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Treatment of Atopic Dermatitis From the Perspective of Traditional Persian Medicine: Presentation of a Novel Therapeutic Approach

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Abstract

There is a strong current trend for using complementary and alternative medications to treat atopic dermatitis. Atopic dermatitis is a common, chronic, pruritic, and inflammatory skin disease. It can have a profound, negative effect on patients' quality of life. Mild cases of atopic dermatitis can be controlled by the application of moisturizers and topical corticosteroids. However, in severe cases, application of immunosuppressive medication is unavoidable but it can have adverse effects. In traditional Persian medicine, diseases similar to resistant atopic dermatitis are treated with whey in combination with decoction of field dodder. Both whey and field dodder have anti-inflammatory properties. Consumption of whey can also aid skin repair, mitigate pruritus, and help combat the high level of stress experienced by patients. Therefore, it is hypothesized that consumption of traditional medicinal treatment of whey with decoction of field dodder can be applied as a complementary treatment for atopic dermatitis.

Keywords

traditional medicine, atopic dermatitis, whey, field dodder

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Atopic dermatitis is a chronic and pruritic inflammatory skin disease characterized by exacerbation and remission of symptoms. Pruritus is a characteristic feature of atopic dermatitis that can be followed by disease flare-up and secondary infection through creating a vicious cycle of pruritus-scratching. Pruritus can flare up both in affected areas of the skin and in seemingly healthy regions.[1,2]

Atopic dermatitis has a relapsing and chronic pattern. Clinical manifestations can be different, but diagnosis is usually based on Hanifin and Rajka criteria.[3] Atopic dermatitis usually emerges during infancy or childhood, but it can continue through to adulthood or its onset may be in adulthood. Atopic dermatitis has different patterns according to different age of onset. In infants, it is usually manifest as exudative erythematous papules and vesicles with severe pruritus in the face and scalp. From the age of 2 years until puberty, the disease pattern varies and exudative lesions are replaced by papules and chronic lichenified plaques affecting mostly hands, feet, popliteal and ante cubital areas, knees, and wrists. In adults, the most commonly affected areas are hands, feet, fingers, toes, face, neck, flexural folds, arms, and the back. Evidence has shown that before the emergence of atopic dermatitis, there is atopy and the disease can be accompanied by other atopic diseases such as asthma and allergic rhinitis.[4-6] Less than half of children suffering from atopic dermatitis may be in complete remission by the age of 7 years; however, at most 60% of patients recover by adulthood, demonstrating the chronic nature of the disease.[7]

Atopic dermatitis is a chronic disease and as such it has a profoundly unpleasant impact on quality of life among people suffering from the condition.[5,8] Pruritus and skin lesions disrupt sleeping patterns and affect social performance of patients, and unsightly skin lesions can cause patients to isolate themselves from other people.[9,10]

Prevalence of atopic dermatitis has become 3-fold since 1960. Atopic dermatitis is a general public health problem and affects more than 20% of children and 3% of adults.[2,11] The female-to-male ratio for incidence of the disease is 1/3 to 1.[5] Research has shown that prevalence of atopic dermatitis is over

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10% in developing countries. This figure is increasing, but it has reached a constant level of about 20% in developed countries.[12]

In the United States, the annual cost of medication and medical care spent controlling this disease amounts to approximately US$1 to 4 billion. This value does not include significant indirect costs related to loss of working hours for patients.[13]

Atopic Dermatitis and Complementary and Alternative Medicine

Pathophysiology of Atopic Dermatitis

Skin dryness and pruritus are 2 characteristic features of atopic dermatitis. Atopic dermatitis occurs in individuals who are genetically predisposed. Genetic studies have noted the role of epidermal differentiation complex in atopic dermatitis.[14] In addition, mutations in the filaggrin gene, related to an important protein in the structure of epidermis, have also been observed.[15,16] The amount of endogenic proteolytic enzymes in the skin increases in people suffering from atopic dermatitis. The skin faces decreased amounts of ceramides in both affected and unaffected areas. Ceramides are the main water-preserving molecules within the extracellular space in the cornified layer.[17] These aforementioned skin conditions result in skin dryness that then allows pathogens, antigens, and irritants to enter the body through microscopic pores leading to inflammation and infection.[18,19] Furthermore, dysregulation of the immune system occurs particularly in 2 main subgroups of CD4+ cells, T-helper 1 and T-helper 2.[2] The number of blood eosinophils increases. In the allergic or extrinsic type accounting for 70% to 80% of the cases, patients have high levels of serum IgE. However, in 20% to 30% of patients, there is no significant increase in the level of IgE, and accordingly, it is termed as nonallergic or intrinsic-type atopic dermatitis.[19] The intrinsic type can be a harbinger of extrinsic atopic dermatitis.[20]

In this disease, disorders in the immune system lead to problems related to skin barrier function. These problems themselves bring about further problems that culminate in an abnormal response to irritants, allergens, and microbial organisms.[2,21]

Treatment of Atopic Dermatitis in Modern Medicine

Atopic dermatitis has an exacerbating-remitting pattern that varies from one patient to the next. In modern medicine, the major objective is to reduce intensity and frequency of disease flare-ups, for which different pharmacological and nonpharmacological methods are used.[2] The first line of defense is to detect irritant factors and avoid them.[1] Preventive treatment can reduce disease episodes through proper skin humidification. This is managed by relieving itching and thereby disrupting the vicious cycle of pruritus-scratching.[22,23] Application of a humid bandage, immersion in a warm water bath for a short period, application of hydrophilic ointment, and restorative ceramide-rich covers are examples of appropriate treatments.[24-26]

Topical corticosteroid medication is commonly applied to treat atopic dermatitis, but can have side effects; hence, many physicians prefer to prescribe such medication only in cases of an acute attack.[27,28] However, pharmacological studies have shown that there is potential for systemic absorption, even in weak topical corticosteroids.[29,30]

Calcineurin inhibitors are also effective by inhibiting T cells and mast cells.[31,32] Although tacrolimus ointment and pimecrolimus cream are both effective and particularly useful in individuals unable to tolerate other topical treatments, they have numerous complications and long-term safety has not yet been proven.[33,34]

Sedative antihistamines are used as an auxiliary medication mainly applied to relieve sleep disturbance caused by pruritus.[35,36]

Severe and resistant cases of atopic dermatitis may require systemic treatment such as administration of oral steroids, cyclosporine, mycophenolate mofetil, azathioprine, methotrexate, or interferon. Phototherapy can also provide therapeutic response in such cases. However, numerous investigations have been done to determine the effectiveness and identify complications of these treatments, and results have shown that they do not necessarily have suitable efficacy long term and can have serious unwanted side effects.[22,37-41]

In summary, there is no definite treatment for atopic dermatitis in modern medicinal practice, and disease control is based on identification and avoidance of factors that stimulate a flare-up, sufficient hydration of the skin, control of pruritus and infection, and proper usage of topical corticosteroids in mild cases. Severe and resistant cases are often treated with immunosuppressive medication.[1] Due to numerous adverse effects associated with immunosuppressive drugs, safer therapeutic treatment is required. Nowadays, there is a strong tendency toward complementary therapeutic methods for treating atopic dermatitis.[42] Traditional Persian medicine is a complementary medicine that presents an effective treatment. Among these traditional Persian medicinal treatments is whey with the decoction of field dodder, used to treat skin diseases with symptoms similar to atopic dermatitis.[43-46]

Atopic Dermatitis From the Traditional Medicine Perspective and Its Treatment

In traditional Persian medicine, *Ghouba* disease is cited as having symptoms, types, and a clinical course very similar to atopic dermatitis. Among different types of *Ghouba*, melancholic *Ghouba* is very similar to chronic and resistant atopic dermatitis. In traditional medical texts, *Ghouba* has been defined as a kind of roughness apparent in the skin, which accompanies severe pruritus that is first manifest as small and slightly hard papules that produce discharge after being scratched and that then spread across the body. The margin of lesions is slightly lumpy, where some circular thin scales like fish scales might

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become detached from a lesion. *Ghouba* can be accompanied by discharge or have no discharge; it can cause burning sensation or have no burning sensation, desquamation of the skin or not, and the condition may be progressive, acute, or chronic. *Ghouba* has 3 types: bloody, phlegmatic, and melancholic. Lesions are red, white to red or yellow, and dark in bloody, phlegmatic, and melancholic types, respectively. Bloody and phlegmatic type lesions improve faster than melancholic ones. Scratching induces secretion in the bloody type. When lesions are dry with no discharge, they are mostly melancholic. The worst and most chronic form is melancholic; this type of lesion is dark, lumpy, and rough.[43-46]

Ghouba has 3 stages: initially, the causative agent is only subcutaneous, and the condition may heal easily. In the second stage, the causative agent penetrates to deeper regions resulting in delayed recovery. In the third stage, whereby the agent has spread, it is problematic to heal and can become chronic, particularly when the agent is melancholic. Traditional medicine attributes such conditions to consumption of certain types of food such as fish, beef, banana, mango, and eggplant.[43,45]

In traditional medicine, blood donation, avoidance of its developing factors, short but frequent warm-water baths, and application of topical medicines after bathing can be useful to treat *Ghouba*. In both secreting and dry lesions, topical drying agents and moisturizers can be used, respectively.[43-46]

In terms of symptoms, bloody and phlegmatic types of *Ghouba* have great similarity to childhood- and adolescence-onset of atopic dermatitis, but the melancholic type is more similar to chronic and resistant atopic dermatitis. Traditional medical texts mention that chronic and melancholic *Ghouba* require identical treatment. One treatment that is emphasized in traditional Persian medicine is that of whey with a decoction of field dodder. In traditional medicine, application of whey has been highly recommended for hydration of the body and has been mentioned as the best medicine for melancholic diseases. Whey is of particular significance in the treatment of this disease because it has a high level of digestive absorption, lack of any side effect, aids in excretion of melancholy and body hydration, and provides fats that are essential to the body. Decoction of field dodder used with whey is among medicinal treatments commonly used to treat melancholic diseases.[43-46]

Whey

Whey is a by-product of cheese production. After adding rennet (chymosin) or organic acids (lactic, acetic, or citric acids) or mineral acids to milk, casein proteins are coagulated and separated to form crud, and whey is the yellow-greenish liquid remains of the process. This protein complex derived from milk contains valuable constituents.[47]

Whey has antioxidant, antitumor, antiviral, antibacterial, and antifungal properties and can reduce problems with blood pressure and hyperlipidemia. The beneficial effect of whey consumption for prevention and treatment of cardiovascular diseases, cancer, HIV, hepatitis B, and osteoporosis has been confirmed in clinical trials reported in various studies.[48]

Whey proteins contain essential amino acids in higher concentrations than plant proteins, so absorption is more effective compared with free amino acid solutions.[49,50] Whey is also rich in sulfur-containing amino acids such as cysteine and methionine that provide whey with antioxidant properties, because cysteine changes into glutathione, a potent intracellular antioxidant. This antioxidant activity has made whey an anti-ageing agent.[50,51] It has a high concentration of branched amino acids, valine, isoleucine, and in particular leucine. Leucine is an essential amino acid involved in the process of protein synthesis.[52]

Biological components of whey consist of β-lactoglobulin, α-lactalbumin, lactoferrin, lactoperoxidase, bovine serum albumin, glycomacropeptide, and immunoglobulins that support the immune system.[48]

Lactoferrin in whey is able to activate natural killer cells and neutrophils.[53-56] It has antiviral, antibacterial, antifungal, and anti-inflammatory properties.[57,58] α-Lactalbumin in whey can diminish oxidative stress by chelating heavy metals.[47,59]

Although investigations have shown that the components of whey have anti-inflammatory properties and help repair skin structure, no studies have evaluated the efficacy of whey on atopic dermatitis thus far.

Field Dodder

Field dodder, with the scientific name of *Cuscuta campestris* Yuncker and the traditional name *Aftimoun* is used to treat epilepsy, cancer, insanity, paralysis, and dermatological diseases in traditional medicine.[60] It is a parasitic plant belonging to the family Convolvulaceae. This family includes species such as *Cuscuta campestris*, *C. epithymum*, *C. chinensis*, and *C. reflexa*. Field dodder has the highest diversity among various *Cuscuta* species and can grow in various areas of the world.[61]

Field dodder is an annual parasitic plant. It has no leaves and chlorophyll.[62] This plant has anti-inflammatory, antiproliferative, and analgesic properties.[63] Quercetin and kaempferol flavonoids present in extract of field dodder seeds have immune-modulating and anti-inflammatory properties.[64] Based on studies, consuming dodder at the conventional doses has no complications, but its high dose may cause diarrhea or intestinal colic.[65] In modern phytotherapy, the average safe amount of field dodder for daily use has been mentioned to be 2 grams.[66] No research has been done to date on potential effects of field dodder on atopic dermatitis.

Discussion and Conclusion

Important pathophysiological dimensions of atopic dermatitis are dysregulation of the immune system and abnormal skin barrier function as a result of genetic and environmental factors. The water content of the cornified layer of the skin and superficial lipids, where ceramides are the main constituents, play an important role in skin appearance and function. Disruptions in the balance between these 2 constituents contribute to dryness of the skin.[17,19]

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Table 1. The Probable Mechanism of Action of Whey With Field Dodder Extract in Atopic Dermatitis.

	Components	Mechanism of Action	Efficacy in Atopic Dermatitis
Whey	Branched amino acids particularly leucine	Tissue regeneration and development	Improvement of skin lesions Modification of skin barrier function
	Lactoferrin; β-lactoglobulin; lactoperoxidase; lysozyme; anionic peptides; some free fatty acids	Antibacterial, antifungal, and antiviral properties	Reduction of secondary bacterial and fungal infections of lesions
	Lactoferrin	Regulation of TNF-α level	Decrease of inflammation
	α-Lactalbumin	Enhancement of serotonin level	Improvement of stress coping Inhibition of T cells and relief of pruritus
	Milk Basic Protein	Stimulation of osteoblast proliferation and differentiation	Reduction of the risk of osteoporosis and osteopenia development
Field dodder extract	Quercetin and kaempferol	Regulation of underlying inflammation factors such as inducible nitric oxide synthase and cyclooxygenase-2	Decrease of inflammation
	Quercetin	Inhibition of mast cell secretions Inhibition of the production of T-helper 2 cytokines	Reduction of flare-ups Decrease of inflammation

In atopic dermatitis, there is an abnormality in cornified envelope genes that contributes to reduce ceramide levels. Ceramides constitute a major part of cornified layer lipids and have an important role in preserving water at the extracellular space in this layer. The amount of endogenic proteolytic enzymes increases and this disrupts the skin barrier function and thus water loss through the skin is intensified. This induces skin dryness, generating microscopic breaks and pores through which pathogens, irritants, and allergens are easily absorbed into the skin, which causes inflammation and infection.[18]

In atopic dermatitis, dysregulation of the immune system exists particularly in 2 main subgroups of CD4+ T cells: T-helper 1 and T-helper 2 cells. Analysis of biopsies in patients suffering from atopic dermatitis indicates that T-helper 2 immune responses increase compared with responses in healthy skin.[67] In atopic dermatitis, treatment is comprehensive and complete when we consider pathophysiological aspects of this disease, dysregulation of the immune system, and disruptions in skin barrier functioning, simultaneously. Administration of whey with the decoction of field dodder has been widely used in traditional Persian medicine to treat *Ghouba* disease, a disorder very similar to atopic dermatitis in terms of symptoms, stages, and course of the disease.[43-46] Possessing unique characteristics, this medication may be effective in both improving skin barrier function and modification of disruption of the immune system (Table 1). Whey is a food supplement containing valuable components with important nutritional and biological properties. No severe adverse effects or complications have been reported for this substance so far. Whey is considered a highly nutritional material as it contains a wide range of essential and nonessential amino acids, biologically active proteins, minerals, and lipids.[48] It has a high concentration of branched amino acids particularly leucine, an important component in the process of tissue regeneration and development.[52] Therefore, it can aid improvement of skin lesions and modification of skin barrier function.

The skin's defense mechanism against various external factors such as transient pathogens has components including antimicrobial lipids such as sapienic acid and sphingosine and antimicrobial peptides such as β-defensins and cathelicidin.[68-72] The extent of these antimicrobial components is lower in the skin of patients suffering from atopic dermatitis compared with levels in healthy individuals. This contributes to higher incidence of secondary infection in skin lesions of atopic dermatitis patients.[68,69,73] Lactoferrin, β-lactoglobulin, lactoperoxidase, lysozyme, anionic peptides, and some free fatty acids in whey have antibacterial, antifungal, and antiviral properties.[74-77] This explains the effect of whey in reducing secondary bacterial and fungal infections of lesions in atopic dermatitis. Lactoferrin also has anti-inflammatory properties capable of relieving symptoms of the disease through regulation of tumor necrosis factor-α level elevated in atopic dermatitis, which initiates or contributes to inflammation.[58,78]

Atopic dermatitis is a disease in which relapse often occurs, and its chronic course and complications have a negative influence on the quality of life. Research has indicated that consumption of whey can enhance serotonin levels in the brain, thereby enabling patients suffering from atopic dermatitis to cope with the high level of stress associated with the disease.[79] Furthermore, serotonin has an immune-modulatory effect that inhibits T cells and relieves pruritus, one of the most annoying symptoms of atopic dermatitis.[80]

Whey contains Milk Basic Protein, which provides another advantage in controlling atopic dermatitis. Milk Basic Protein stimulates osteoblast proliferation and differentiation and is able to reduce the risk of osteoporosis and osteopenia development, usually caused by the inflammatory nature of the disease and long-term consumption of corticosteroids.[81,82] Studies have demonstrated that even substitution of whey for standard formula to feed infants with a positive familial history of atopic dermatitis can reduce the chance of developing further outbreaks of the disease.[83]

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Seeds of field dodder contain quercetin, kaempferol flavonoids and have been used in traditional medicine as a decoction to treat melancholic disease; these flavonoids have anti-inflammatory and antiproliferative properties.[84] Quercetin blocks the intermediates involved in allergies and can act as an inhibitor of mast cell secretion, a very important factor in the pathogenesis of atopic dermatitis attacks.[85] Quercetin and kaempferol flavonoids exert anti-inflammatory features by regulating underlying factors that cause inflammation such as inducible nitric oxide synthase and cyclooxygenase-2.[64] Nitric oxide derived from inducible nitric oxide synthase is involved in atopic dermatitis flare-ups and in pathogenesis of allergic rhinitis.[86] In atopic dermatitis, cytokines produced by T-helper 2 cells reduce the expression of skin barrier proteins.[87] Quercetin abundant in decoction of field dodder is able to present significant anti-inflammatory effects by inhibiting the production of cytokines from T-helper cells.[85] Recent research has shown that when field dodder seeds are used in decocted form, the heating process leads to significant elevation of quercetin levels compared with unheated seeds, and this serves to reinforce anti-inflammatory and antiproliferative properties of the substance.[88] Accordingly, it can be stated that field dodder can be advantageous in improving atopic dermatitis lesions by activating an inflammation-reducing mechanism. Consumption of therapeutic doses of field dodder has no adverse effects, but overdose can cause intestinal colic and diarrhea.[65]

It is hypothesized that consumption of whey, together with field dodder, can target important pathophysiological aspects of atopic dermatitis by reducing inflammation, aiding immunomodulation, improvement of skin lesions, and modification of skin barrier function. This combination can also be used as a complementary treatment for atopic dermatitis, with the least complications, for reducing intensity and frequency of attacks. It is suggested that efficacy of this medication be investigated by conducting clinical trials after preparation of standard formulations.

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Author Contributions

Dr Rasool Choopani conceptualized and planned the study and designed the protocol. Dr Mehrzad Mehrbani managed and collected the data. Drs Alireza Fekri, Mitra Mehrabani, and Mehrzad Mehrbani analyzed and interpreted the data. Dr Mehrzad Mehrbani wrote the manuscript, and Dr Rasool Choopani reviewed the article.

Declaration of Conflicting Interests

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Ethical Approval

Ethical approval was not required for this study as no human participants were involved.

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