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ANTIPSORIATIC ACTIVITY OF GENISTEIN: A REVIEW

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ABSTRACT: Psoriasis is a chronic inflammatory skin disease characterized by red, scaly and raised patches, and it has affected nearly 2-3% of the population worldwide. This skin disorder occurs when the immune system sends faulty signals that result in the speeding up of the skin cell cycle. Psoriasis is histologically characterized by marked hyperproliferation of keratinocytes, neutrophils, and a dense inflammatory infiltrate of T cells. Vascular dilation and proliferation are also observed. The primary defect in psoriasis patients was believed to be an abnormal epidermal cell proliferation. Psoriatic skin exhibits an advanced state of lipid peroxidation. It has been suggested that antioxidant treatment can help in the management of the disorder. Literature indicates that polyphenolic compounds found in plants have a positive effect on many chronic diseases. Natural polyphenols, recognized as potent antioxidants, are multi-functional molecules that can act as anti-inflammatory and antiproliferative agents through the modulation of multiple signalling pathways. This characteristic could be advantageous for the treatment of multi-causal diseases, such as psoriasis. Genistein is one of such polyphenolic compounds that can be used for the treatment of psoriasis. Genistein prevents cytokines & TNF-α-induced NF-κB nuclear translocation, with no effect on the PI3K signalling cascade. It leads to attenuation of TNF-α and LPS-induced inflammatory responses by suppressing ROS activation.

INTRODUCTION: Psoriasis is a chronic inflammatory dermatosis that is non-communicable in nature. It has been found to affect 2% of the world population. It is derived from Greek words wherein psoriasis means "itchy condition" [1]. It is characterized by red and scaly skin plaques that are sharply demarcated from adjacent normal skin and exhibit recurrence; coin-sized lesions are observed on elbows, knees, scalp, feet, *etc.* [2]. This disease may occur due to a genetic predisposition or other environmental factors [3].

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This serious skin disorder has a major impact on the daily life of the patient. The patient may feel stinging & itchy sensations that may induce pain. Psoriasis may have psychological & physical impact comparable to heart disease, cancer, or depression [4]. Mild (<2%), moderate (2–10%), and severe (>10%) psoriasis may be observed in different people [5].

Chronic plaque psoriasis or psoriasis vulgaris is the most common type of psoriasis [6]. The thickened epidermis, epidermal hyperplasia, and reduced or absent granular layer are the histological characteristics of a typical psoriatic lesion. This is because of hyperproliferation and differentiation of epidermal keratinocytes, which occurs in 7 to 10 days. For healthy skin the proliferation & differentiation takes around 28–50 days.

The epidermis exhibits infiltration of immune cells (T cells) 7 and the dermis shows infiltration of CD11c+ dendritic cells. Neutrophils & CD8+ cells are also found in the epidermis [8]. Angiogenesis *i.e.* the process of formation of new blood vessels and inflammation of the skin [9] can also be observed.

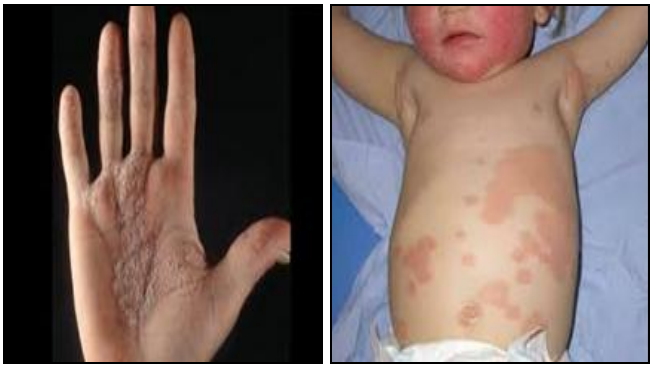

FIG. 1: PSORIATIC LESIONS

The immunohistochemical, genetic and pharmaco-logic investigations have led to an observation that there is an important role for the nuclear factor kappa B (NFκB) pathway in pathophysiology of psoriasis [10]. A number of dermatological evidences support the fact that tumor necrosis factor (TNF)-α is a significant immune mediator involved in pathogenesis of psoriasis. The antiapoptotic proteins are induced by this inflammatory cytokine in psoriatic skin [11, 12]. Interleukin (IL)-1β and IL-6 are also believed to be of significance in psoriasis.

Genetic polymorphisms related to IL-6 genes are associated with psoriasis and could have a an effect on counselling and management of the disorder [13]. Recently, elevated production of IL-8 and/or their receptor in patients with psoriasis has been demonstrated [14]. It has also been suggested that tissue angiotensin-converting enzyme (ACE) activity in the skin is significantly increased in patients with psoriasis. The determination of tissue ACE activity as a good nonspecific parameter has been used for the assessment of therapeutic efficacy in psoriasis [15]. It has been found that soybean contains isoflavones structurally similar to 17-beta-estradiol, as the most abundant phytoestrogens [16].

Pathophysiology of Psoriasis: It was believed that psoriasis is caused due to hyperproliferation of keratinocytes. The immune system was also found to be an important factor in the development of psoriasis. It is a chronic inflammatory disorder in which T lymphocytes, dendritic cells, neutrophils, macrophages, and keratinocytes are responsible for initiating lesions on the skin. Antigen presentation and immunological synapse formation will cause the secretion of various cytokines and allow T cell differentiation into effector cells such as Th1, Th2, and Th17. Each effector cell secretes specific cytokines [17]. IFN-α, TNF-α and IL-2 increase the proliferation of keratinocytes. TNF-α brings about acceleration in the development of lesions by leading to a marked increase in the number of molecules involved in the inflammatory response. IL-2 stimulates the T cells, but it does not lead to alteration in the production of cytokines from psoriatic or healthy keratinocytes [18]. Activation of keratinocytes triggers the production of cytokines and chemokines that direct the lymphocytes towards the site of inflammation, and this deregulates their proliferation. The subpopulations of Th1 and Th17 are generally found in psoriatic skin lesions [19].

Recent data suggest that IL-23 and Th17 T cells could be regarded as significant inducers of epidermal hyperplasia and have the ability to modify epidermal differentiation in psoriasis [20]. The excessive production of vascular endothelial growth factors in psoriatic keratinocytes is responsible for the angiogenesis. This leads to increased vascularization and inflammation. Neutrophils are found in significant amounts in psoriatic lesions. It has been observed that some cytokines such as IL-8 cause the accumulation of neutrophils in the skin [21]. Although a number of studies have been conducted to investigate the possible factors causing psoriasis, the origin of the disease still remains a question.

Several treatments are available to manage psoriasis; however, the available treatments seem to only relieve the symptoms of the disease. The choice of appropriate treatment depends on factors like, age, the general health of the patient, comorbidities, severity of the pathology, form and, the body parts affected by the disorder [22]. New lines of treatments for psoriasis are derived from biotechnology and are termed as biological drugs. This new class of treatments consists of protein and monoclonal antibody fusion that specifically targets the activity of T cells or inflammatory cytokines by inhibition or modulation of specific immune system

effectors. Biological drugs minimize the side effects of psoriasis therapy & save other body parts from getting affected. These treatments have a high cost and considerable side effects; therefore, they are used in severe cases only. Phototherapy and systemic medication that is generally used for the treatment of the disease have been associated with patient frustration; thereby, use of biological therapy has become important [23]. Though biologics are more expensive than other treatment modules in psoriasis, they may prove to be cost-effective for some patients by decreasing the length & need of hospitalization [24]. Patients on biologics have exhibited greater improvement than patients on phototherapy, conventional systemic agents, or topical therapy. Patients, as well as their dermatologists, express greater satisfaction with biological therapy [25]. Research still continues to demonstrate new pathological mechanisms in psoriasis.

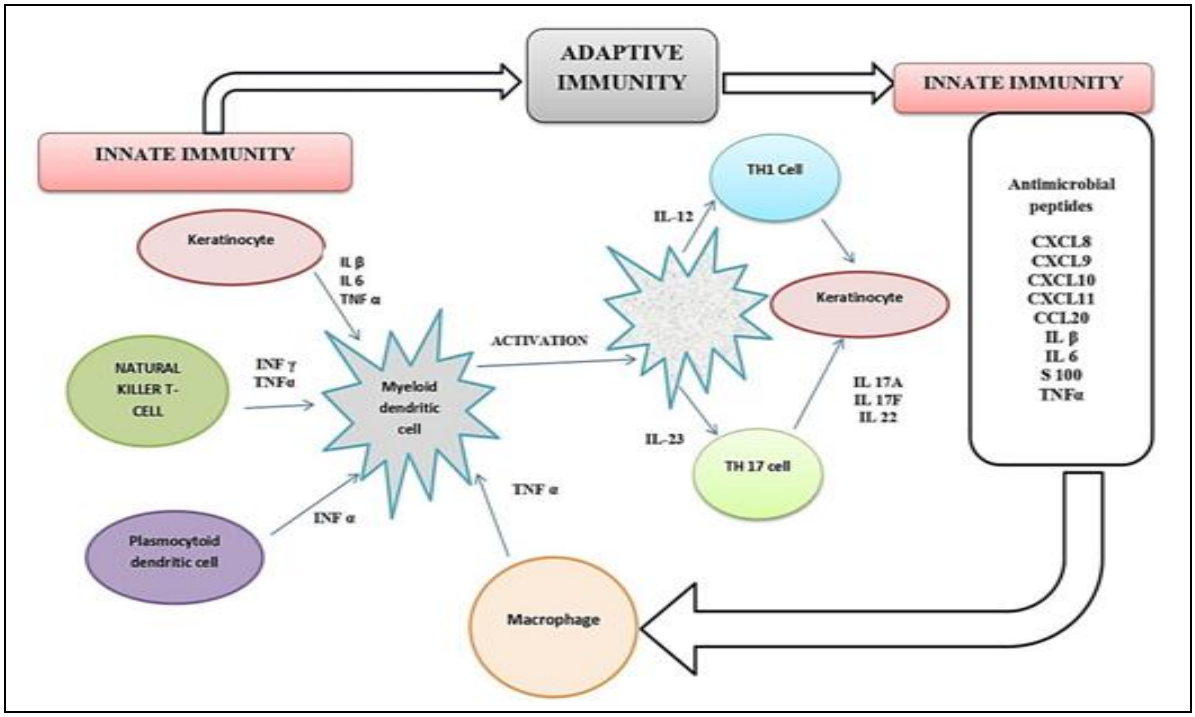

FIG. 2: PATHOPHYSIOLOGY OF PSORIASIS

Current Therapies Available for Psoriasis:

Corticosteroids: Mild to moderate psoriasis is treated with formulations containing cortico-steroids. They reduce inflammation and itching by immunosuppression. Sensitive areas such as skin folds or face as well as widespread patches of skin damaged by psoriasis are treated using low potency corticosteroid ointments. However, telangiectasia, thinning of the skin may be observed as adverse effects of corticosteroid usage. Systemic side effects such as diabetes & hypertension may also be observed [26].

Vitamin D Analogues: Vitamin D analogues bind to cytoplasmic Vitamin D Receptor then translocate into the nucleus. In the nucleus, they bind to nuclear receptors and lead to the transcription of vitamin D responsive genes. The transcription proteins regulate cell differentiation and reduce the cell proliferation and inflammatory processes associated with this condition.

Vitamin D analogues, however, cause irritation and erythema. In some cases, increased serum and urine calcium levels are observed. Therefore, the total concentration of Vitamin D analogues per week should not exceed 100 gm [27]. Clinical trials have often indicated that combination treatment of vitamin D and corticosteroid is usually more effective than monotherapy [28].

Dithranol: Dithranol induces reactive oxygen species release. This effect inhibits hyper proliferation of keratinocytes and the trans-formation of leucocytes. It is generally used in increasing concentrations for application on the scalp. Discolorations of the hair and skin irritation are the side effects observed due to dithranol usage [29].

Methotrexate: Methotrexate is an immune-suppressant that is one of the most effective low-cost therapies to treat psoriasis. It is dihydrofolate reductase inhibitor. Folic acid is supplemented to decrease the toxicity of this drug. It is administered as a single oral dose per week. Myelosuppression, hepatotoxicity, pulmonary toxicity, nephrotoxicity, neurotoxicity, nausea, oligospermia, gastro-intestinal upset etc. are the side effects of methotrexate usage [30, 31].

Cyclosporine: It is used as an oral treatment option to treat moderate to severe psoriasis. It inhibits calcineurin, binds to cyclophilin, and induces immunosuppression by preventing T-cell activation. It inhibits the activation of the Nuclear factor of activated T-cells (NFAT) as well further inhibits the gene transcription of Interleukin 2 by T cells [32]. Hypertension, nephrotoxicity, hepato-toxicity, diabetes mellitus, neurotoxicity, hirsutism, increased risk of infection are the adverse effects observed due to cyclosporine therapy [33].

Phototherapy: Patients not responding to topical therapies or patients with psoriatic plaques covering 20% or more portion of the body surface are treated with phototherapy. The exact mechanism is not clear. It is believed that photo-therapy induces apoptosis along with enhancement in transcription and expression of Interleukin 10 in keratinocytes.

The success rate of phototherapy is reported to be more than 80% of the patients [34]. Coal tar (Goeckerman therapy) or anthralin (Ingram regimen) in combination with ultraviolet B (UVB) radiation has been observed to be effective in patients with moderate-to-severe psoriasis. Psoralen combined with Ultraviolet A radiation (UVA) (PUVA therapy) is highly effective in clearing skin lesions. Both these therapies the risk of skin cancer; hence they require maintenance treatment [35]. Novel therapies for the treatment of psoriasis aim at providing more selective, immunological effects that are specific. Target-based therapies, new drug development are based on the following strategies [36].

1. Initial cytokine release and APC migration blockade
2. Targeting of activated T cells, prevention of further T-cell activation subsequent immunological cascade

3. Inhibition of differentiation of the activated T cells

4. Cytokine Inhibition:
Biologics: These agents act on different steps involved in the pathogenesis of psoriasis. These molecules are developed for target-based therapy. They have precise action and comparatively lesser side than the broad traditional therapies.

Anti Tnf-α Agents: These molecules block the TNF-a receptors or act on the tumor necrosis factor. Psoriatic plaques contain a proinflammatory cytokine TNF- α, which is one of the important inflammatory mediators involved in psoriasis. TNF- α stimulates the production of other inflammatory mediators, activates other immune cells, and induces the adhesion of molecules by keratinocytes, thus increasing the recruitment of immune cells [36].

Anti TNF- α agents, binds to TNF- α, neutralizes them or blocks the TNF- α receptor on the keratinocytes stops the immunological cascade.

Janus Kinase (JAK) Inhibitor: Tofacitinib is a Janus kinase inhibitor that selectively inhibits signaling by blocking JAK3 and JAK1 [37]. This results in a decrease in signalling by additional proinflammatory cytokines, such as IL-6. Additionally, it also inhibits IL-23 signalling by suppression of IL-23 receptor expression, resulting in inhibition of immune cells like T cell differentiation [38, 39].

Phosphodiesterase-4 Inhibitor: Phospho-diesterase 4 (PDE4) enzyme hydrolyses cyclic adenosine monophosphate (cAMP), an intra-cellular second messenger which is responsible for controlling a group of pro-inflammatory and anti-inflammatory mediators. Adverse effects like upper respiratory infections, diarrhoea, nausea, headache, and weight loss are observed [40].

Anti CD-6 Monoclonal Antibodies: Pre-clinical studies have also shown that anti-CD-6 monoclonal antibodies inhibit the mitogen-activated protein kinase (MAPK) and (STAT-3). These are involved in intracellular signalling pathways which triggered

by CD6 [41, 42, 43]. STAT-3 is responsible for the production of Th17 as well as downregulation of gene transcription of cell adhesion molecules and pro-inflammatory cytokines. This leads to a reduction in the immune T-cell infiltration at the inflamed sites and thus controls psoriatic plaque formation. Adverse effects include lymphopenia, infusion reaction, and urinary tract infection (UTI).

Use of Isoflavones in Treatment of Psoriasis: As per recent studies, isoflavone extract was found to attenuate skin inflammation and hyperplasia in a murine IMQ–induced model. When IMQ was repetitively applied onto mouse skin, it induced psoriasis-like inflammation with considerable thickening, scaling, and redness caused on account of hyperproliferation of keratinocytes and leukocyte infiltration into the skin. Upon histological analysis, the lesion showed a reduction of inflammatory cell infiltrate in mice pre-treated with isoflavone extract when compared with IMQ-treated mice when the biopsies using H&E staining were carried out. Besides, it was also found that isoflavone extract treatment had the potential to prevent epidermal hyperplasia characteristically induced by IMQ. Pre-treatment of skin with isoflavone extract prior to IMQ application was found to ameliorate lesion formation in a dose-dependent fashion, and the development of erythema at the site of application was significantly reduced. It was concluded that isoflavone extract inhibits TNF-α-, IL-17A-, and IL-22-induced MAPK pathway phosphorylation in NHEKs [44, 45, 46].

Genistein in Psoriasis Treatment: Genistein is the main isoflavone in soybean and is found to possess potent anti-inflammatory [47] and anti-oxidant properties [48, 49]. The topical use of genistein may be recommended as adjuvant along with corticosteroids in psoriasis management due to its safety [50] specifically during treatment of patients resistant to the treatment. It has been noted that genistein exerts antiproliferative activity by inhibiting NFκB signaling [51]. A considerable amount of immunological evidence shows that by reducing the production and expression of pro-inflammatory biomarkers such as TNF-α and interleukins, genistein modulates inflammatory responses [52, 53, 54]. Genistein is also found to suppress ACE and has an inhibitory effect on elastase release. It could therefore be proposed that topical application of genistein can be a possible therapeutic strategy against psoriasis. (Glyteer or soyabean tar) GL a topical dosage form was found to inhibit edema in mice. The inhibitory action of GL on edema was found to be comparable to that of betamethasone 17-valerate, cyclosporine & indomethacin [55]. The researchers suggested that soybean may have a significant therapeutic effect on psoriatic lesions. Topical genistein was found to appreciably decrease the (PUVA)-induced skin thickening as well as cutaneous ulceration & erythema dose-dependently [56]. In patients with psoriasis, a combination of genistein with PUVA therapy may potentiate the therapeutic response of PUVA and protect against further arising complications.

Chemistry of Genistein:

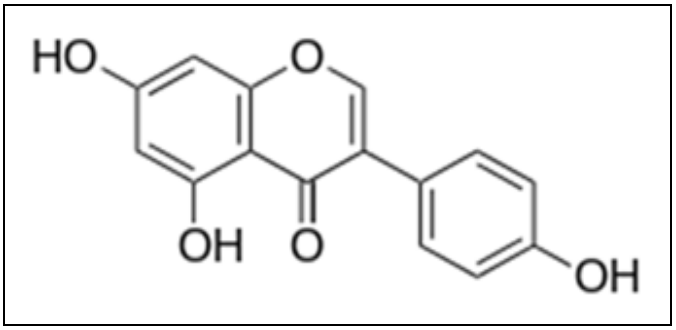

FIG. 3: CHEMICAL STRUCTURE OF GENISTEIN

Genistein is an isoflavone obtained from soy products, such as soybeans. It is a secondary metabolite obtained from plants that has a 3-phenylchromen-4-one nucleus containing two aromatic rings (A and B). These rings are linked to another carbon pyran ring (C) **Fig. 1**. Other functional groups present in its basic carbon skeleton include an oxo group at the C4 position of ring C & C2–C3 double bond. There are three hydroxyl groups present at C5, C7, and C4′ positions of ring A and ring B, respectively. In 1899 genistein was first isolated from a species of the plant Genistatinctoria (Dyer's broom) belonging to family Fabaceae (Perkin and Newbury, 1899). Later, was found to be present in many plants, like kudzu, lupin, fava beans, soybeans, etc. It was successfully synthesized for the first time in the year 1928 (Baker and Robinson, 1928). As of now, many alternative methods for genistein synthesis have been devised.

Mechanism of Action of Genistein: One study also suggests that when the skin was treated with genistein (5 µM, 60 minutes prior to UV exposure), skin roughness and wrinkling and epidermal hyperproliferation was reduced. This effect was observed in hairless mice that received daily doses of chronic & acute UVB irradiation. The photo-protective effects of genistein are proposed to result from its impact on the DNA damage induced by UV as topical genistein was found to decrease CPD formation besides restoration of proliferating cell nuclear antigen (PCNA, a marker of proliferation and DNA repair) expression was also observed [57]. The researchers also performed a small study on six men so that they could extend their observations to human beings. In this study, topical genistein (5 $\mu M/cm^2$) was applied 30 min before exposure to UVB (1X MED). When evaluated photographically after 24 h of treatment, it was observed that erythema formation was blocked [57]. Pre-treatment with topical genistein was also found to reduce CPD formation dose-dependently. Increased PCNA expression was also found in samples of human reconstituted skin [58, 59].

The current hypothesis suggests that psoriasis is an innate and adaptive immune-mediated disorder. In this disorder, the T cells become active & migrate to the dermis. The T cells then trigger the release of cytokines which leads to inflammation and the rapid production of skin cells. The translocation of the NF-κB p65 subunit into the nucleus is a significant event for its transcription, which is mediated by PI3K signaling. It has been reported that PI3K pathway as an important regulator of growth and inflammation. This pathway is mostly involved in inflammation-mediated diseases such as psoriasis. Genistein prevents "cytokine mix" as well as TNF-αinduced NF-κB translocation [60, 61].

Genistein, being of natural origin, has lesser side effects and is well tolerated. It, therefore, represents safe & effective treatment option for psoriasis when compared with conventional drug therapies being used currently.

Some findings also suggest that genistein could suppress ROS activation & thereby attenuated TNF-α- and LPS-induced inflammatory responses in HaCaT cell lines. The antioxidant properties of genistein are attributed to protection cells against ROS by enhancing the activity of antioxidant enzymes, reducing the production of hydrogen peroxide & scavenging free radicals. In the case of inflammatory skin diseases like psoriasis, ROS are involved in TNF-α-mediated signaling pathways via TNF-α-dependent NF-κB activation. The anti-inflammatory activity of genistein has been examined by studying the expression of certain inflammatory mediators when the cells exposed as well as not exposed to genistein. This was done by carrying out the stimulation of the cells with the cytokines TNF-α, or LPS. It was observed that, regardless of the type of cell activation used, the levels of Interleukin 8, Interleukin 20, and CCL_2 out of five cytokines tested in the keratinocyte supernatant decreased in response to the isoflavone.

Besides, an increased expression followed by reduction was seen in both RNA and protein levels of these three cytokines. The study concluded that in activated HaCaT cells, genistein may partly suppress inflammatory cytokine production by inhibition of the ROS/NF-κB pathway. The hypothesis that genistein attenuates ROS-mediated NFκB activation and subsequent inflammatory cytokine production in "psoriasis-like" keratinocytes was proposed on the basis of this study [61].

CONCLUSION: In conclusion, genistein represents a promising option in the treatment of psoriasis because it works at molecular levels against the disorder. Another important advantage of this agent is well tolerated, and there is a possibility of it being self-administered. Genistein may also be suitable as an oral treatment option for the patients who opt to discontinue treatments due to ineffectiveness or intolerability to the currently available drugs.

Monotherapy with systemic agents is found to be effective for many patients with psoriasis; however, some of the patients seem to require combination approaches. Therefore the use of genistein still needs to be investigated and studied in more depth with respect to clinical and therapeutic approaches.

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