Influence of phytochemicals in induced psoriasis (Review)

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Abstract. Cytokines involved in pathogenesis of psoriasis such as interleukins (IL-1β, IL-6, IL-17, IL-22, IL-23), interferon-α, tumor necrosis factor-α and interferon-γ can also become therapeutic targets. Research currently uses murine models of imiquimod-induced psoriatic-type dermatitis in order to analyze potentially helpful phytotherapeutics for psoriasis treatment: *Curcuma longa*, *Aloe vera*, *Nigella sativa*, *Rubia cordifolia*, *Smilax china*, *Thespesia populnea*, *Wrightia tinctoria*, *Scutellaria baicalensis*, *Cassia tora*, *Pongamia pinnata* and various Chinese herbal formulas. Psoriasis is a chronic inflammatory disease with complex pathogenic mechanisms that yield abnormal immune responses with clinical and morphological echoes (erythematous, scaly plaques with a histopathological basis made up of alterations i.e. keratinocyte aberrant proliferation, parakeratosis or chronic inflammation). The current therapeutic approach has only been able to manage the disease, without ensuring a certified treatment, thus giving rise to the need for better medications. This novel therapeutic approach has shown promising results in preclinical studies, giving hope for future phytochemical animal-based studies.

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Contents

1. Introduction

Cytokines that are involved in psoriasis and can represent therapy targets are Interleukins, IL-1β, IL-6, IL-17, IL-22 and IL-23 (these form an important and highly targeted inflammatory axis), interferon-α, tumor necrosis factor-α (TNF-α) and interferon-γ. With a global prevalence of 2-4%, psoriasis is one of the most frequent chronic inflammatory, stress-related diseases with recurrent evolution and consequences concerning the physical and mental well-being of patients. Being a non-infectious but stigmatizing skin disease, psoriasis benefits from the current conventional therapy, which unfortunately does not represent a cure, as it only manages signs and symptoms of the disease. From the 5 types of psoriasis (vulgaris, guttate, intertriginous, pustular and erythrodermic), psoriasis vulgaris is the most common clinical form, while the erythrodermic form is the most severe (1-6).

The pathogenic mechanisms underlying the disease are highly complex, combining several key role-players: Inflammatory cells, cytokines, growth factors and keratinocytes. Inflammatory cells which take part in the development of psoriatic-type dermatitis are $CD4^+$ and $CD8^+$ T cells, various types of dendritic cells, neutrophils, natural killer T cells and mast cells; keratinocytes participate in the inflammatory process through their surface cytokine receptors. Abnormal immune response triggers keratinocyte hyperproliferation translated clinically through irregular, erythematous, scaly plaques, characterized morphologically by parakeratosis, acanthosis, Munro's microabscesses, dermal inflammatory cells and congestive blood vessels.

The current therapeutic approach is only managing the disease, not curing it, psoriasis having a life-long recurrent

episodic evolution (7-14). Psoriasis patients, females in particular, are at risk of aggravating the disease or at risk for adverse reactions from substances used in cosmetic procedures such as dermal filler treatment with (reticulated) hyaluronic acid or hyperpigmentation treatment with trichloroacetic acid, which could aggravate the disease (15-19). Treating physicians have a relatively wide range of therapeutic approaches for psoriasis: From a large number of topicals, to nonbiologic and biologic systemic medications, to phototherapy. Each patient has a personalized treatment plan in concordance with the severity of the disease, the patient's comorbidities and least, but not last, its compliance. The exogenous type of therapies includes vitamin D derivatives, topical steroids, retinoids or UV therapy; systemic therapy encompasses anti-inflammatory drugs, methotrexate, cyclosporine, and biologics such as secukinumab, adalimumab or ustekinumab. The increase in efficacy and safety standards concerning the aforementioned therapies does not guarantee their success, affordability or patient compliance (20-25).

2. Literature data

Current research concerning psoriasis, selected from 2008 until 2019, has based itself on preclinical models of experimental mice by inducing psoriasis-type dermatitis to murine models (knockout mice, transgenic mice) with the help of imiquimod 5% used in the treatment of actinic keratosis or basal cell carcinoma. Imiquimod is an imidazoquinoline amine, a Toll-like receptor TLR7/TLR8 ligand and an agent with local immunomodulatory properties which by topical applications induces psoriatic-type dermatitis both clinically and morphologically. These applications also have a more general effect by elevating the levels of inflammatory cells and subsequently the level of cytokines that they produce; through these actions, murine models with imiquimod-induced psoriasis become ideal for studying the efficacy of herbal therapeutics on psoriasis (26,27).

Because it affects mainly the skin and due to the fact that it is a life-long disease, psoriasis generates high levels of distress and it has many associated psychiatric disorders, such as anxiety and depression. There is a clear necessity for therapies and medicines which offer relief for longer periods of time or which can effectively cure it. The acute requisite for innovative therapies stems also from the fact that the current ones have many side-effects including skin atrophy, sensitivity to solar light, skin irritations, high risk for infection, carcinogenesis, immune system suppression and organ toxicity (28-30). Patients could benefit from these phytotherapeutics through their low costs, low number of adverse effects and multiple biochemical activities, thus improving the overall patient compliance.

3. Results and Discussion

Western researchers have turned their focus to the east: in recent years there have been intense investigations made concerning Chinese medicine and other herbal remedies.

Curcuma longa. Turmeric/*Curcuma longa* is a non-toxic, perennial rhizomatous plant with many medicinal properties, including anti-inflammatory, anticarcinogenic, antioxidant, antimicrobial and wound-healing. This South-East Asian herb is part of the Zingiberaceae family (ginger family) and has been used in traditional Chinese medicine for centuries (for respiratory and cardiovascular diseases, liver or gastrointestinal ones or arthritis), having more than one hundred active components, of which turmeric being the most important one. The cellular background for the inhibition of inflammation and that of keratinocyte abnormal proliferation resides on nuclear factor-κB (NF-κB) suppression, TNF-α, IL-1β and IL-6 downregulation and inactivation of JNK, p38 MAPK and STAT-3 pathways. It modulates dendritic cells and also reduces the levels of IL-2 and interferon-γ (27,31).

Materials and methods used in the studies had common grounds: many used BALB/c mice, had several days of imiquimod 5% applied on the hairless back skin and ear followed by topical curcumin ointments or gel applications. The evolution and involution of psoriatic lesions were evaluated by the PASI Score, Psoriasis Area and Severity Index which follows the erythema, scales and thickness of the affected skin (26,31-34).

Curcumin is an important agent in the fight against psoriasis through dose-dependent inhibition of pathological changes in psoriasis-type dermatitis. Important attenuation of the intense dynamic processes of hyperkeratosis and acanthosis were observed microscopically, the PASI score showing a parallel clinical curve of the skin changes. By immunohistochemistry, the infiltrate of $CD8^+$ T cells were reduced in the group of experimental mice treated with *Curcuma longa* extract. Also, through Western blot and immunohistochemical methods the inflammatory signaling pathways, JNK, p38 MAPK and STAT-3 were suppressed by the herbal extract (27,31,35-38).

The same imiquimod-induced psoriasis murine model was used in another preclinical trial with the help of curcumin-loaded ethosomes (which enhance the local and transdermal delivery of the needed drug). It was demonstrated that *Curcuma longa* is a viable treatment for psoriasis through the inhibition of cytokines such as IL-17A, IL-17F and other inflammatory factors (TNF-α); this translated clinically as lower PASI scores (reflected by reduced skin erythema and desquamation) (32).

A study which involved a small number of Indian phytotherapeutics, one of which was curcumin, used the stem and from this an aqueous extract was made. The group treated with topical curcumin (combined with *Aloe vera* as local applications) showed an important reduction in skin thickness and inflammatory infiltrate by reducing the levels of TNF-α, IL-6 and IL-1β, decreasing neutrophil infiltration and by inhibiting the STAT-3 pathway, and therefore it is necessary for us to study the interference with skin microbioma in future studies (33,39-41).

Aloe vera. One of the most commonly used medicinal plants, *Aloe vera*, part of the Liliaceae family, is well known for its antiseptic, anti-inflammatory, wound-healing and antidiabetic properties, its immune system enhancing properties, and many others such as high density lipoprotein enhancer, antiallergenic bioproperties through its numerous bioactive components (>200). This compound has been widely used in clinical trials, with promising antipsoriatic effects. A preclinical study on a mouse tail model of psoriasis used an ethanolic extract of *Aloe vera* gel which had significant positive effects on psoriatic

skin (differentiation with orthokeratosis), comparable to those of tazarotene applications (42-44).

Other experimental formulas and phytotherapeutics

PSORI-CM01 and PSORI-CM02. PSORI-CM01 is the basis of the second formula and it has been proven through animal studies to have antipsoriatic properties by inducing autophagy and inhibiting the cytokines and chemokines involved in psoriasis (34,45).

PSORI-CM02 is a medicinal formula which encompasses five different plants that are frequently used in China: *Curcuma longa*, *Paeoniae* radix rubra, *Smilax glabra* and *Sarcandrae herba*. PSORI-CM02 had no side effects in a study on BALB/c mice and it improved murine body mass (an important indicator for overall health and for imiquimod induced inflammation). This formula has immunomodulatory properties by reducing the T cell infiltrate, lowering the levels of interferon-γ, IL-17A and increasing the levels of IL-4, an anti-inflammatory agent, GATA3 pathway is an important therapeutic target (34).

Other studies focused on extracts obtained from different herbs with pharmacological properties: *Nigella sativa*, *Rubia cordifolia*, *Smilax china*, *Thespesia populne*, *Wrightia tinctoria*, *Scutellaria baicalensis*, *Piperum nigrum*, *Kombоucha*, basil, propolis and other natural extracts used for complementary and alternative anti-psoriatic medicine products targeted against other skin disorders such as lichen planus, lichen sclerosus or other immune associated disorders are key factors in recent research studies (46-55). Mouse-tail experimental models were used and observations were made that all of these plants reduced epidermal acanthosis, they promoted normal epidermal differentiation with ortokeratin formation and they also had significant antipsoriatic properties, as compared with control groups. *Kigelia africana* used as a methanol extract-based ointment had increased orthokeratosis and reduced epidermal thickness dose-dependenty. *Cassia tora* and *Pongamia pinnata* extracts had significant effects by decreasing epidermal thickness and maintaining a normal stratum granulosum (56).

4. Conclusions

Herbal therapeutics are part of the novel approach to current medicinal therapy having established evidence by extensive research that supports their use through the many bioproperties that they possess. Although preclinical studies with murine models of induced psoriasis are highly necessary in identifying and selecting herbal therapeutics with anti-psoriatic properties, further clinical studies are imperative for them to be used globally by patients. The surge in phytotherapeutic research is a direct response to the need for better psoriasis treatments without adverse effects.

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Availability of data and materials

The information generated and analyzed during the current study is available from the corresponding author on reasonable request.

Authors' contributions

EN, LB, MM, MA and ALT were involved in the conception of the study and had major contribution in the writing and revising of the manuscript. DSR, FN and MD assisted in the acquisition, analysis and interpretation of the data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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