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JAK Inhibitors: Emerging New Drug In The Treatment Of Dermatitis.

CHINU KUMARI, DEV PRAKASH DAHIYA, NIKHIL RANA*, KANIKA, RAHUL SHARMA

*Corresponding author: Nikhil Rana

address: - school of pharmacy, department of pharmaceutics abhilashi university chail-chowk mandi h.p

Pincode - 175028

Abstract:

Dermatitis, a common inflammatory skin condition, poses challenges in terms of effective and well-tolerated treatment options. It is characterized by inflammation of the skin, often necessitates treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids which may pose some limitations, side effects and significant health challenges with conventional treatments. This article provides a thorough exploration of the therapeutic potential of medicinal plants in the management of dermatitis exploring an alternative therapeutic approach by focusing on Janus kinase (JAK) inhibitors, a class of drugs that have shown promise in modulating inflammatory pathways Dermatitis is a common inflammatory skin condition that requires minimally invasive therapeutic interventions to be effective. Many reviews reveal the involvement of JAK-STAT signaling in dermatitis pathogenesis and highlights the potential of JAK inhibitors in mitigating inflammation. discussing the specific mechanisms of action of JAK inhibitors, their role in regulating immune responses, and their potential benefits in comparison to traditional treatments centred on qualities that are skin-soothing, antimicrobial, and anti-inflammatory.

Keywords: - Atopic dermatitis, Juan kinase inhibitors, Interleukins, jak-stat signaling pathway.

INTRODUCTION

Dermatitis, a complex and pervasive dermatological condition, stands as a testament to the intricate interplay of genetic, environmental, and immunological factors that shape the landscape of skin health.[1] Dermatitis is a global inflammatory disorder that affects people in varying degrees, from minor irritations to debilitating chronic conditions.[2] With dermatitis becoming more common, people are becoming more aware of the shortcomings of traditional treatments and more interested in exploring alternative treatment options.[3] “Dermatitis" is a term used to refer to a variety of skin rashes and irritations brought on by infections, allergies,

overactive immune systems, genetics, and other factors. Redness, itching, and dry skin are typical symptoms.[4] The term "dermatitis" "Itis" denotes inflammation, and "derma" denotes skin. The entire word refers to "skin inflammation.

" Depending on what is causing them, the rashes can range in severity from mild to severe and result in a number of issues.[5] Dermatitis doesn't seriously damage your health. It does not indicate that your skin is dirty or infected, nor is it communicable. You can control your symptoms with certain medications and treatment plans. The treatment of dermatitis poses a unique challenge due to its multifactorial nature, with diverse triggers and manifestations that often defy a one-size-fits-all approach.[6] Although many people find symptomatic relief from conventional pharmacological interventions, these strategies may not be sufficient to address the underlying complexities of the condition, necessitating the development of more complex and comprehensive therapeutic approaches.[7]

It becomes obvious that researching the therapeutic potential of medicinal plants is a worthwhile effort. With its vast biodiversity, nature has given us access to a wealth of botanical remedies that have long been a part of conventional medical procedures. In addition to their historical effectiveness, medicinal plants provide an abundant supply of bioactive compounds with a variety of pharmacological actions, which makes them a promising tool for medicine. These substances, which frequently have anti-inflammatory, antioxidant, and immunomodulatory qualities, fit the complex pattern of dermatitis and offer a comprehensive method of treatment.[8]

Eczema, also known as dermatitis, is a chronic (long-lasting) skin condition that is characterized by skin irritation, redness and inflammation. Though anyone can contract the disease at any age, it is a prevalent ailment that typically first manifests in childhood.[9] Since the condition is not communicable, it cannot be passed from one person to another. Skin that has atopic dermatitis becomes very itchy.[10]

Additional redness, swelling, cracking, "weeping" transparent fluid, crusting, and scaling are caused by scratching. Generally speaking, there are times when the illness is worse, known as flares, and times when the skin gets better or clears up completely, known as remissions.[11]

Advantages of medicinal herbs Containing Jak inhibitors in treatment of dermatitis

Many cultures have been using medicinal plants to treat dermatitis for centuries. This practice has its roots in traditional medicine. Several possible advantages of using medicinal plants to treat dermatitis include:[12]

- Natural Compounds: Alkaloids, flavonoids, terpenoids, and essential oils are just a few of the bioactive substances found in medicinal plants. These compounds may have anti-inflammatory, antibacterial, and antioxidant qualities. These substances have the potential to reduce dermatitis symptoms.[13]
- Anti-Inflammatory Properties: Skin inflammation is a common symptom of dermatitis. Numerous therapeutic plants have anti-inflammatory qualities that can aid in lowering dermatitis-related redness, swelling, and itching. Calendula, chamomile, and aloe vera are a few examples.[14]

- Antimicrobial Effects: Some medicinal plants naturally contain antimicrobial qualities that can aid in the treatment or prevention of dermatitis-related secondary infections. Neem and tea tree oil are two examples of plants that have shown antimicrobial activity and may help treat dermatitis.
- Soothing and Moisturizing: A lot of medicinal plants have soothing and moisturizing qualities that help hydrate the skin and relieve dryness, which is a common dermatitis symptom. Shea butter, coconut oil, and olive oil are a few examples.
- Reduced Side Effects: Medicinal plants frequently have fewer side effects than some synthetic drugs. They might be a better choice for people searching for natural alternatives and may be more tolerable for those with sensitive skin.
- Cultural and Traditional Knowledge: The use of medicinal plants to treat skin conditions, such as dermatitis, has long been a part of traditional medicine systems across many cultures. The collective wisdom from these customs can offer important new perspectives on potent plant-based treatments.[15]

Role of JAK Inhibitor's in the Pathogenesis of dermatitis: -

The primary intracellular signaling pathway for cytokines is the JAK-STAT signaling pathway. It is connected to numerous bodily functions and plays a crucial role in biological processes. Haematopoiesis, immune regulation, apoptosis, differentiation, and cell proliferation.[16] Four JAK family protein types (JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2) are found in mammals, and seven STAT family protein types (STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6) are known to exist. Additionally, the JAK-STAT pathway transmits signals from more than 50 cytokines.[17] The JAK-STAT route is involved in the IL-2, IL-3, IL-6, and IL-10 families' signaling.[18]

List of cytokines that signal through the JAK-STAT pathway.[19]

Family	Members	Functions
IL-2	IL-2	Immune response, T-cell differentiation
	IL-4	Th2 differentiation
	IL-9	Pleiotropic, Stimulates T-, B-, and NK cells
	IL -15	Stimulates, T-, and NK cells
	IL-21	Stimulates T-, B-, and NK cells
IL-3	IL-3	Multi-lineage hematopoietic growth factor
	IL-5	B-cell development, eosinophils GM-CSF Multi-lineage hematopoietic growth factor, especially monocytes, neutrophils, eosinophils, and basophils

IL-6	IL-6	Pleiotropic, haematopoiesis, acute phase response, lymphoid differentiation LIF Pleiotropic, blastocyte implantation, bone remodelling, CNS CNTF Neuronal growth factor CT1 Cardiac myocytes growth factor CLC Neurological growth factor OSM cone formation.
	IL-31	Inflammatory, cell-mediated immunity NP Neural growth factor
IL-10	IL-10	Anti-inflammatory, inhibits macrophage activation.
	IL-20	Inflammatory, acts on dermal cells
	IL-22	Inflammatory, secreted by Th1 and Th17 cells, acts on dermal cells
	IL-24	Inflammatory, acts on dermal cells
	Il-26	Antimicrobial, Th17 cytokine

JAK-STAT in Epidermal Keratinocytes

1. **Cell proliferation and differentiation:** The JAK/STAT pathway regulates the proliferation and differentiation of epidermal keratinocytes. Upon activation by cytokines or growth factors, such as interleukins and interferons, JAKs phosphorylate and activate STAT proteins.[20] Activated STATs then translocate to the nucleus where they regulate the transcription of genes involved in cell cycle progression, differentiation, and apoptosis. In epidermal keratinocytes, this pathway helps to maintain the balance between cell proliferation and differentiation, which is crucial for the proper formation and maintenance of the epidermal barrier.[21]

2. **Immune responses:** Epidermal keratinocytes are not just passive structural components of the skin; they also actively participate in immune responses. The JAK/STAT pathway is involved in mediating the response of epidermal keratinocytes to pro-inflammatory cytokines and microbial antigens.[22] Activation of this pathway leads to the production of antimicrobial peptides, cytokines, and chemokines, which recruit immune cells to the site of infection or injury and help to eliminate pathogens.[23], [24]

3. **Wound healing**: The JAK/STAT pathway is essential for wound healing in the skin, which involves a complex series of events including inflammation, re-epithelialization, granulation tissue formation, and tissue remodelling. Epidermal keratinocytes at the wound edge proliferate and migrate to cover the wound site.[25] The JAK/STAT pathway regulates the expression of genes involved in these processes, such as

those encoding growth factors, matrix metalloproteinases, and cell adhesion molecules, thereby promoting efficient wound closure and tissue repair.[26]

4. **Barrier function**: One of the primary functions of epidermal keratinocytes is to form a physical and chemical barrier that protects the body from external insults, such as pathogens, UV radiation, and chemical irritants.[27] The JAK/STAT pathway regulates the expression of proteins involved in the formation and maintenance of the epidermal barrier, including structural proteins like keratins and proteins involved in lipid metabolism.[28] Dysregulation of this pathway can lead to impaired barrier function, resulting in conditions such as atopic dermatitis and psoriasis.[29], [30]

T cell subsets in AD

The skin barrier, pruritus, and Th2-mediated immune response are all part of the intricate etiology of AD. The JAK-STAT pathway mediates the signaling of several key cytokines in the pathophysiology of AD during the acute phase, including IL-4, IL-5, IL-13, and IL-31. Th17 and Th22 cytokine profiles are more common in Asian AD patients or in the chronic phase of the disease.

Th2 cytokines

The pathophysiology of AD depends on Th2 immune responses. Specifically, the Th2 cytokines (IL-4, IL-13, and IL-31) that are critical for Th2-type immune responses are signalled by the JAK-STAT pathway. Two varieties of IL-4 receptors exist: type II IL-4 receptors, which are made up of IL-4Rɤ and the IL-13 receptor 1 (IL-13Ra1) chain, and type I IL-4 receptors, which are made up of an IL-4Ra chain and a common g chain.[31], [32]

Helper T-cells, Th1 and Th2

Even though a robust Th2 immune response appears to be the hallmark of all AD cases, some AD types may also be influenced by the Th1, Th17, and Th22 cytokine pathways.[31] Th17 cells are identified by the release of IL-17A and IL-17F, two inflammatory cytokines. Patients with AD, whether acute or chronic, consistently have elevated levels of Th17-associated molecules. Th17 cells in particular are correlated with eosinophils that express matrix metallopeptidase (MMP)-9 and are involved in tissue remodelling. Consequently, Th17 cells may contribute to tissue remodelling in AD that is chronic. The IL-17 receptor complex, comprising IL-17RA and IL17RC, is extensively expressed on hematopoietic, mesenchymal, and epithelial cells. When IL-17 binds to its receptor, the adaptor protein Act1 is drawn in.[33] Act1 then interacts with scaffold proteins such as tumour necrosis factor receptor-associated factor 6 and transforms growth factor-activated kinase 1 to activate p38/MAPKs and nuclear factor (NF)-kB.20 Consequently, Th17 is independent of JAK/STAT signaling.

The skin of AD has a marked increase in Th22. Chronic AD lesions are associated with enhanced Th2 and Th22 responses. It has been determined that IL-22, a glycoprotein that is a member of the IL-10 family, is a major mediator of epidermal hyperplasia. IL-22R and IL-10Rb make up human IL-22 receptors. Epithelial cells found in the skin, stomach, and lungs expressIL-22R. Upon binding to its receptor, IL-22 phosphorylates JAK1 and Tyk2, thereby initiating STAT3.[34]

JAK-STAT in Mast Cells

Mast cells are more prevalent in the skin lesions of AD patients as well as AD mouse models. In an in vitro experiment,[35] IL-9 activates STAT3 to promote the production of VEGF from human mast cells. Interestingly, despite the fact that IL-9 and its receptors are upregulated in the lesional skin of AD patients, the serum levels of IL-9 in these patients are not different from those of non-AD controls. This suggests that the upregulation of VEGF in mast cells via IL-9 may be a localized cutaneous phenomenon. The significant upregulation of angiogenesis and mast cell VEGF production in an AD animal model corroborates JAK-STAT's function in this immune pathway.[36], [37]

Treatment with JAK inhibitors: --

JAK (Janus kinase) inhibitors work by targeting the Janus kinase signaling pathway, which plays a crucial role in the immune response and inflammatory processes. In dermatitis treatment, JAK inhibitors primarily act by modulating the immune response and reducing inflammation in the skin.[38] Here's a more detailed explanation of their mechanism of action:

1. **Inhibition of Janus Kinases (JAKs):** Janus kinases are enzymes involved in signal transduction pathways, particularly those mediated by cytokines and growth factors. These pathways play a critical role in regulating immune responses and inflammation. JAK inhibitors specifically target and inhibit the activity of one or more Janus kinase enzymes, such as JAK1, JAK2, JAK3, or TYK2.[39]

2. **Interference with Cytokine Signaling:** By inhibiting Janus kinases, JAK inhibitors disrupt the signaling cascades triggered by various cytokines, such as interleukins (ILs) and interferons (IFNs). These cytokines are key mediators of inflammation and immune responses in dermatitis and other inflammatory skin conditions. By blocking JAK-mediated signaling, JAK inhibitors reduce the production and release of pro-inflammatory cytokines, thereby dampening the inflammatory response.[38]

3. **Downregulation of Immune Cell Activation:** JAK inhibitors also modulate the activation and function of immune cells, such as T cells, B cells, and dendritic cells, which are involved in the pathogenesis of dermatitis.[40] By interfering with intracellular signaling pathways essential for immune cell activation and proliferation, JAK inhibitors help regulate the immune response and prevent excessive inflammation in the skin.[41]

4. **Normalization of Epidermal Barrier Function:** Chronic inflammation in dermatitis can disrupt the integrity of the skin barrier, leading to increased permeability and susceptibility to irritants and allergens. JAK inhibitors may help restore the epidermal barrier function by reducing inflammation and promoting

skin barrier repair mechanisms. This normalization of the skin barrier contributes to symptom relief and prevents disease exacerbations.[42], [43]

First generation and newer JAK inhibitors are common categories for JAK inhibitors. Newer JAK inhibitors show greater selectivity for particular JAKs, while first-generation JAK inhibitors are less selective and therefore show activity against three or all four members of the JAK enzyme family.[42] To treat AD, certain JAK inhibitors were created. Japan developed delgocitinib,[44] a diazaspiroalkane derivative topical JAK inhibitor[45] with a molecular weight of 310.35. This is a pan-JAK inhibitory profile of the first generation, which in enzyme assays inhibits all JAK activities. It improves skin barrier dysfunction by preventing inflammatory cells like T cells, B cells, monocytes, and mast cells from becoming activated.

Delgocitinib ointment was administered to Japanese healthy volunteers and AD patients in **phase 1** clinical trials to evaluate pharmacokinetics, tolerability, and safety through patch testing and photo testing. For 16-year-old children,[46] **phase 2** multicentre randomized double-blind vehicle-controlled clinical trials were also conducted. According to these, the modified EASI (mEASI) scores' least-squares mean percentage changes from baseline were approximately 54.2% in the group taking 0.25% delgocitinib, 61.8% in the group taking 0.5% delgocitinib, and 4.8% in the vehicle group.[47]

In phase 3, mEASI scores increased by 44.3% from a randomized, double-blind, vehicle-controlled study involving patients who were approximately 16 years old.[48] following four weeks of treatment, by 1.7% in the vehicle group and by 0.5% in the delgocitinib group. From the baseline, the pruritus numeric rating scale (NRS) score dropped dramatically. In a long-term, open-label, 52-week study, 51.9% of patients with mild-to-severe AD who were ~16 years old had mEASI-50, compared to 27.5% with mEASI-75 at week 52.[49] The percentage of patients who reported adverse events (AEs) and AEs related to treatment was 15.4% and 69.0%, respectively. 3.4% of patients experienced a study interruption due to adverse events (AEs). Contact dermatitis and application site irritation were the most common AEs that resulted in study discontinuation, occurring in 1.0% and 0.6% of patients, respectively. However, delgocitinib ointments at 0.25% and 0.5% proved beneficial for Japanese pediatric AD patients. Japanese pediatric AD patients between the ages of 2 and 15 participated in a phase 3 randomized, double-blind, vehicle-controlled study. An open-label, long-term study was then conducted afterward. After four weeks of treatment, the mEASI scores improved by 10.9% in the vehicle group and 39.3% in the 0.25% delgocitinib group from baseline. As soon as the treatment began, there was a noticeable decrease in pruritus scores. Through week 56, there was also an improvement in the pruritus score and ease of use. The first approved JAK inhibitor that inhibits JAK1, JAK2, and JAK3 is called tofacitinib.35 Oral preparations of it have been approved for the treatment of polyarticular course juvenile idiopathic arthritis, psoriatic arthritis, ulcerative colitis, and rheumatoid arthritis. Adult patients with mild-to-moderate AD participated in a phase 2a study using 2% tofacitinib ointment.36 At week 4, tofacitinib's mean percentage change in EASI scores from baseline was significantly higher ($P < 0.001$) than that of the vehicle group (~29.9%). On the other hand, by week 1, patients treated with tofacitinib ointment demonstrated significant improvements in body surface area and physician global assessment, and by day 2, they

demonstrated significant improvement in pruritus. Thus, it is believed that topical JAK inhibitors can safely and quickly reduce the symptoms and rash associated with AD.[50]

CONCLUSION

Dermatologists worldwide face a great deal of difficulty in treating dermatitis due to the complex interaction of genetic, environmental, and immunological factors. The growing prevalence of dermatitis has brought attention to the shortcomings of traditional treatments, which has sparked curiosity about alternative therapeutic modalities.
Because medicinal plants contain a wealth of bioactive compounds that have anti-inflammatory, antioxidant, and immunomodulatory qualities, they present a promising treatment option for dermatitis. Furthermore, new treatment options become available when the pathophysiology of dermatitis is understood in relation to the JAK-STAT pathway. JAK inhibitors provide a focused method of treating dermatitis symptoms by regulating inflammation and immune responses. New developments in the development of JAK inhibitors, like tofacitinib and delgocitinib, show encouraging outcomes in clinical trials, suggesting their potential as efficacious treatments for dermatitis.

In conclusion, the convergence of traditional herbal medicine and cutting-edge pharmacology presents a new approach to dermatitis management. Through the utilization of medicinal plants and targeted interventions such as JAK inhibitors, we can work towards providing patients with dermatitis with comprehensive and individualized care.

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