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ANDROGRAPHOLIDE LOADED TOPICAL NANOCARRIERS FOR MANAGEMENT OF PSORIASIS : A SAFE AND EFFECTIVE APPROACH

Shammy Jindal^{1,2}, Rajendra Awasthi¹, Dhananjay Singare³ and Giriraj T. Kulkarni^{1*}

¹Amity Institute of Pharmacy, Amity University Uttar Pradesh, Sector-125, Noida 201303, India

²Laureate Institute of Pharmacy, Kathog, Jawalamukhi, Himachal Pradesh 176031, India

Email Id : shammyjindal@gmail.com

³Piramil Healthcare Ltd., Sarkhej - Gandhinagar Highway, Ahmedabad, Gujarat, India

Giriraj T. Kulkarni^{1*} (Corresponding Author) ⁽¹⁾

Professor and Head of Institute, Amity Institute of Pharmacy, Amity University Uttar Pradesh,
Sec 125, Noida, 201303, Uttar Pradesh, India

Email: gatkulkarni@gmail.com, gatkulkarni@amity.edu

ABSTRACT

Psoriasis is a chronic inflammatory and hyper proliferative dermatological condition. It has affected an estimate of more than 125 million people worldwide. Topical corticosteroids, topical steroids paring agent, phototherapy or biologics are the major treatment approaches for psoriasis. These therapeutics have several limitations to use in the treatment of psoriasis. Traditional system of medicine utilizes crude herbs for the treatment of chronic diseases which is reasonably safer than the synthetic drugs. Andrographolide is the major active constituent of *Andrographis paniculata* which is used to treat several diseases. However, Andrographolide delivered using conventional formulations limit its clinical outcomes. Oral bioavailability of andrographolide is poor due to its low aqueous solubility, high lipophilicity, rapid transformation and efflux by P-glycoprotein. Poor oral bioavailability of Andrographolide makes it difficult to synthesize as oral preparation. Liposomes are widely used topical drug delivery carriers to treat skin disorders. Design of andrographolide loaded nanocarrier gel for the management of psoriasis and to reduce the side effects associated with conventional therapies. This hypothesis aimed to incorporate Andrographolide isolated from *Andrographis paniculata* into a lipid based nanocarrier system. Further, the optimized liposomal formulation would be incorporated into topical gel using different polymers and will be characterized for various evaluation parameters. The synthesized formulation is expected to combine the benefit of small size and structural similarity of the lipid nanocarriers and skin to achieve effective targeting of the diseased skin for psoriasis management.

Keywords: Andrographolide, *Andrographis paniculata*, nanocarrier, psoriasis, liposome, topical delivery.

Introduction

Psoriasis is a noncontagious persistent dermatological condition affecting the quality of life in patients globally (Mehrmal *et al.*, 2017). The incidences of psoriasis vary depending on factors like age, ethnic differences and geographical regions (Parisi *et al.*, 2013). Psoriasis leads to the appearance of red and white scales on skin (Chuang *et al.*, 2018; Golińska *et al.*, 2019). Clinically five different types of psoriasis have been described, namely guttate, inverse, plaque, pustular, and erythrodermic. About 90% of total psoriatic cases are due to the plaque psoriasis (Scarpa *et al.*, 1989; Ayala *et al.*, 2007; Ritchlin *et al.*, 2017; Sobchak *et al.*, 2017; Coto-Segura *et al.*, 2013). Histologically, psoriasis can be diagnosed by the presence of epidermal hyperplasia known as acanthosis with elongated rete ridges, hypogranulosis (discrete epidermal granular layer), leukocyte infiltration and parakeratosis of epidermis and dermis layer (Krueger *et al.*, 2005; Lowes *et al.*, 2007; Nickoloff *et al.*, 2004). Psoriasis is associated with various disorders like psychological disorders, autoimmune diseases, endocrine

disorders, gastrointestinal and respiratory problems (Yen *et al.*, 2019; Yang *et al.*, 2015).

Currently available therapeutic options involve Allopathy, Ayurvedic, Naturopathy, Unani, Siddha and Chinese system of medicines (Saranya *et al.*, 2017; Meng *et al.*, 2018). Allopathic system of medicines includes both topical (emollients, moisturizers, tars, anthralins, topical corticosteroids, vitamin A analogues and vitamin D analogues) and systemic treatments (corticosteroids, methotrexate, ciclosporin, and etretinate. Affordability, availability and side effects of Allopathic therapies still remain a challenge and concern (Dhanabal *et al.*, 2012; Lebwohl *et al.*, 2001; Naldi *et al.*, 2010; Reddy *et al.*, 2007).

Traditional system of medicine utilizes crude herbs for the treatment of chronic diseases which is reasonably safer therapeutic approach with minimum or no side effects when compared with the synthetic drugs (Gisoni *et al.*, 2017; Deng *et al.*, 2013). The herbs and their formulations are used abundantly; however, still there is need of standardized and rational dosage form for the effective management of

disease. Efficacy of various crude drugs such as *Alpinia galanga*, *Curcuma longa* and *Annona squamosa* and their formulations has been tested and reported for the treatment of psoriasis (Arora *et al.*, 2003; Deng *et al.*, 2014; Pan *et al.*, 2013). Plant based bioactives have anti-proliferative and apoptotic properties for the treatment of psoriasis (Kabir *et al.*, 2014).

Andrographis paniculata (Burm. f.) Wall. ex Nees (*A. paniculata*) is an important herb belongs to the family Acanthaceae. Major active constituents of *A. paniculata* are andrographolide, diterpene glycosides, diterpenoids, lactones, and flavonoid glycosides. Traditionally, various plant parts are used to treat kidney malfunctioning, tuberculosis, cancer, inflammation *etc* (Yu *et al.*, 2008). *A. paniculata* possess a variety of therapeutic effects, including cardiovascular, cytotoxic, hepatoprotective, anticancer, antidiarrheal, anti-HIV, antihepatitis, antihyperglycemic, anti-inflammatory, antimicrobial, antimalarial, antioxidant, and immunostimulatory and antiproliferative (Subramanian *et al.*, 2008; Chiou *et al.*, 2000; Shen *et al.*, 2002). Since *A. paniculata* is used in the treatment of numerous diseases, still its benefits need to be evaluated for treatment of psoriasis as antiproliferative activity. Therefore, the present communication aimed to isolate and characterize andrographolide from *A. paniculata* and evaluate its anti-proliferative activity in the management of psoriasis via topical delivery of liposomes containing isolated andrographolide.

Liposomes are widely used topical drug delivery carriers to treat skin disorders. These are bilayer phospholipids molecules prepared using various fatty acids, cholesterol and various solvents in aqueous media. Topical liposomes improve drug transport across the skin. This additionally demonstrates that the liposomes can migrate into the stratumcorneum as intact vesicles (Dadwal *et al.*, 2018). Thus, liposome containing andrographolide will be developed for safe and effective management of psoriasis.

Hypothesis

This study hypothesizes the synthesis of liposomal gel containing andrographolide isolated from *A. paniculata* for the safe and effective treatment of psoriasis. This study hypothesizes the (1) characterization of the antipsoriatic potential of isolated andrographolide from *A. paniculata* (2) synthesis of liposomal carriers for safe and effective delivery of andrographolide via topical route (3) reduce side effects associated with synthetic drugs (4) overcome limitations associated with conventional systemic therapeutic approaches for the psoriasis (5) improved patient compliance using herbal medication.

Evaluation of hypothesis

Liposomal gel loaded with methotrexate and tretinoin effectively delivered the drug across the skin. The prepared liposomes were stable and delivered both the drugs at a predetermined rate which showed the effectiveness of the liposomal delivery system for the treatment of skin conditions (Kochar *et al.*, 2020). Various studies have reported effective skin permeability using liposomal nanocarriers (Fang *et al.*, 2011; Amer *et al.*, 2019; Vyas *et al.*, 2013). Formulation with higher lipid (Guggu lipid) concentration showed good drug retention after 24 h. The formulation was stable at higher temperature for longer

duration. Guggul lipid (a planar molecule might be stacked in the vesicle wall with cholesterol) showed the good retention properties and stability in the skin (Gaur *et al.*, 2014).

A. paniculata is used conventionally due to its anti-inflammation and anti-bacterial properties. Andrographolide is the major active component of this plant, which is used for various pharmacological activities like anti-inflammatory, anticancer, anti-obesity, anti-diabetes, and psoriasis (Dai *et al.*, 2019). The management of psoriasis, Andrographolide act by targeting the Toll Like Receptors (TLR) signaling pathways in imiquimod induced psoriatic animal models. The mechanism involves degradation of myeloid differentiation primary response 88 (MyD88), hence blocks the recruitment of tumor necrosis factor associated with factor 6 (TRAF6) to MyD88, and then inhibits mRNA expression of IL-23, IL-6, and IL-1 β in mice with microtubule-associated protein 1 light chain 3 β expression (Shao *et al.*, 2016).

Various side effects of synthetic drugs have been reported (Zeichner *et al.*, 2010; Horn *et al.*, 2010). Reports suggested that the use of herbal formulations reduces the side effects associates with synthetic medicines. Shraibomet *et al.*, reported potential of polyherbal formulation containing *Rheum palmatum* L, *Lonicera Japonica* and *Rehmannia glutinosa* Libosch as an antipsoriatic activity with reduced systemic and other side effects as compared to synthetic (Shraiborn *et al.*, 2017). Several topical herbal formulations are available in the market for the cure of psoriasis. These formulations offer less side-effect, low costs, easy availability, patient compliance and more than one mode of biochemical action (Singh *et al.*, 2014)

Experimental proof of hypothesis

To prove the hypothesis, extraction of andrographolide from *A. paniculata* would be done by soxlation technique (Chao *et al.*, 2010). The extracted andrographolide will be characterized using various analytical techniques. Antipsoriatic activity (Antiproliferative) would be performed using HaCaT cell line (contains human keratinocytes multiples at a higher than normal rate similar to psoriasis skin) along with their cytotoxicity studies (Deng *et al.*, 2014). Liposomes containing andrographolide would be developed by incorporating soy lecithin, cholesterol and surfactants using thin film hydration method followed by extrusion method (Zhang *et al.*, 2017).

The developed liposomes would be characterized and optimized based on their zeta potential, entrapment efficiency, polydispersibility index and skin retention studies. The optimized formulation would be incorporated into topical gel using different polymers along with permeation enhancer and will be characterized for various evaluation parameters (Dave *et al.*, 2017).

For the proof of the concept of hypotheses, *in vivo* permeation of the liposomal formulations would be done using skin samples under confocal laser microscopy. The anti-psoriatic activity of developed formulation would be determined using imiquimod induced BALB/c mice model. The efficacy of formulation will be compared with standard betamethasone and commercially available tacrolimus ointment using ELISA method; histopathological examination and PASI score (Doppalapudi *et al.*, 2017).

Conclusions

Presently, various choices are available like Allopathic system of medicine, Complementary and traditional systems of treatment such as Ayurveda, Siddha, Unani, and Yoga and naturopathy. Allopathic system of medicine has several side effects. Thus, there is a need to focus on alternative system of medicine which has a minimum or no side-effects and better patient compliance. A topical nanocarrier containing herbal isolated compounds would be a better and safer option for management of psoriasis. Thus, from this proposed hypothesis, we expect that herbal isolated andrographolide with the nano carrier approach would possess potential against the treatment of psoriasis.

Contributions

All authors should have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

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Conflict of interest statement

The authors declare no conflict of interest

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