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Review Article

MANAGEMENT OF PSORIASIS: A FOCUS ON PHYTOCHEMICALS

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ABSTRACT

Psoriasis is a hyperproliferative, autoimmune skin disorder. There are several therapeutic agents used topically and systemically, but they have adverse effects. It has been reported that beta-blockers intensify psoriatic plaque and decrease the concentration of intracellular cyclic adenosine monophosphate (cAMP). In the psoriatic epidermis, the level of cAMP decreases. Caffeine is a methylxanthine that inhibits phosphodiesterase enzyme and results in a higher concentration of intracellular cAMP. Adding caffeine to topical skin treatments would be a simple way to reduce inflammation in patients with psoriasis. Furthermore, phenolic acids like chlorogenic acid (3-CQA) have recently gained substantial attention due to their various biological and pharmacological effects. Curcumin (dihydroferuloyl-methane) is a flavonoid that possesses anti-inflammatory, antitumor, and antioxidative properties. Cell proliferation arrest is caused by curcumin and apoptosis is induced in several types of human and animal cells. Imiquimod-induced murine psoriasis is most used animal models to study this disease, due to the usage of healthy mice. Xenotransplants of human psoriatic skin in immunodeficient mice were the first approach for the association of immunologic problems with the development of psoriasis and have been also useful for the evaluation of new therapeutic agents.

Keywords: Psoriasis, Curcumin, Caffeine, Chlorogenic acid, Animal models.

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INTRODUCTION

Psoriasis is a chronic autoimmune inflammatory disease which is characterized by epidermal hyperplasia and inappropriate immune activation that affects both skin and joints. Multiple erythematous scaly lesions are characteristic features in the skin where well-defined plaques arise mainly in the scalp, knees, elbows, lower back, and navel. It may also spread throughout the body in a systemic way as erythroderma [1-3]. In the joints, it attacks the insertions of tendons leading to pain and inflammation followed by a joint deformity, especially in small joints [2]. It can occur in both sexes and any age group, but psoriatic arthritis usually develops between the ages of 30 and 50 years [4]. It is an organ-specific autoimmune disease, i.e., a clinical syndrome caused by the activation of T cells and B cells, or both, in the absence of an ongoing infection or other distinct cause, that is triggered by an activated cellular immune system [5-10]. It is similar to other immune-mediated diseases such as rheumatoid arthritis, multiple sclerosis, Crohn's disease, and juvenile-onset diabetes. Since psoriasis occurs in an accessible organ, it has been possible to study its cellular and genomic features in tremendous detail compared with those of other human autoimmune diseases [11].

Clinical manifestations of psoriasis are different. Types of psoriasis include plaque, guttate, pustular, and erythrodermic. Any part of the skin may be affected; the most common sites are the scalp, elbows, knees, shins, umbilicus, sacrum, and genitalia. Plaques may range in various sizes. Guttate psoriasis is characterized by small scaly erythematous papules, usually occurring in adolescents or younger adults often after infectious conditions. Erythrodermic psoriasis affects more than 90% of body surface with scales and intense subacute or chronic erythema and deprived health. It may occur due to deterioration of psoriasis plaques or generalized pustular form and possibly as an early symptom of the disease. Pustular psoriasis can have a local or generalized presentation. Mostly, it occurs in patients with psoriasis plaque, after exposure with irritating factors, such as hypocalcemia, interruption of systemic corticosteroid therapy, untimely topical therapy, and infection [3,4,12].

IMMUNOPATHOGENESIS OF PSORIASIS

The immunopathogenesis of psoriasis involves changes in the innate (dendritic cells and keratinocytes) and acquired (T lymphocytes) immune system. Growth factors, chemokines, and cytokines are produced by cells of the innate immune system when activated. These act on cells of the acquired immune system and vice versa [13,14].

Usually, the skin regeneration takes around 28–30 days with the formation of fresh cells on its lower layer, while the old ones migrate to the top layer of skin falling in an unnoticed way. In psoriasis, the cell cycle changes at once and can be reduced to 4 days. These altered cells gather and form whitish plates with erythroderma originating typical lesions of the disease [15].

There is activation of the dendritic cells and keratinocytes. Several environmental factors such as mechanical trauma, infections, drugs, and emotional anxiety are considered trigger factors of the disease [1]. For example, the mechanical strain can activate keratinocytes in a similar manner as that of binding of infectious agents antigens to Toll-like receptors of dendritic cells and keratinocytes. This leads to their activation by producing several cytokines, chemokines, tumor necrosis factor (TNF)-α, growth factors, and interleukin 1 (IL-1) [14]. In addition, interaction of T cells with dendritic cells and macrophages forming new "immunological synapse" takes place in the dermis. This interaction leads to the assembly of several cytokines, which retain and intensify the inflammatory process [13]. IL-12 and IL-23 are produced by the dendritic cells and the activated macrophages. The proliferation of Th1 and Th17 is promoted by IL-12. Increase of Th1 and Th17 in psoriasis condition leads to the reduction in regulatory T cells [16]. The dendritic cells present in dermal layers function as antigen-presenting cell to T cells and inflammatory cells and work by producing IL-20, IL-23, and TNF-α. The proliferation of keratinocytes is stimulated by IL-20; proliferation of Th17 IL-17, TNF-α, IL-6, and IL-22 is promoted by IL-23. Keratinocytes act as pro-inflammatory cells and produce cytokines, such as TNF-α, IL-1, IL-6, and IL-8 [17].

GENETIC FACTORS

Scans of human genome explain almost nine various loci (PSORS1-9) which are susceptible to psoriasis. The main genetic factor of this disorder is PSORS-1, which consequences up to 50% of genetic sensitivity to psoriasis. Certain variations and changes lead to an increase in the risk of psoriasis, which is related to autoimmune diseases such as type 1 diabetes, celiac disease, Grave's disease, and rheumatoid arthritis. This shows that all the above disorders have identical genetic factors [18].

Diagnosis

Psoriasis is diagnosed based on medical studies such as skin rash, joint involvement, and alterations in nails. Uncommon skin sores may occur rarely in patients who have to be distinguished from other clinical manifestations such as mycosis fungicides; seborrheic dermatitis, tinea, discoid lupus, and genital lesions. Careful examination of the body areas must be done to identify unrecognized, clinically useful characteristics. In some cases, a skin biopsy may be necessary. Diagnosis of psoriasis is easy if silvery white scales, which are filled with dark pink or red lesions with prominent edges, are seen. Tiny blood droplets appear under the scales after removing the moist skin, which is seen under pinkish moist tender skin. To approve the diagnosis, blood analysis and skin biopsy may be essential sometimes [19].

Severity of disease[20]

Based on the percentage of skin impacted, physicians generally classify psoriasis as mild to severe, which helps in identifying the suitable treatment for a patient.

- Mild: Affected body area is <3%
- Moderate: 3–10% skin is influenced
- Severe: >10% of the body is impacted.

Treating severe psoriasis is harder. Although not categorized under severe psoriasis, few types of psoriasis are unaffected to treatment which include,

- Psoriasis that is seen in the fold of the skin (inverse)
- Psoriatic arthritis
- Hand and foot psoriasis (any psoriasis that occurs on palms and soles)
- Scalp psoriasis.

CAFFEINE AND PSORIASIS

Pharmacological action of caffeine

Caffeine (1,3,7-trimethylxanthine) is a purine alkaloid and is obtained from coffee tree (Coffea arabica), green tea (Camellia sinensis), Cola acuminata, cocoa, etc. It inhibits the adenosine suppressive activity by showing action as a nonselective A1 and A2 adenosine receptor antagonist. Accumulation of cyclic adenosinmonophosphate in the tissues is caused by phosphodiesterase (PDE) enzyme, and it is blocked by this alkaloid [21].

When an imbalance occurs between the overproduction of reactive oxygen species (ROSs) from exogenous or endogenous source and the decline in antioxidant defense mechanisms, it is known as oxidative stress. It is discussed in the pathogenesis of aging and different human diseases such as neurodegenerative diseases including Alzheimer, Parkinson, amyotrophic lateral sclerosis (Lou Gehrig's disease), Down's syndrome, atherosclerosis, vascular disease, cancer, diabetes mellitus type 1 and type 2, age-related macular degeneration, and psoriatic arthritis [23].

Body cells are protected from damage that results from certain chemical reactions involving oxidation by antioxidants [22].

Antioxidant role of caffeine is linked with scavenging the hydroxyl radical (OH.)[24]. 1-methylxanthine and methyluric acid are the major metabolites of caffeine and are highly useful antioxidants [25,26] (Fig. 1).

Psoriasis increases the use of β-adrenergic blocking agents [26,27]. Catecholamine effects such as mast cell degranulation and affect platelet function are blocked by them [26,28].

Caffeine is a methylxanthine and has the ability to inhibit the PDE enzyme that hydrolyzes cyclic nucleotides. This results in higher concentrations of intracellular cyclic adenosine monophosphate (cAMP). Another proposed mechanism is the inhibition of cell surface receptors for adenosine [29].

Adenylate cyclase (AC), a plasma membrane-bound enzyme is activated through G protein coupling. This catalyzes the conversion of ATP to cAMP. Once a ligand bind to a G protein-coupled receptor, activation of AC as the heterotrimeric G protein occurs and dissociates into separate alpha and beta/gamma subunits (Fig. 2). The activated form of AC then breaks ATP to cAMP. Intracellular cAMP levels can increase 5 times in seconds following AC activation. cAMP-dependent protein kinases (e.g., protein kinase A and PKA) can also be activated by cAMP by altering their enzymatic activity.

There are two important types of PKA, an intracellular form and a membrane-bound form. On activation, both of these forms can move to the nucleus to phosphorylate gene regulatory proteins (such as cAMP response element-binding protein), which influence DNA transcription [30] and eventually cellular behavior. These effects could explain the probable therapeutic effect of caffeine in psoriasis. Studies showed that application of 10% caffeine produced significantly greater improvement in Psoriatic Area and Severity Index scores than placebo. The only side effect of caffeine appeared to be mild itching [31].

From previous studies, it is also known that caffeine also has proapoptotic and anti-necrotic properties due to which swelling can be reduced by influencing cell death pathways. As an ATM (ATM-and Rad3-related) kinase inhibitor and ATR (ataxia-telangiectasia-mutated) kinase inhibitor, caffeine promotes on-time apoptosis (programmed cell death) of damaged cells. Caffeine also possesses anti-necrotic effects which prevent damage of cells due to oxidative stress from dying prematurely through necrosis (a process which can lead to further inflammation).

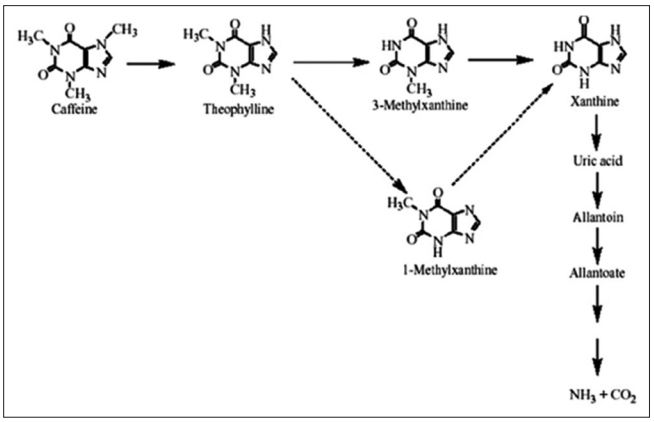

Fig. 1: Caffeine metabolism 65

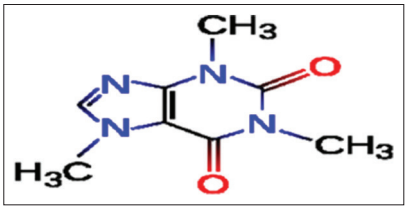

Fig. 2: Caffeine chemical structure

Primary treatments such as corticosteroids for atopic dermatitis and psoriasis are associated with side effects. As an alternate, caffeine, which is a cheaper, safer alternative that could harmonize the long-term therapy of atopic dermatitis and psoriasis patients, can be used. More research is needed to fully elucidate its potential [32,33].

The topical application of caffeine on plaque psoriasis was studied in a double-blinded placebo controlled study which demonstrated a significant improvement in psoriasis area and severity index in patients that used the topical formulation of caffeine [31].

There is an exclusive biological feature of psoriasis that leads to more complex interactions with caffeine, for example, with sarcomas and lymphoma, in which caffeine may augment the therapeutic effect of methotrexate [34-37]. In the case of psoriasis, alteration in the concentration ratio of cAMP to cyclic guanosine monophosphate in keratinocytes takes place [38]. This study led to numerous trials of PDE inhibitors, which showed improvement of symptoms in psoriasis patients [39,40]. Although succeeding trials have been not up to mark, PDE inhibitors are still being investigated for the treatment of psoriasis [41]. Any inhibitory effect of caffeine during methotrexate therapy is offset, in psoriasis patients, by direct effects of caffeine on keratinocyte cyclic nucleotides or by some other mechanism [39,42].

CHLOROGENIC ACID (CGA) AND PSORIASIS

Several polyphenols, especially chlorogenic acids (CGAs) (Fig. 3) that are well-known antioxidant agents, are isolated from coffee [40,43]. It is a group of secondary phenolic metabolites which are produced by certain plant species including tea, green roasted bean, coffee, berry fruits, cocoa, citrus fruits, apples, and pears [44,45]. CGA, a small molecular compound, is a biological response modifier focusing on the overall regulation and has a good effect on rebuilding the homeostasis of immune function. CGA is safe and efficient, with low recurrence rate. It has a noticeable effect on psoriasis, especially on plaque psoriasis and pustular psoriasis.

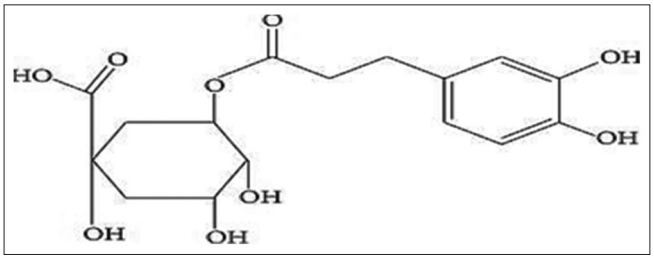

Fig. 3: The chemical structure of chlorogenic acid

PHARMACOKINETICS OF CHLOROGENIC ACID (CGA)

In a different experimental model of humans and animals, CGA and its metabolites were evident in blood circulation [46-48]. After regular consumption of CGA, coffee or green coffee extract, the major CGA metabolites seen in the systemic circulation were ferulic, isoferulic, and caffeic acid. One-third of ingested CGAs in beverages and foods are physiologically absorbed in the small intestine which can be measured by high-performance liquid chromatography in the forms of 5-CQA, 4-CQA, and 3-CQA in plasma [49,50]. The remaining two-thirds are passed into the large intestine where phenolic acid is further metabolized by gastrointestinal microflora and then absorbed [51]. The small intestine is the site where breakage of quinic acid from FQA (feruloylquinic acid) and CQA and then the release of ferulic acid and CA take place biochemically, whereas the colon plays a significant role in the conversion of both caffeic and ferulic acid to dihydroferulic acid and a major role in its absorption (Fig. 4).

MECHANISMS OF ACTION (MOA) OF CHLOROGENIC ACID (CGA)

During metabolic syndrome, CGAs exert their effective activities, and it is interpreted by different modes of actions. A few of these mechanisms are connected with CGA's anti-inflammatory and antioxidant features. Oxidative stress, which is accumulated in fat, has also been proposed as an early initiator of the obesity-associated metabolic syndrome [53,54]. Chronic inflammation has been also associated with metabolic syndrome [48]. Another study reported that CGA treatment in mice fed a high-fat diet and obese mice highly decreased the expression of macrophage marker genes in adipose tissue such as Cd11c, Cd11b, Cd68, and F4/80 and pro-inflammatory mediator genes such as MCP-1 and TNF-α in macrophages [55].

CURCUMIN AND PSORIASIS

The main ingredient and active component of turmeric are curcumin (dihydroferuloyl-methane), which contains two phenolic rings (a common structure of many flavonoids), that imparts potent antioxidant activities. Anti-inflammatory, antitumor, and antioxidative properties are exhibited by curcumin [56-59]. However, the mechanisms underlying these diverse effects are not yet fully understood. Cell proliferation arrest is caused by curcumin and apoptosis is induced in several types of human and animal cells. The initiated cell death pathway seems to depend strongly on the cell type used. TNF-α induces some pro-inflammatory cytokines including IL-1ß, IL-6, IL-8,

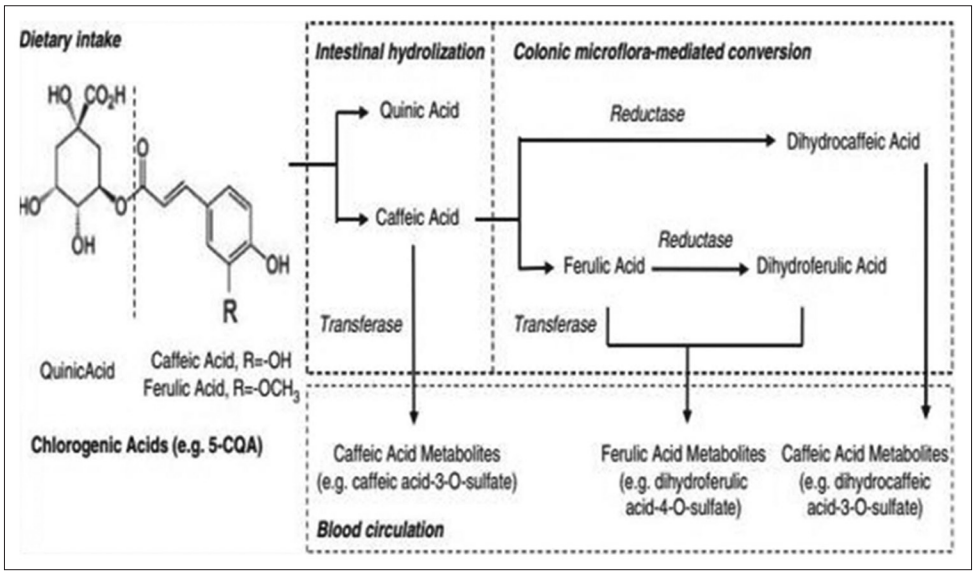

Fig. 4: The major metabolic pathway of chlorogenic acids[52]

and itself by activation of NF-κB or MAPKs (p38, JNK, and ERK). These cytokines play important roles in various inflammatory skin diseases, such as psoriasis [60]. Use of curcumin in the treatment of psoriasis is effectively based on subjective reports; however, few previous studies investigated its efficacy in psoriasis patients [61].

Curcumin was found to be a very potent antioxidant [62-68]. It generates hydroxyl radicals through the Fenton reaction by reducing Fe3+ to Fe2+ [66]. Effect of curcumin as superoxide scavenger was studied, and curcumin was found to be a potent scavenger of superoxide [67]. They also reported a better correlation between anti-inflammatory activity and superoxide scavenging property. Curcumin has the ability to be developed as an antipsoriatic drug due to its ability to curtail keratinocyte proliferation [67] and has found to be effective in the mouse tail animal model of psoriasis [69]. Curcumin decreases the expression of proinflammatory cytokines such as IL-6 and IL-8 in human keratinocytes [70]. These cytokines are both proinflammatory and are growth factors for keratinocytes. Hence, their inhibition by curcumin might reduce psoriasis-linked inflammation as well as psoriasis-related keratinocyte hyperproliferation. Moreover, HO-1 is being produced at higher levels in the skin of psoriatic patients and might be involved in heme degradation and the protection of cells from the toxic effects of ROSs [71]. Curcumin regulation of HO-1 and counteracting oxidative stress was a major highlight in its protection against scleroderma as well.

As previously reported, curcumin can be effective in treating psoriasis by affecting several pathogenetic pathways. Moreover, recent studies performed in autoimmune models suggest that curcumin can modulate T helper immune responses, downregulating the Th1 and Th17 cell pathways [66,72]. Accordingly, such activities might operate even in psoriasis. In fact, in a mouse model of imiquimod (IMQ)-induced psoriasis-like inflammation, topical curcumin was demonstrated to improve the skin lesions with an effect comparable to that of clobetasol and to significantly decrease the cutaneous levels of IL-17A, IL-17F, IL-22, IL-1 β, IL-6, and TNF-α mRNA [65].

There are several reasons to believe that curcumin may have potential for treating psoriasis. First, on irradiation with visible light, curcumin has been proven to be phototoxic for Salmonella typhimurium and *Escherichia coli*, even at very low concentrations [73]. This observed phototoxicity makes curcumin a potential photosensitizing drug, which could be used in phototherapy of psoriasis. Second, when curcumin was tested as an antipsoriatic drug in the modified mouse tail test, an animal model of psoriasis, it exhibited some activity [74,79]. Third, curcumin has been shown to inhibit the proliferation of human keratinocytes through suppression of pro-inflammatory pathways [58,75]. Curcumin inhibited the expression of TNF-α-induced IL-1 β, IL-6, TNF-α, cyclin E, MAPKs (JNK, p38 MAPK, and ERK), and NF-κB in HaCaT cells. Since curcumin can reverse the anti-apoptotic function of TNF-α in skin cells, it may have the potential for the treatment of psoriasis [76]. Fourth, as TNF blockers have been successfully used to treat psoriasis and since curcumin can block both the production and the action of TNF, curcumin may have potential as a treatment of psoriasis. Fifth, our laboratory has shown that curcumin is a potent inhibitor of phosphorylase kinase activity [77] the elevation in which has been correlated with psoriatic activity [78,79].

ANIMAL MODELS

Mouse tail test

Topical treatment of the mouse tail with antipsoriatic drugs enhances orthokeratotic cell differentiation in the epidermal scales. This test is useful for studying dermatological therapeutics that influences epidermal differentiation. In general, antipsoriatics such as retinoic acid and dithranol are induced, which produces a granular layer in the mouse tail epidermis (Orthokeratosis) which is a relevant parameter for antipsoriatic activity measurement [80].

However, the main drawback of this method is this test in its qualitative form is not very appropriate for screening drugs because dose-response curves and comparisons between drugs are not possible in this form. Due to the lack of quantification, this model was hardly used for pharmacological screening in the past. At present, this problem is being overcome by measuring the microscopical length of the granular layer in a scale (Orthokeratotic differentiation) and relating it to the total scale length. This allows a quantitative comparison of various antipsoriatic drugs and can be used to construct dose-response curves for the individual compounds [81].

Imiquimod (IMQ)-induced murine psoriasis

In this model, psoriasis-like disease was induced to nongenetically modified healthy mice. They were treated daily with topical IMQ for 6 days. This simple model shows wide characteristics described in the human psoriatic skin lesions. IMQ-Mu-Pso model is generated due to acute inflammation in the epidermis induced by IMQ, hyperactivating the innate immunity and leading the adaptive immunity to produce great amounts of IL-17. IL-17, in turn, induces angiogenesis and proliferation of keratinocytes, as biological characteristics of psoriatic lesions. IMQ-Mu-Pso also demonstrated that undisrupted molecular and cellular mechanisms are able to break inflammation, as mice used for this model are healthy mice that show the highest production of inflammatory cytokines on the 3rd day of treatment and show the highest development of psoriatic skin on the 6th day, but after this time, the mice are able to revert the inflammatory process as they are not genetically compromised. The short-lasting presence of psoriatic lesions is an inconvenience of this model, although it has been widely used to elucidate the pathogenesis of psoriasis, and very interesting data have been published [82].

Xenotransplantation of human skin

In xenotransplantation models, human psoriatic skin is grafted on the nude mice. Using T cell-deficient nude mice as recipients, the persistence of the psoriatic phenotype for more than 2 months after transplantation of lesional psoriatic skin was observed. It was suggested that the remaining B cells and/or murine inflammatory cytokines may trigger these nonspecific alterations. Depending on the purpose of the study, either full-thickness or split skin can be grafted from the clinically affected or unaffected sites of a patient, or many relevant components of the human skin are retained at least for several months. Dermis taken from clinically affected sites is overgrown by murine keratinocytes that subsequently form a multilayer psoriasis-like epidermis that is usually not seen in murine skin. The dermal compartment can thus drive proliferation and differentiation of the epidermis. Clinically unaffected skin from patients with psoriasis was grafted onto SCID mice, which subsequently received activated leukocytes from the same individual, to directly study the importance of the adaptive immune system. This protocol triggered the development of psoriasis in the formerly unaffected skin. In contrast, grafts from nonpsoriatic donors retained their normal phenotype even after injecting the recipient mice with activated leukocytes. In these experiments, grafts were derived from the clinically unaffected skin of either patient with psoriasis or healthy donors [83-87].

In vitro models for the study of psoriasis

Animal models have been very useful to dissect the molecular and cellular mechanisms for psoriasis development. These models have been also advantageous to evaluate new pharmaceuticals. Although humanized models have also been developed, immunodeficient animals are frequently used. Alternative methods such as 2D, 2D+ membrane, and 3D cell cultures have been developed to analyze the effect of new anti-psoriatic drugs [88]. 2D model consists of primary explants of keratinocytes or fibroblasts from psoriatic patients cultured over extracellular matrix proteins to evaluate cellular proliferation, cellular differentiation, and cytokines production [89]. In the 2D+membrane model, two cell types are cocultured separated by a synthetic membrane to evaluate the interconnection between two cell types in the pathology [90]. 3D cultures, also known as organotypic culture system (OCS), allow the growth of complex biological systems *in vitro* in a way that resembles part of their normal physiology and function. OCSs are powerful as experimental platforms in preclinical

dermatological research, helping to validate mechanisms of diseases and to test the therapeutic potential of candidate drugs [91]. The new generation of 3D cultures connected to biosensors or chips allows real-time monitoring of biological parameters such as loss of water and electrophysiologic parameters [92].

HERBAL CONSTITUENTS

Constituents that possess antipsoriatic activity are isolated from many herbal plants and used in the treatment of psoriasis.

- Capsaicin is derived from Capsicum annuum of family Solanaceae [93]
- Colchicine, an active constituent Colchicum autumnale of family Colchicaceae [94]
- Psoralen is derived from *Psoralea corylifolia* of family Fabaceae. It inhibits cell division by stopping epidermal DNA synthesis [87]
- Artesunate is an active constituent which is a derivative of Artemisinin that is processed from plant Artemisia annua L. of family Asteraceae. It acts by controlling the expression of CXCR2 and increases the secretion of TGFβ, *in vitro* [88]
- Koumine is derived from plant *Gelsemium elegans* belonging to the family Loganiaceae. It acts by inhibiting epidermal cell proliferation, promoting formation of granular cells, decreasing serum IL-2 levels [89].

FUTURE SCOPE

There has been extensive interest in understanding and studying the bioactivity of caffeine and CGA associated with anti-mutagenic and antioxidant activities related to oxidative stress. Use of caffeine ad CGA in the treatment of psoriasis need to be focused more as a lot of research work is not available. Researchers and scientists are currently working to develop drug delivery systems of these constituents that can treat psoriasis with minimal side effects.

AUTHORS' CONTRIBUTIONS

All the authors of this manuscript have contributed equally in its preparation.

COMPETING INTEREST

The author(s) confirms that this article content has no conflicts of interest.

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