of starch present in potato, corn and many more carbohydrate rich plants[81]. In spite of numerous applications of different nanoparticles in drug delivery, they also possess some disadvantages like low drug loading capacity, low specificity to target, poor stability etc. The problems related to nano-particles can be resolved by their complexation with cyclodextrins as it has the capability to improve solubility, stability and have site specific delivery application[82, 83]. Owing to these, cyclodextrin mediated nanoparticles are widely used in the management of psoriasis, and many naturally active ingredients are incorporated in them, which are mentioned in Table VI.

Microemulsion (ME) and Nanoemulsion(NE): These are clear, monophasic, optically active colloidal dispersion of oil, water and surface active agents with

particle size in nano-range[88, 89]. Both ME and NE have gained considerable interest in the management of skin diseases due to their high bioavailability and negligible skin irritancy[90, 91]. A range of plant derived bioactives have been incorporated in NE and ME for the management of psoriasis. Pleguezuelos-Villa M. *et al*[92] developed mangiferin nano emulsion by using hyaluronic acid to treat inflammatory diseases. On topical application of developed mangiferin on TPA-inflamed mice the skin gave a debilitation excellent anti-inflammatory effect. Kang C. *et al*[93] formulated salvianolic acid B microemulsion to improve the symptoms of dry skin and imiquimod induced psoriasis in mice model. The research concluded that salvianolic microemulsion has the capability to reduce the inflammatory symptoms and cytokine level. It also reduced desquamation and managed skin hydration.

Carbon dots: Carbon dots are well defined, carbon based nanosized particles, which is a latest innovation in the field of nanotechnology. They are extensively used in the field of biomedical and bioengineering[94, 95], due their high electron transferability, excellent aqueous solubility, stability, biocompatibility, insignificant toxicity and enormous surface area[96, 97]. Due to their complex structure, carbon dots have vast applications in the management of psoriasis and other skin related problems[98]. Zhang M. *et al*[99] formulated and evaluated the green *Phellodendri chinensis* cortex mediated carbon dots for the management of imiquimod induced psoriasis in animals. This study concluded that the formulated carbon dots could be an excellent alternative treatment to treat this horny disease. Zhang M. *et al*.[100] synthesized carbon dots using *Zingiberis rhizoma* extract (curcumin) by a green hydrothermal method. The research concluded that the carbon dot loaded with *Z. rhizoma* exhibits an excellent potential in pain related disorders like psoriasis.

CONCLUSION

Psoriasis is a hyper-proliferative autoimmune inflammatory skin disorder with no permanent cure and highly affects the patient's quality of life. In psoriasis, the *stratum corneum* is a major permeation barrier that arises in the topical delivery of medicament by conventional drug delivery systems due to the thickening of keratinocytes, which can be overcome by the implementation of nanotechnology.

Different classes of nano formulations were studied during the writing of this review paper and many of them are reported to be effective even when used without incorporation of active ingredient. As we all know, metals and some metalloids cause cell death via apoptosis and can control hyperproliferation of keratinocytes in psoriasis. Remarkably, metallic and ceramic nanoparticle can provide synergistic effect with active component to manage this hyperproliferative disorder. Vesicles like liposomes, niosomes etc, offered high structural flexibility, which overcome the penetration barrier in psoriasis. Along with the mentioned application of these nano formulations, they also offered the ease of application to affected area hence increases the patient compliance. So, by managing this disease with incorporation of best suitable active ingredient in nano formulations, the physiological and social burden of patients may be reduced.

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