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Flavonoids: A Natural Remedy for Atopic Dermatitis

Khatoon M[1], Ijaz S[2]*, Ahmad A[2], Ahmad M[2] and Rashid F[2]

[1]Department of Pharmacognosy, University of the Punjab, Pakistan

[2]Quaid-e-Azam College of Pharmacy, Pakistan

***Corresponding author:** Shakeel Ijaz, Quaid-e-Azam College of Pharmacy, Sahiwal 57000, Punjab, Pakistan, Tel: +923347315016; Email: shakeelijaz80@gmail.com

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Abstract

Atopic dermatitis (AD) is a chronic autoimmune inflammatory skin disorder that affects both children and adults physiologically as well as psychologically. Despite recent advancements in the prevention and treatment of AD, currently available products have shown variable results with potential side effects. Because of their better safety profile, natural products are preferred for the treatment and prevention of various disorders especially for skin ailments. Flavonoids belong to the polyphenol group of natural compounds widely distributed in fruits, vegetables, flowers, seeds, and other plant parts. In the recent era, flavonoids have gained the attention of researchers as they have diverse biological and pharmacological activities including antioxidant, anti-inflammatory, and anticancer etc. This review will discuss the beneficial effects of different flavonoids for AD owing to their different pharmacological attributes.

Keywords: Autoimmune Disorder; Natural Products; Polyphenols; Antioxidants; Anti-Inflammatory

Abbreviations

AD: atopic dermatitis; NMFs: natural moisturizing factors; DNCB: dinitrochlorobenzene; INOS: inducible nitric oxide synthase; LPS: lipopolysaccharide.

Introduction

Atopic dermatitis (AD), also known as atopic eczema, is a persistent inflammatory skin condition that flares up occasionally. AD is a multifaceted disorder with a wide range of clinical manifestations and symptom combinations, including persistent itching, dry skin, cracked or scaly skin, and red or brownish skin patches. It typically manifests as little pimples on the cheeks, rashes on the backs of the hands, the top of the head, or knees or elbows (frequently in the creases of the joints). Allergies, asthma, and allergic rhinitis are linked to AD [1]. Its incidence and prevalence are still rising, and there are notable variations between children and adults, typically indicating that children are more likely than adults to have it. Up to 2-10% of adults and 15-30% of children suffer from AD [2].

Pathophysiology of Atopic Dermatitis

The pathophysiology of AD involves immunological dysregulation, epidermal barrier dysfunction, and skin microbiome modification, all of which are influenced by environmental and genetic variables. Specifically, the disruption of the function of the epidermal barrier and a modified immunological response are the main pathological mechanisms of AD development [3]. Microbes, allergens, and

irritants can enter the body more easily when the epidermal barrier is compromised. This leads to the immune system becoming activated and pro-inflammatory cytokines being released. Therefore, immunological dysregulation of both innate and adaptive responses to environmental stimuli results from disruption of epidermal barrier function. Th2 cytokines, specifically IL-4, IL-5, IL-13, and IL-31; eosinophilic activation; and the generation of allergen-specific IgE are recognized as indicators of the adaptive response [4]. Furthermore, the filaggrin protein, which is the most significant structural protein of the stratum corneum together with keratin, is linked to disruption of the function of the epidermal barrier. Patients with AD frequently have a mutation in the filaggrin gene on chromosome 1q21, which is strongly linked to abnormalities in the composition and functionality of the epidermal barrier. TEWL rises as a result, and the production of natural moisturizing factors (NMFs), which are created during the filaggrin deamination process, decreases [5,6].

Acute and chronic phases are the two stages of atopic dermatitis. During the acute stage, CD4+T cells penetrate skin lesions and primarily release the Th2 (T helper) cytokines IL-4, IL-5, and IL-13. The activation of Th2, Th22, and Th17 cells is associated with the acute phase. Th1 cells release the interferon IFN-γ during the chronic phase. Because of an IFN-γ response that causes tissue remodeling, skin thickening, and increased collagen deposition, the chronic phase exhibits Th1-type inflammation and delayed-type hypersensitivity [7-9].

Treatment of Atopic Dermatitis

There are currently a number of therapeutic options available for treating and managing AD categorized as first, second and third line treatment. First-line treatments include cosmetics and wet-wrap treatments. Second-line treatments include antihistamines, antibiotics and mild anti-inflammatory drugs such as topical corticosteroids and topical calcineurin inhibitors. Systemic treatments like as phototherapy and targeted immunotherapy are considered as third-line treatments [10]. Additional treatments are also employed such as antibiotics to treat Staphylococcus aureus infections, probiotics, UV-A, UV-B and Psoralen + UV-A therapy. For patients who do not respond well to traditional topical treatments, immune-suppressants are recommended. As biologic therapies work well for long-term treatment, they are frequently used to treat severe atopic dermatitis [11].

These medications do, however, have certain drawbacks and negative side effects. As a result, demand for using natural plant products is rising. Phytochemicals use several signal transduction pathways for their pharmacological action rather than a single mode. So, this multi-target regulatory approach make them ideal candidate for treating complex diseases like AD. The safety and efficacy of phytochemicals such as flavonoids in the treatment of AD are supported by scientific research. Numerous studies on cells and animal models demonstrate that a range of natural compounds can undo the pathological alterations caused by AD [12].

The present mini-review focuses on flavonoids' role as an antioxidant, anti-inflammatory, anti-allergic, photo-protective, and immune modulator for the treatment of AD. These phytochemicals can be used in the development of new therapeutic options for its prevention and treatment.

Flavonoids for Treating Atopic Dermatitis

Flavonoids are widely distributed secondary metabolites in the plant kingdom found in flowers, fruits, vegetables, etc. They are amongst the most studied, researched, and isolated classes of phytochemicals. They are regarded as dietary supplements that promote health and prevent a number of diseases. They have diverse biological and pharmacological properties and act as antioxidants, antibacterial, anti-inflammatory, anti-allergic, photo-protective, etc. These properties of flavonoids make them potential candidates for the management and treatment of AD [13].

Liquiritigenin

Liquiritigenin, a flavonoid extracted from the root of Glycyrrhiza uralensis, has been studied for its diverse pharmacological activities such as antitumor, antioxidant, anti-inflammatory, and antimicrobial [14]. It was tested by Lee and co-researchers for its anti-atopic effects via control of T-cell activation. Liquiritigenin pretreatment of Jurkat T cells reduced IL-2 production and CD69 surface expression of stimulated cells with PMA/A23187 or anti-CD3/CD28 antibodies through the NF-κB and MAPK pathways, according to in-vitro tests. Additionally, surface molecules CD40L and CD25 that are important in the late phase of T-cell activation were less expressed when liquiritigenin was present. Oral administration of liquiritigenin decreased the redness and swelling of draining lymph nodes (dLNs) in mice, according to experimental data conducted in-vivo. It also had a systemic effect on the expression levels of effector cytokines that exacerbate atopic dermatitis, such as IL-4, IL-5, IL-13, IL-31, TNF-α, etc., [15].

Formononetin

Formononetin is an isoflavone phytoestrogen. Legumes, numerous clover species, particularly red clovers, and the traditional Chinese herb Astragalus membranaceus are abundant sources of this isoflavone. It has very potent antioxidant, anticancer, and neuroprotective potential [16]. Formononetin has been shown to alleviate the early stages of AD, lower the rate of AD relapse, and lower the incidence of severe recurrence. Its hormone-like structure was the

cause of these pharmacological actions. It was administered to TNF-α and polyinosinic-polycytidylic acid (poly(I: C)) co-stimulated HaCaT cells and a fluorescein isothiocyanate (FITC)-induced mice AD model to determine the probable mechanism. The findings demonstrated that formononetin activated GEPR on HaCaT cells to suppress TSLP synthesis, which in turn increased A20, a crucial anti-inflammatory protein that is crucial for controlling immunity and inflammation as a negative regulator of NF-κB [17].

Naringenin

In the NC/Nga mouse model of atopic dermatitis, the effects of naringenin on skin inflammation, proinflammatory cytokines, and M1 to M2 macrophage polarization shifts were examined. In the skin of mice with atopic dermatitis, the treatment successfully reduced the expression of the M1 marker CD68 and altered the expression of HMGB1, RAGE, ERK1/2, and NF-κB p65. Treatment with naringenin markedly improved M2 phenotypes, such as CD36 and IL-10 levels. Naringenin activates the anti-inflammatory gene, according to the results [18].

Chamaejasmine

Chamaejasmine, a bifalvonoid, is the major constituent of Stellera chamaejasme. It is investigated for its strong pain-relieving effects, as well as anticancer and anti-inflammatory potential in animal models [19]. In the DNCB-induced murine model of AD, Chamaejasmine was discovered to restore skin barriers by reducing TEWL and improving skin moisture. It also inhibits the overexpression of IL-4 and IgE in AD skin. As a result, it significantly reduced the dermatitis development in the AD mouse model. Antigen-mediated β-hexosaminidase release from RBL-2H3 cells was efficiently inhibited by 30 μM chamaejasmine, according to in vitro antiallergic and anti-inflammatory tests [20].

Naringenin

Naringenin's ability to treat 2, 4-dinitrofluorobenzene-induced atopic dermatitis in NC/Nga mice was investigated. Kim, et al. [21] showed that naringenin inhibited the production of interferon-gamma (IFN-γ) by activated CD4+ T-cells and also reduced the infiltration of skin lesions by CD8+ T-cells, CD4+ T-cells, mast cells, and eosinophils, thereby reducing the growth of atopic dermatitis skin lesions. After a histological examination of the thickness of the epidermis, the authors also noticed a reduction in ear edema in the mice receiving naringenin [21].

Chrysin

Chrysin (5,7-dihydroxyflavone) was employed in the BALB/c mice model of atopic dermatitis, where skin lesions resembling AD were produced by repeated alternate treatment of 2,4-dinitrochlorobenzene/Dermatophagoides 12hosph extract. Chrysin taken orally reduced ear thickness, which a histological examination also verified. According to the study's findings, chrysin inhibited the inflammatory responses of Th1, Th2, and Th17 cells in mouse lymph nodes and ears, which decreased mast cell infiltration, decreased serum histamine levels, and suppressed atopic dermatitis. Chrysin suppressed TNF-α/IFN-γ-stimulated IL-33 production, according to experiments conducted on HaCaT cells. Additionally, it was shown that via down-regulating p38 MAPK, NF-κB, and STAT1 in tumor necrosis factor (TNF), chrysin greatly reduced the production of cytokines, Th2 chemokines, CCL17, and CCL22.Human keratinocytes activated by α/interferon (IFN)-γ [22].

By specifically targeting IKK, chrysin inhibited CCL5 production, reducing mast cell infiltration to inflamed areas and at least partially reducing inflammatory responses. The molecular mechanism behind the regulation of C-C motif chemokine ligand 5 (CCL5) gene expression by chrysin in an inflammatory milieu resembling atopic dermatitis (AD) was examined in this study. We demonstrated that chrysin suppressed nuclear factor kappa B (NF-κB) in the inflammatory milieu, hence inhibiting CCL5 expression at the transcriptional level. The inhibitor of κB (IκB) kinase (IKK) may attach to chrysin's ATP-binding pocket, preventing IκB degradation and NF-κB activation. Chrysin's ability to target IKK clinically was assessed in BALB/c mice with skin lesions caused by 2,4-dinitrochlorobenzene [23].

Quercetin

The impact of quercetin on skin lesions resembling atopic dermatitis (AD) was investigated in a mouse model of AD produced by MC903. After applying MC903 to the mice's left ear, quercetin was administered every day for eight days. Model ear epidermal thickness and the severity of atopic dermatitis were both markedly reduced by quercetin. Additionally, it can lower the expression levels of CCL17, CCL22, IL-4, IL-6, IFN-γ, and TNF-α, as well as prevent mast cell infiltration in the skin lesions. The study's findings demonstrated that quercetin's protective effect in a mouse model of atopic dermatitis was primarily demonstrated via controlling mast cells, keratinocytes, and Th1/Th2 cells [24]. Moreover, Quercetin may alleviate atopic dermatitis-related symptoms via its antioxidant and anti-inflammatory activities. It also accelerates wound healing process through ERK1/2 MAPK and NF-κB pathways. This was investigated by Beken et al. [25] using immortalized human HaCaT keratinocytes cell lines. AD-induced IL-1β, IL-6, IL-8, and thymic stromal lymphopoietin were dramatically reduced in expression when cells were pretreated with 1.5 μM quercetin. In contrast, superoxide dismutase-1 (SOD1), SOD2, catalase, glutathione peroxidase, and IL-10 were strongly increased.

The elevation of Twist and Snail mRNA expression supported quercetin's ability to induce an epithelial–mesenchymal transition, which aided in wound healing. Surprisingly, quercetin pretreatment of AD-induced cells decreased the levels of matrix metalloproteinase 1 (MMP1), MMP2, and MMP9 while increasing the mRNA expression of occludin and E-cadherin [25].

Puerarin

Puerarin, is a primary isoflavonoid isolated from Pueraria lobata root, has been shown to have extensive pharmacological effects. These include vasodilation, cardioprotection, neuroprotection, antioxidation, anticancer, anti-inflammatory, analgesic, and insulin resistance reduction [26]. By controlling a number of inflammatory and atopic mediators, puerarin reduces skin inflammation and AD-like skin lesions. BALB/c mice were given 2,4-dinitrochlorobenzene (DNCB) for 17 days to cause skin lesions resembling atopic dermatitis (AD). Additionally, puerarin was given orally to the BALB/c mice. Puerarin reduced the mice's DNCB-induced AD-like symptoms by controlling serum immunoglobulin E (IgE), mast cell degranulation, and skin thickness. Puerarin's effects on the release of pro-inflammatory cytokines were also clarified using human keratinocytes, or HaCaT cells. Puerarin suppressed the release of chemokines and inflammatory cytokines [27].

Diosmetin

Lee et al. investigated the effects of diosmetin on the development of AD using a mouse model of AD induced by dinitrochlorobenzene (DNCB). Using an anti-F4/80 antibody, an immunohistochemical examination showed that diosmetin dramatically reduced macrophage infiltration into the AD lesion. Diosmetin treatment was found to reduce the levels of pro-inflammatory cytokines (TNF-α, IL-4, and IL-1β) in the skin lesion. Additionally, a mouse macrophage cell line generated by IL-4 was used to assess diosmetin's anti-inflammatory properties. Diosmetin reduced the expression of inducible nitric oxide synthase (iNOS) and hindered the synthesis of nitric oxide. Diosmetin inhibited JAK/STAT signaling in addition to MAP kinase phosphorylation (ERK 1/2, p38, and JNK) [28].

Sulfuretin

Sulfuretin alleviates atopic dermatitis in mice by suppressing Th2 cell activity. In a mouse model, they assessed sulfuretin's therapeutic impact on AD-like damage brought on by 2,4-dinitrochlorobenzene (DNCB). Measurements were made of the cytokine accumulation at the lesions, serum IgE level, and overall symptomatic score. Finally, we looked into how sulfuretin regulates the GATA3 pathway in primary CD4+ cells from mice. Sulfuretin decreased IL4 production in a dose-dependent way without causing any cytotoxicity, according to a study on in vitro differentiated Th2 cells. According to an in vivo investigation, 10 μM sulfuretin reduced the severity of skin lesions, the frequency of scratches, the serum level of IgE, and the buildup of proinflammatory cytokines at the location of the skin lesion. According to mechanistic research, sulfuretin inhibited the generation of Th2 cytokines by reducing the expression of GATA3 [29].

Fisetin

Fisetin helps NC/Nga mice with AD-like clinical symptoms brought on by repeated DNFB treatment. Fisetin lowers the expression of cytokines and chemokines linked to dermal infiltrates in AD-like skin lesions and markedly reduced the infiltration of inflammatory cells, such as mast cells, eosinophils, and CD4+ T and CD8+ T cells. Fisetin also significantly decreases total serum immunoglobulin E (IgE) levels and the ratio of phospho-NF-κB p65 to total NF-κB p65.

Additionally, fisetin decreases the dose-dependent synthesis of IL-4 and IFN-γ by activated CD4+ T cells, while increasing the production of the anti-inflammatory cytokine IL-10 [30]. Owing to these immunosuppressive properties of fisetin, Ghosh and co-researchers topically applied fisetin in an oxazolone-induced AD model of the mouse. At the tissue, cellular, and molecular levels, the inflammatory parameters were examined. The diseased group showed a considerable rise in ear thickness as measured during the treatment regimen, while the group treated with fisetin showed a significant repair.

Additionally, fisetin restored systemic circulation and cell infiltration at the site of inflammation. Also, other characteristics such the number of eosinophils, T cells, B cells, neutrophils, and macrophages increased, serum IgE levels rose, and the expression of pro-inflammatory cytokines and signaling molecules was upregulated [31].

Nepetin

Nepetin is a newer flavonoid obtained from dried aerial part of Saussurea involucrata. This herb is a well-known Chinese medicine used to alleviate chronic inflammation. Gong and co-workers checked the efficacy of nepetin in modulating lipopolysaccharide (LPS)-stimulated inflammation in cultured human keratinocytes. They found that, in cultured keratinocytes, nepetin diminished the production of inflammatory mediators, i.e. iNOS, COX-2, PGES2 and NO. Moreover, nepetin in LPS-induced cultures suppressed the expressions of cytokines, i.e. IL-1β, IL-6 and TNF-α, in a dose-dependent manner. These results suggested that nepetin could suppress chronic skin inflammation in atopic dermatitis [32].

Miscellaneous

In a study, tamanu oil, which is rich in the neoflavonoids calophyllolide, dalbergichromene, dalbergin, nivetin, and coutareagenin, was used to downregulate the expression of genes related to inflammation and upregulate the expression of genes related to skin on TNF-α and IFN-γ-induced HaCaT cells [33].

Conclusion

Because of their diverse pharmacological potential, flavonoids have been extensively used to treat numerous skin diseases. Their anti-inflammatory, anti-allergic, and antioxidant qualities have demonstrated their therapeutic potential in the treatment of AD. More in-vivo human experiments are required because the majority of the investigations were conducted in-vitro or on animal models. To make progress in this area, more research is needed to assess the safety and rule out any potential side effects of the used flavonoids as well as to establish the right dosage and dosage forms.

Conflicts of Interest

The authors declare no conflict of interest.

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