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Research Article

The Potential of Orthosiphon Aristatus Extract in Improving Skin Lesions in Atopic Dermatitis: A Mice Model Study

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ABSTRACT

Introduction: This research discusses the potential of Orthosiphon aristatus, a medicinal plant, in improving skin lesions in Atopic Dermatitis by regulating Th2 cytokines and showing anti-allergic activity. **Methods**: The study was conducted using BALB/C mice induced with DNCB for 21 days to create an atopic dermatitis model. Then, the mice were orally administered Orthosiphon aristatus extract for 14 days (after 7 days of induction). The doses given were divided into six groups: 17.5 mg/kgbw, 35 mg/kgbw, 70 mg/kgbw, and 140 mg/kgbw. Molecular levels such as IgE, IL4, IL22, and PGE2 were analyzed from blood samples. In addition, the severity of skin lesions was assessed morphologically, and histological examination was performed to confirm clinical improvement. **Results**: This study showed that the administration of Orthosiphon aristatus extract reduced the severity of skin lesions in all intervention groups. Histologically, this extract reduced epidermal thickness and mast cell infiltration. These findings were also supported by dose-dependent decreases in IgE, IL4, IL22, and PGE2 levels. So, the conclusion of this study is that Orthosiphon aristatus extract shows potential for improving skin lesions in atopic dermatitis by regulating Th2 cytokines and demonstrating anti-allergic activity in a mice model with DNCB-induced atopic dermatitis. **Conclusion;** The administration of Orthosiphon aristatus extract clinically and histologically exhibits anti-atopic effects that can be explained through the regulation of molecules such as IgE, IL4, IL22, PGE2, and NO. Orthosiphon aristatus has the potential to be a valuable herbal therapy for managing atopic dermatitis.

Keyword: Orthosiphon aristatus, Atopic Dermatitis, Th2 cytokines, Skin lesions.

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INTRODUCTION

Atopic dermatitis is a common chronic skin disease that often affects the quality of life of individuals. It is characterized by symptoms such as itching, dryness, redness, and sometimes inflammation and skin lesions[1]. Atopic dermatitis (AD) is a chronic inflammatory skin disease affecting 10-30% of children and 2-10% of adults worldwide. It is divided into infantile, childhood, and adult forms. Diagnosis relies on clinical features due to the lack of specific laboratory or histological findings. Conventional therapies have been unsatisfactory due to long-term side effects of glucocorticoid and immunosuppressant drugs[2].

The etiology of Atopic Dermatitis (AD) is not fully understood, but current research suggests that it may be multifactorial, involving various factors such as genetics, skin barrier destruction, immunological responses, environmental influences, and oxidative stress[3]. AD is a complex and heterogeneous disease, with different individuals experiencing varying symptoms and responses to treatment. Recent studies have highlighted the additional activation of Th22, Th17/IL23, and Th1 cytokine pathways in AD, further adding to the complexity of the condition[2]. These pathways play a crucial role in the immune response and inflammation seen in AD patients. However, it is important to note that the precise interactions and mechanisms between these factors and pathways are still being investigated.

Atopic dermatitis begins with the impairment of the skin barrier function, leading to increased cytokine production by keratinocytes such as TLSP, IL33, 1, 6, 8, and TNFα. These cytokines stimulate Th2 cells to produce IL4, IL13, and IL5, as well as stimulate B cells to produce IgE. Moreover, these cytokines also play a role in endothelial cell adhesion and eosinophil proliferation[4,5]. Increased serum IgE levels are commonly found in cases of atopic dermatitis and have a significant correlation with disease severity. Th2 cells and IL22 are also reported to be involved in this condition. IL22 is known to cause epidermal hyperplasia and inhibit keratinocyte differentiation and filaggrin formation, which is an important protein in skin barrier function. There is a connection between prostaglandin and IL22 secretion.

Previous studies have reported that in atopic dermatitis (AD) lesions, there is an increase in the production of prostaglandin (PG) D2 and PGE2, which is followed by an increase in interleukin-22 (IL-22) production[6,7]. PGD2 is a major prostanoid produced by activated mast cells and plays a role in inducing chemotaxis of Th2 cells, eosinophils, and basophils, ultimately exacerbating the inflammatory process in atopic dermatitis[6]. Oxidative stress, both in acute and chronic forms, can cause damage to keratinocytes by affecting DNA, enzymes, and cell membrane structures, thereby reducing the integrity of the skin's protective layer. During the inflammation process, inflammatory cells, such as macrophages, can release pro-inflammatory cytokines and nitric oxide (NO)[8,9]. Nitric oxide (NO) is an important parameter in measuring skin damage caused by oxidative stress and inflammation in patients with atopic dermatitis.

Based on these mechanisms, it can be concluded that effective therapy for atopic dermatitis involves

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improving the integrity of the skin's protective layer, inhibiting the inflammatory process, and reducing oxidative stress. Efforts to improve the skin barrier can be made by using skincare products that contain ingredients that can strengthen the skin barrier function, such as peptides and lipids. Additionally, the use of anti-inflammatory and antioxidant agents can also help control the inflammatory process and counteract the oxidative stress that occurs in the skin of patients with atopic dermatitis[6,8,9].

The currently available therapy modalities for atopic dermatitis (AD) include systemic therapy, topical therapy, and phototherapy. The main goals of these therapies are to reduce the severity of symptoms, prevent infections, and manage the condition in the long term. However, these therapies do have the potential for serious long-term side effects.[10,11.] As an alternative, natural bioactive compounds from nature, such as Orthosiphon aristatus, can be a promising therapy for AD. Orthosiphon aristatus has antioxidant and anti-inflammatory activities[12,13]. A study reported that the compounds eupatorin and sinensetin found in Orthosiphon aristatus leaves can inhibit the expression of iNOS (inducible nitric oxide synthase) and reduce the production of nitric oxide (NO) and prostaglandin E2 (PGE2), ultimately reducing the production of IL-22 [14.] Furthermore, ethanol extract and ursolic acid from Orthosiphon aristatus have also been shown to suppress the production of NO and PGE2 induced by LPS (lipopolysaccharide) by inhibiting the formation of reactive oxygen species (ROS), such as the expression of iNOS and COX2 in RAW 264.7 cells [15.]

Based on the findings described above, orthosiphon aristatus has the potential to be an alternative therapy for atopic dermatitis. However, more research is needed to investigate the effects of Orthosiphon aristatus on AD, especially in human studies. The study mentioned in this context is the first study to examine the effects of Orthosiphon aristatus on a mice model of AD induced by DNCB (2,4-dinitrochlorobenzene). This study observed clinical symptoms and histological features, as well as analyzed serum levels of IgE, NO, IL-4, IL-22, PGE2, and NO as molecular parameters[14]. Through this research, it is hoped that new scientific evidence can be found regarding the potential benefits of Orthosiphon aristatus in managing atopic dermatitis, providing a safer and more natural alternative treatment for individuals with this condition.

METHOD

In this study, a total of 36 BALB/C mice aged 6 weeks and weighing between 15-20 grams were used. The mice were housed in cages under specific conditions, including a room temperature of 22 ± 2°C, humidity ranging from 40-60%, and a 12:12 hour dark-light cycle. They were given unlimited access to food and water throughout the experiment. Before starting the experiment, the hair on their backs was shaved to prepare for the application of the allergen.

To induce atopic-like lesions, the mice were treated with 200 µL of DNCB 1% daily for 7 days, followed by DNCB 0.5% three times a week for 2 weeks. This regimen aimed to mimic the characteristics of atopic dermatitis in the mice[16.]

For the treatment groups, the mice were orally administered Orthosiphon aristatus leaves extract once daily for a duration of 6 weeks. The extract was given at different doses: P1 (17.5 mg/kgbw), P2 (35 mg/kgbw), P3 (70 mg/kgbw), and P4 (140 mg/kgbw). The administration of the extract was carried out to assess its potential in improving the atopic-like skin lesions.

At the end of the study, on the 22nd day, the mice were sacrificed, and samples were collected from the heart blood and skin scrapping. These samples would be used for further analysis and evaluation of the effects of the Orthosiphon aristatus extract on the molecular and histological aspects of the atopic-like lesions.

With this method, the researchers can evaluate the potential of Orthosiphon aristatus extract in improving skin lesions in atopic dermatitis in a mice model. Blood sampling and skin scraping allow for further analysis to understand the effects of the extract at the molecular and histological levels. This will provide deeper insights into the extract's mechanism of action and its impact on inflammation, the production of pro-inflammatory molecules, and the histological changes associated with atopic dermatitis. Thus, this research can provide more solid evidence of the potential of orthosiphon aristatus as an alternative therapy for this condition.

RESULTS

Potential of Orthosiphon aristatus Extract in Alleviating Symptoms of Atopic Dermatitis

The study revealed that administering Orthosiphon aristatus extract for a duration of six weeks resulted in a notable decrease in the severity of AD-like signs and symptoms in the sensitized BALB/C mice group. The scores for skin lesions exhibited a significant reduction (P=0.000), indicating the effectiveness of Orthosiphon aristatus in alleviating the symptoms of atopic dermatitis in this experimental model (Figure 1).

These findings highlight the promising potential of Orthosiphon aristatus extract as a therapeutic option for individuals suffering from atopic dermatitis. However, it is important to note that further studies and clinical trials are necessary to validate these findings in human subjects.

Based on Figure 1, it can be seen that the Skin Lesion Severity Score indicates the severity of lesions in the research subjects. In this study, Orthosiphon aristatus was given to several observed groups, namely the Positive, Negative, P1, P2, P3, and P4 groups (Figure 2). Additionally, the Clinical Score was also used as an assessment indicator.

The research results show that the administration of Orthosiphon aristatus significantly reduces the severity of skin lesions compared to the control group. This indicates that Orthosiphon aristatus has the potential to reduce symptoms of atopic dermatitis.

Furthermore, the thickness of the epidermis also decreased according to the severity of the lesions after the administration of the extract (Figure 3). Eosinophil infiltration and mast cell counts showed a significant increase after DNCB sensitization. However, after the administration of Orthosiphon aristatus extract, the counts decreased. This improvement seems to occur in a dose-dependent pattern.

Figure 2 illustrates the measurements of epidermal thickness, eosinophil infiltration, and mast cell infiltration in the skin. Part A displays the staining using H&E (hematoxylin and eosin) and Toluidine Blue. Part B shows the quantification of epidermal thickness, eosinophil count, and mast cell count that have infiltrated the skin. It is important to note that the black rectangle represents the epidermal thickness, the yellow arrows indicate eosinophils, and the black arrows indicate mast cells. The asterisk (*) indicates a statistically significant difference (P<0.05) compared to the positive control group.

Effect of Orthosiphon aristatus on Reducing Serum Levels of IgE and Th2-Related Cytokines

Orthosiphon aristatus, also known as cat's whiskers, has been proven to have effects on reducing serum levels of IgE and TH2-related cytokines. In a study conducted on sensitized BALB/C mice with DNCB, it was found that the levels of IL4, IL22, and serum IgE increased significantly. However, after administration of Orthosiphon aristatus extract, there was a significant decrease in these molecules. It is important to note that this reduction is dose-dependent. In this study, a dose of 17.5 mg/kg/w was sufficient to reduce serum levels of IgE and TH2-related cytokines. However, the most effective dose was seen at 140 mg/kg bw.

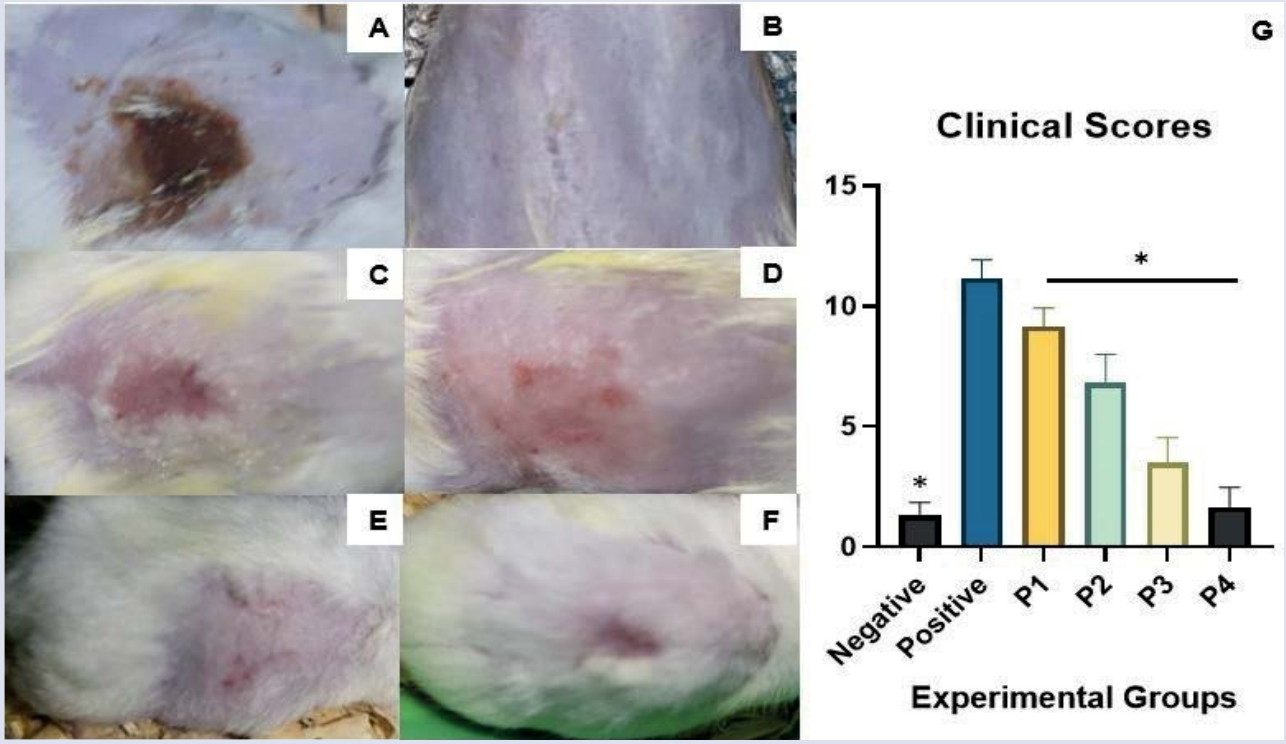

Figure 1: Orthosiphon aristatus Reducing Skin Lesion Severity.

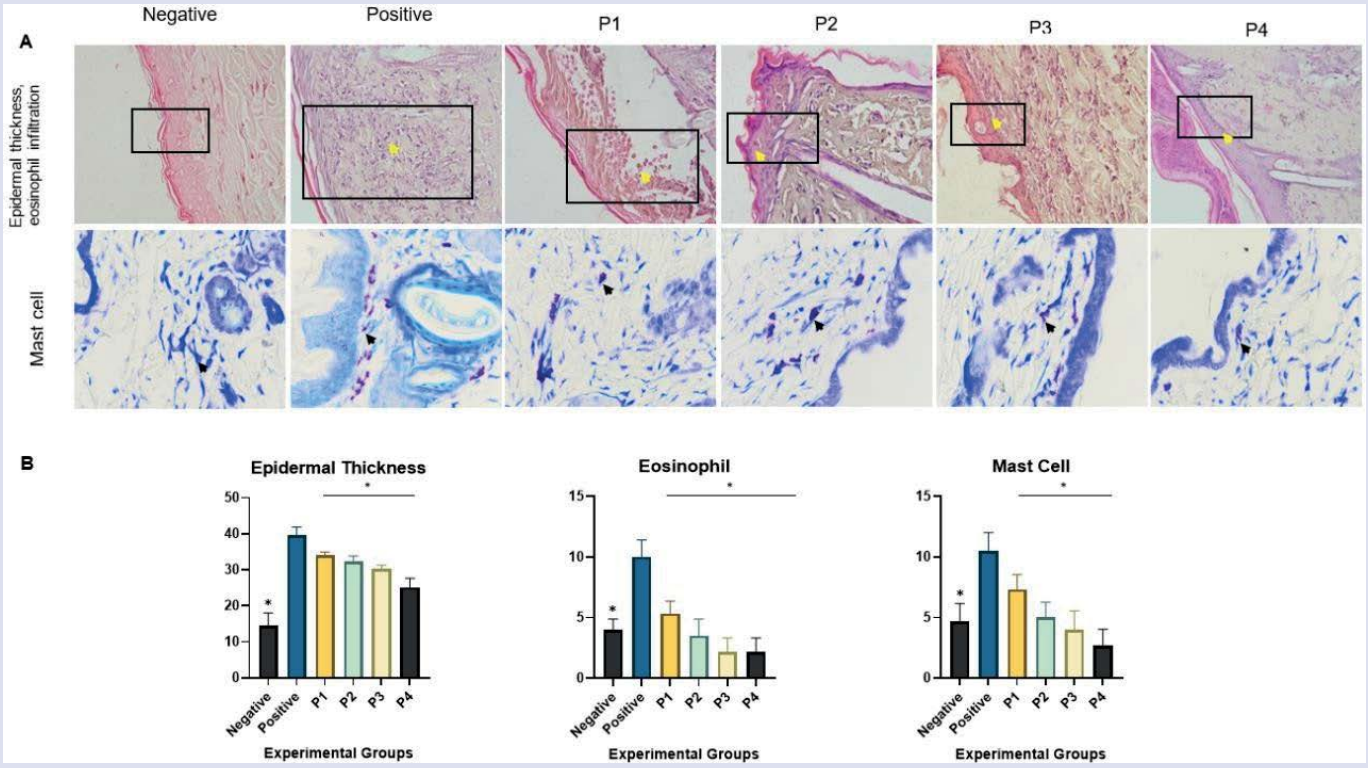

Figure 2: Measurement of Epidermal Thickness and Infiltration of Eosinophils and Mast Cells in Atopic Dermatitis.

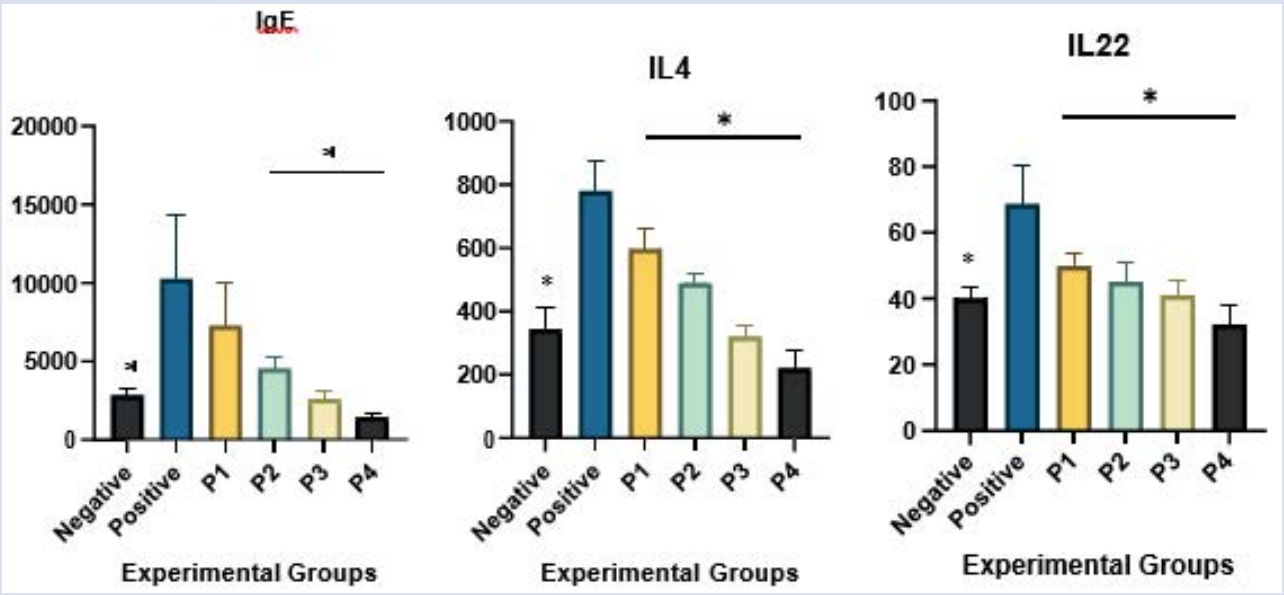

Figure 3. Serum Levels of IgE, IL4, and IL22. *P<0.005 with positive control group.

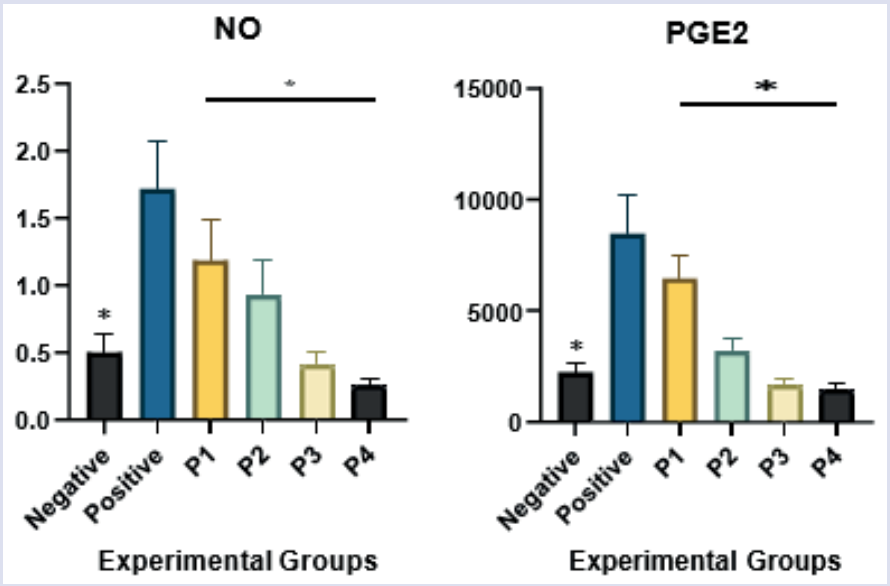

Figure 4. Serum Levels of NO and PGE2. *P<0.05 with positive control group.

These findings indicate the potential of Orthosiphon aristatus as an anti-inflammatory and immunomodulatory agent. The decrease in serum levels of IL4, IL22, and IgE suggests that Orthosiphon aristatus extract can inhibit excessive immune responses associated with allergies and inflammation. This suggests the potential use of Orthosiphon aristatus in the treatment of allergic conditions or TH2-related immune disorders.

Effect of Orthosiphon aristatus on Reducing Serum PGE2 Levels

Orthosiphon aristatus, also known as cat's whiskers, has been proven to have a positive effect on reducing serum levels of PGE2 in BALB/C mice with DNCB-induced atopic dermatitis. This study demonstrates that in the condition of atopic dermatitis, there is an increase in serum levels of PGE2 and NO in mice. However, administration of Orthosiphon aristatus extract has been shown to effectively reduce serum levels of PGE2 and NO. This effect is dose-dependent, where higher doses of the extract result in a more significant reduction in serum levels of PGE2 and NO.

These results suggest that Orthosiphon aristatus has potential as an anti-inflammatory agent, as reduced serum PGE2 levels indicated reduced inflammation in mice with atopic dermatitis. PGE2 is a prostaglandin involved in the inflammatory process, and reducing PGE2 levels may help reduce the symptoms and severity of atopic dermatitis.

DISCUSSION

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by symptoms such as pruritus (itching), erythematous

lesions (redness) during the acute phase, and lichenification (hardening of the skin)[17,18]. In this study, we focused on the development of atopic skin lesions in mice sensitized to DNCB (2,4-dinitrochlorobenzene). Interestingly, administration of Orthosiphon aristatus leaf extract has been proven to relieve these symptoms. Previous studies have shown that mice with AD experience dermis and epidermis hypertrophy, hyperkeratosis, and immune cell infiltration[19,20]. Thickening of the epidermis in AD is caused by abnormal proliferation and differentiation of keratinocytes, as well as infiltration of immune cells[18].

In previous research, the anti-proliferative effects of Orthosiphon extract have been demonstrated through increased tumor cell necrosis and decreased expression of the proliferation protein Ki67 compared to the untreated group[21]. This study also showed a decrease in immune cell infiltration[22] . In this study, a decrease in eosinophil infiltration can be observed after administration of Orthosiphon aristatus extract. Additionally, the number of mast cells in the rat group with atopic dermatitis (DA) significantly increased compared to the negative control group, but decreased after extract administration. These findings indicate that Orthosiphon aristatus leaf extract may have beneficial effects on DA by reducing epidermal thickening, immune cell infiltration, and mast cell activation.

Orthosiphon aristatus, also known as Java tea, has been proven to have anti-allergic effects. Mast cells play a role in the pathophysiology of atopic dermatitis, both in the acute and chronic phases. Mast cells release cytokines to initiate an immune response and disrupt the integrity of the skin barrier, such as keratinocyte proliferation and filaggrin degradation[18, 23]. To determine the beneficial effects of Orthosiphon aristatus at the molecular level, serum levels of IgE, IL22, IL4, PGE2, and NO were measured. All of these contribute to the breakdown of the skin barrier through inflammation and oxidative stress[3,4]. Evidence shows that serum levels of IgE, IL22, IL4, PGE2, and NO decrease after administration of Orthosiphon aristatus extract. This is the first study to demonstrate the beneficial effects of Orthosiphon aristatus on allergy, inflammation, oxidative stress, and skin lesions through the regulation of IgE, IL4, PGE2, NO, and IL22.

Orthosiphon aristatus is an important herbal medicine, with more than 20 phenolic compounds detected, including caffeic acid, rosmarinic acid, sinensetin, eupatorium, and polymethoxyflavones[12,24]. The beneficial effects of phenolic compounds in Orthosiphon aristatus include antioxidant[25], antibacterial[26], antifungal[27], antidiabetic[28], anti-inflammatory[15], antimutagenic[29], and anti-arthritic properties[30]. A study using a 200μg extract showed inhibitory effects on TPA (tetradecanoylphorbol)-induced inflammation in rats[31]. Another study showed that Orthosiphon aristatus extract reduced NO production and increased arachidonic acid oxidation in LPS-activated J774.1 macrophage-like cells, as well as inhibitory effects on 15-lipoxygenase with an IC50 value of 0.018% (w/v), in a dose-dependent manner compared to quercetin (positive control)[32]. Furthermore, its antioxidant activity based on the autoxidation mechanism of linoleic acid-paired β-carotene is comparable to quercetin and butylated hydroxyanisole[33]. Another study identified the mechanism of inhibiting NO, PGE2, and ROS production, including iNOS and COX-2 gene expression, in LPS-stimulated RAW 264.7 cells[15].

The results of this study support the beneficial effects of phenolic compounds in Orthosiphon aristatus. Previous studies have shown that phenolic compounds in Orthosiphon aristatus extract have anti-inflammatory, antimutagenic, and antioxidant properties. This study adds evidence that Orthosiphon aristatus extract also has inhibitory effects on skin inflammation. Histologically, administration of Orthosiphon aristatus extract reduced epidermal thickness and mast cell infiltration in skin lesions. This indicates that the extract can reduce inflammation occurring on the skin[34]. Additionally, this study also found that administration of Orthosiphon aristatus extract resulted in a dose-dependent decrease in IgE, IL4, IL22, and PGE2 levels. This suggests that the extract also has inhibitory effects on allergic responses and the production of substances involved in inflammation.

Thus, the results of this study attribute the inhibitory effect of skin inflammation to the phenolic compounds contained in Orthosiphon aristatus. This provides a scientific basis that supports the use of Orthosiphon aristatus as a herbal medicine to reduce skin inflammation and inhibit allergic reactions.

CONCLUSION

This study is the first report on the therapeutic effects of Orthosiphon aristatus leaves on atopic dermatitis using a mice model with lesions similar to DNCB-induced atopic dermatitis. The study found that administration of Orthosiphon aristatus extract clinically and histologically had an antiatopic effect, which could be explained through the regulation of molecules such as IgE, IL4, IL22, PGE2, and NO. These findings suggest that Orthosiphon aristatus has potential as a valuable herbal therapy for treating atopic dermatitis.

DECLARATION OF INTEREST

The authors declare that we have no conflict of interest regarding the research conducted or the publication of these findings. This means that we have no personal or financial relationships that could potentially bias the results or influence the interpretation of the study. By declaring no conflict of interest, this ensures the integrity and credibility of this research.

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