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The efficacy of whey associated with dodder seed extract on moderate-to-severe atopic dermatitis in adults: A randomized, double-blind, placebo-controlled clinical trial

Mehrzad Mehrbani [a], Rasool Choopani [a,b], Alireza Fekri [c], Mitra Mehrabani [d,*], Mahmoud Mosaddegh [b,e], Mehrnaz Mehrabani [d]

[a] Department of Traditional Medicine, School of Traditional Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[b] Traditional Medicine and Materia Medica Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[c] Department of Dermatology, Afzalipour Hospital, Kerman University of Medical Sciences, Kerman, Iran
[d] Herbal and Traditional Medicines Research Center, Kerman University of Medical Sciences, Kerman, Iran
[e] Department of Traditional Pharmacy, School of Traditional Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

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ABSTRACT

Ethnopharmacological relevance: Atopic dermatitis is a common chronic inflammatory skin condition that is on the rise and adversely affects quality of life of the affected individual. Dry skin and pruritus, major characteristics of this disease, are associated with the dysfunction of the skin barrier. Though mild cases of the disease can be controlled with antihistamines and topical corticosteroids, moderate-to-severe cases often require treatment with immunomodulatory drugs, which have many side effects. It is now more common to use complementary and alternative medicines in the treatment of atopic dermatitis. In traditional Iranian medicine, the use of whey with the aqueous extract of field dodder (*Cuscuta campestris* Yunck.) seeds in severe and refractory cases of atopic dermatitis is common and has no side effects.

The aim of this study was to assess the efficacy and safety of whey associated with dodder seed extract in the treatment of moderate-to-severe atopic dermatitis in adults.

Materials and methods: The study was a randomized, double-blind placebo control trial that was conducted on 52 patients with moderate-to-severe atopic dermatitis for 30 days. In this study patients received freeze dried whey powder with spray dried water extract of field dodder or the placebo for 15 days. At baseline (week zero), after the end of the 15 day treatment period (week three) and 15 days after stopping the drug or placebo (follow-up/week five), patients were evaluated in terms of skin moisture, elasticity, pigmentation, surface pH and sebum content on the forearm with Multi Skin Test Center® MC1000 (Courage & Khazaka, Germany) and the degree of pruritus and sleep disturbance in patients were also recorded.

Results: 42 patients completed 30 days of treatment with the medicine and the follow-up period. At the end of the follow-up period a significant increase in skin moisture and elasticity in the group receiving whey with dodder was observed compared with the placebo group ($p < 0.001$). There was a significant difference between the two groups regarding the pruritus after 15 days of receiving treatment or the placebo ($p < 0.05$), and at the end of the 30-day study period the difference was clearly significant ($p < 0.001$). Sleep disturbance showed significant changes at the end of follow-up period ($p < 0.05$). There was no significant difference between the two groups concerning changes in skin pigmentation, however, a significant decrease was observed in the group receiving whey associated with dodder seed extract over time ($p < 0.001$). There were no significant alterations in skin surface pH and the amount of sebum between the two groups. Temporary side effects were reported including anorexia and mild gastrointestinal problems in drug use.

It is noteworthy that in this study despite the fact that patients received whey with dodder for just 15 days, moisture and elasticity of the skin continued to increase in the second half of the study (follow-up period). This shows that the effect of whey with dodder is not transient and this drug really helped skin barrier reconstruction and accelerated the healing process of skin. This positively influenced the skin parameters and consequently the improvement of pruritus and sleep disturbance.

* Correspondence to: Herbal and Traditional Medicines Research Center, Kerman University of Medical Sciences, Haft-bagh Ave., Kerman, Iran. Fax: +98 3432532452.
E-mail address: mmehrabani@hotmail.com (M. Mehrabani).

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Conclusions: The results indicate that whey associated with dodder seed extract can serve as a promising alternative for the treatment of moderate-to-severe atopic dermatitis.
Trial registration: Iranian Registry of Clinical Trials IRCT2013121415790N1.

1. Introduction

Atopic dermatitis (AD) is a common chronic inflammatory and pruritic skin disease, often associated with a positive family history of allergic diseases, such as allergic rhinitis and asthma (Leung et al., 2004). The disease has a devastating effect on quality of life. The eczematous skin lesions with severe pruritus lead to disrupted sleep and decreased daily performance and social activities of patients in addition to significant financial expenses for both the families of patients and society, as well (Fivenson et al., 2002). AD affects 15–30% of children and 2–10% of adults (Bieber, 2008). Prevalence in developing countries is more than 10% in the general population and is increasing day by day, while in developed countries prevalence has reached a level plateau of approximately 20% (Kim, 2013). Atopic dermatitis occurs in those who are genetically predisposed. Mutations in the filaggrin gene, which is a key protein in formation of the skin barrier and skin moistening, lead to skin barrier dysfunction. Skin barrier damage increases transepidermal water loss and permits the entry of environmental antigens and allergens from the epidermis leading to inflammatory responses (Howell et al., 2009). Topical corticosteroids, emollients and oral antihistamines are used in mild disease without too many side effects, but many patients with moderate-to-severe atopic dermatitis require systemic immunomodulating treatment (e.g., cyclosporine, azathioprine, systemic corticosteroids and methotrexate) with unfavourable side effects (Hong et al., 2011; Roekevisch et al., 2014).

Since effective treatments for the disease are limited, there is a tendency toward finding better and safer therapies. Among them, the use of complementary and alternative medicines (CAM) is growing in the treatment of inflammatory skin diseases, particularly AD (Boneberger et al., 2010). Traditional Iranian Medicine (TIM), with a long history of several thousand years, offers effective treatments in this field with diet and lifestyle modification and drugs of a plant or animalistic origin. TIM recommends the use of topical emollients and wet compression in mild AD. In TIM, one of the most common treatments for chronic and severe cases of atopic dermatitis is the use of whey with the aqueous extract of field dodder seeds (Avicenna, 2005; Rhazes, 1990).

Whey is a protein complex derived from milk and considered a functional food. Whey has several properties as an antitumor, antihypertensive, hypolipidaemic, antiviral, antibacterial, anti-ageing and chelating agent. Whey possesses potent antioxidant activity as a result of intracellular conversion of the amino acid cysteine into glutathione, which is an intracellular potent antioxidant (Marshall, 2004). Whey's healing properties have been recognized since the 5th century BC and whey cure has been recommended by Hippocrates, Galen, Avicenna, Rhazes, and other famous names from the history of medicine. Whey has been used for medicinal purposes, including gout, sepsis, wound healing, as well as liver and stomach diseases (Avicenna, 2005; Rhazes, 1990; Smithers, 2008; Vasey, 2006).

Field dodder, with the scientific name of *Cuscuta campestris* Yuncker (Family Convolvulaceae) and traditional name of aftimoun, is a parasitic plant without leaves, yellowish green stems climbing the winder and sweet-scented white flowers (Fernald, 1970). Different *Cuscuta* species are widely used as medicinal plants in traditional medicine in the treatment of epilepsy, psychosis, paralysis, cancer, skin diseases, etc. (Aghili Khorasani, 2011a). *C. campestris* Yunck. is the most widespread species in the genus *Cuscuta* in the world (Holm et al., 1997). This plant has analgesic, hypothermic, anti-inflammatory, anti-proliferative effects and CNS depression activity (Agha et al., 1996). *Cuscuta* seed extract contains a variety of flavonoids, polysaccharides, alkaloids and other chemicals. Among the flavonoids, quercetin is a therapeutic compound for inflammatory and autoimmune diseases with immunomodulating effects (Lee et al., 2011).

The aim of this study was to assess the efficacy and safety of whey associated with dodder seed extract (WaDSE) in the treatment of moderate-to-severe atopic dermatitis in adults that was conducted as a randomized, double-blind, placebo-controlled trial.

2. Materials and methods

2.1. Patients

52 patients with moderate-to-severe atopic dermatitis referred to the Dermatology Clinic of Afzalipour Hospital, Kerman University of Medical Sciences, Iran, have entered into the trial after the confirmation of diagnostic criteria for atopic dermatitis (Hanifin and Rajka, 1980). Inclusion criteria were as follows:

- Hanifin and Rajka criteria approved for atopic dermatitis.
- Moderate-to-severe atopic dermatitis (SCORAD $\geq$ 25).
- Aged 18 and older.
- Poor response to conventional treatment for atopic dermatitis (topical steroids and antihistamines).
- AD consistently symptomatic for at least six months.
- Lack of exudates or infection.
- Lack of pregnancy and lactation.
- The absence of concomitant systemic disease (except asthma and allergic rhinitis).

Patients with abnormalities in blood cell count, liver enzymes and renal function tests, secondary bacterial infections, who were receiving systemic corticosteroids and other immunosuppressant drugs and phototherapy during the study or who demonstrated drug intolerance symptoms were excluded.

Prior to intervention, informed written consent was obtained from all patients and patients in both groups were asked to continue previously received topical steroids with the same strength and frequency. This study was approved by the Medical Research Ethics Committee, Shahid Beheshti University of Medical Sciences.

2.2. Drug and placebo preparation

In traditional medicine, field dodder seed is used in the treatment of chronic atopic dermatitis as a decoction associated with whey. In this study, dosage form change was necessary for uniformity and ease of use. Thus, a powder form of whey was prepared, and as the dodder seed decoction has a bitter taste, dried aqueous extract was prepared and administered in capsule form.

2.2.1. Whey

In traditional medicine, whey is produced using three methods:

(1) the use of rennet, (2) the use of vinegar, (3) the use of oxymel (Aghili Khorasani, 2011b). The second method was used in this study as it is quick and easy. For this purpose, whole cow milk was boiled and 18 g of pure vinegar per kilogram of milk was added. After the curds appeared, they were isolated using fine filters. Casein and whey, major milk proteins with different properties, account for approximately 80% and 20% of milk proteins, respectively (Shah, 2000). The curds consist mainly of casein while whey remains in the aqueous environment. Unlike casein, whey proteins are not coagulated in the acidic environment of the stomach and are quickly absorbed when they reach the intestines (Boirie et al., 1997). As there are heat-sensitive protein structures in the liquid whey, the freeze drying technique was used to convert it into a powder form. In order to standardize, the amount of total protein was measured by the biuret method (Goyal and Gandhi, 2009) and found to be equal to 33 ± 1% (w/w) dry weight. As the therapeutic dose of liquid whey in atopic dermatitis is 450 ml per day (Aghili Khorasani, 2011b), its average dry weight was determined as equal to 30 ± 1.5 g (mean ± SD, $n=3$). Thus, the daily intake of whey powder was defined as 30 g. The produced powder was packed into 15 g vacuum-sealed bags.

2.2.2. Dodder seed extract

C. campestris Yunck. plants (field dodder) grown on *Alhagi persarum* (camel thorn) were collected from the unutilized lands around the city of Kerman, Iran (located at latitude 30°15′N and longitude 57°01′E) in August 2013. The sample was authorized and kept at the Faculty of Pharmacy herbarium, Kerman University of Medical Sciences, by Dr. Mitra Mehrabani (Voucher specimen No. 2002). Plant material was separated from camel thorn, cleaned, dried under shade and pulverized to pass a 40 mesh sieve. Aqueous field dodder seed extract was prepared according to traditional methods (Aghili Khorasani, 2011a). The plant seeds were poured into boiling water and put on medium heat for 20–30 minutes to be decocted and were then filtered. The aqueous extract obtained was dried using the spray drying method. Standardization was done using the rutin flavonoid (quercetin-3-rutinoside) measurement by ultraviolet–visible spectrophotometry, which was equivalent to 11.5 ± 1.5% (w/w) (Harborne, 1998). The spray dried extract was filled in 500 mg capsules. As the average daily use of dodder seeds is 12 g (Aghili Khorasani, 2011a), dry weight of the aqueous extract was measured; the mean value was 2000 ± 500 mg (mean ± SD, $n=3$) and the daily dosage was defined as four 500 mg capsules. For each patient, in order to cover the 15 day trial period, packages containing 30 packets of 15 g of whey powder and 60 dried extract 500 mg capsules were prepared.

2.2.3. Placebo

To prepare a placebo similar to whey in terms of colour, shape, smell and taste, corn starch, cornmeal and lactose in the ratio 6:1:1 were used. The placebo 500 mg capsules were filled with corn starch. Packaging was the same as the original drug. This placebo does not have a known effect on atopic dermatitis.

The drug and placebo were supplied in the School of Traditional Medicine, Kerman, Iran and all products were controlled in the Microbial Control Laboratory of the faculty for possible microbial contamination before use. In order to fingerprint every batch produced, the whey powder was measured using the biuret method for total protein, and in the case of the dried dodder extract, TLC (thin-layer chromatography) was used (Goyal and Gandhi, 2009; Harborne, 1998).

Patients were instructed to prepare the medicine by mixing a 15 g packet of powder in 200 ml of warm water and consuming it with two capsules twice a day 30–60 min. before eating breakfast and dinner.

2.3. Assessment

Patients were randomized into two treatment and placebo groups and received WaDSE or a placebo for 15 days. Five variables were analysed, including skin moisture, elasticity, pigmentation, sebum and surface pH using Multi Skin Test Center® MC1000 (Courage & Khazaka, Germany) with Complete Skin Investigation (CSI) software. The device uses specific probes for measuring skin parameters and makes it possible to assess, compare and quantitatively analyse changes of biophysical skin conditions related to atopic dermatitis during the treatment process. The Corneometer probe measures electrical capacitance of the skin surface for evaluating moisture. The Sebumeter probe estimates sebum secretion on skin with a photometric method which is independent of moisture. The Pigmentation measurement probe works based on the absorption principle. This probe emits light of a defined wavelength that is absorbed by the melanin, then the receiver measures the amount of light reflected from the skin. Recorded values of moisture, sebum and skin pigmentation are expressed as arbitrary units (AU) on a scale from 0 to 99. In order to measure the elasticity of the skin by the suction method, the skin is sucked by a special probe under a negative pressure of 400 mbar for three seconds and, after stopping the negative pressure, the skin is released by the probe within the next three seconds. With this method, the amount of skin resistance to pressure in relation to its ability to return to its original position is expressed as a percentage, where a higher percentage represents healthier skin. The pH meter measures skin surface pH using a glass electrode. The advantage of this method is to minimize the possibility of human error in estimating skin barrier function and the severity of skin changes, using non-invasive bioengineering methods (Knor et al., 2011; Sator et al., 2003).

In this study, the primary outcome variables were measured using the device mentioned above by a physician at three points of the anterior forearm and the average was calculated. The patients were also asked to report pruritus and sleep disturbance due to itching over the preceding three days depending on the severity of symptoms from zero to 10 (zero indicates absence and 10 represents the maximum value) to be included as the secondary outcome variables (The European Task Force on Atopic Dermatitis, 1993). These assessments were carried out in all patients upon admission (week zero), 15 days after receipt of the drug (week three) and 15 days after the end of the treatment for follow-up (week five).

2.4. Sample size

Based on statistical calculations with the default power $(1-\beta)$ 0.95, type I error (α) 0.05, 20% improvement in drug efficacy variables $(\bar{X}_1 - \bar{X}_2)$ and the group variance (S_1 and S_2) about 25%, and with the overall sample size formula

$$n = \frac{\left(S_1^2 + S_2^2\right)\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2}{\left(\bar{X}_1 - \bar{X}_2\right)^2}$$

the estimated sample size was 40 subjects. With a 30% possibility of withdrawal rate, a sample size of 52 patients (26 patients in the medicine group and 26 patients in the placebo group) was considered.

2.5. Randomization and blinding

Using the randomization table designed by an independent statistician, random numbers successively were assigned to the patients and they were equally randomized into two groups. All

patients were informed they may be allocated to the drug or placebo group. In this study, the evaluating physicians had not been in contact with the statistician and clinical pharmacist and were kept blinded to allocation. Patients were also unaware until the study was completed that they had received the drug or a placebo.

2.6. Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS), version 16. Continuous variables were expressed as mean ± SEM.

In the case of each variable, a *t*-test was conducted in order to determine whether there is a significant difference between the drug and placebo groups. Repeated measures ANOVA was used for analysis between and within the groups at weeks zero, three and five. The level of significance was established at 0.05.

3. Results

3.1. Patient enrolment and/or exclusion

A total of 52 patients participated in the study from February to July 2014, 26 patients were randomized in the placebo group and 26 patients in the treatment group. During the 30-day study, 10 patients (two patients in the treatment group and eight patients in the placebo group) were excluded from the study population for the following reasons: within the first 15 days of study, one in the treatment group and three in the placebo group were excluded because of poor compliance and one in the treatment group due to use of prohibited drugs. During the second half of the study period, five patients in the placebo group (one due to disease progression and four due to being busy) refused to continue with the follow-up and were excluded.

The number of patients who completed the study and were analysed was 42 (87%), 24 and 18 patients in the treatment and placebo groups, respectively. This information is summarised in the flowchart shown in Fig. 1.

Table 1 shows the baseline characteristics of the groups. There was no significant difference between the treatment and placebo groups in terms of age, sex, AD family history and duration of disease. In addition, there was no significant difference between the treatment and placebo groups at baseline in terms of skin moisture, elasticity, pigmentation, pH and sebum content.

3.2. Efficacy

The efficacy outcomes are shown in Table 2 and Fig. 2. At the end of the 30-day period of study, in terms of the primary outcome, the value of skin moisture and elasticity variables in the group receiving WaDSE was clearly significant compared to that of

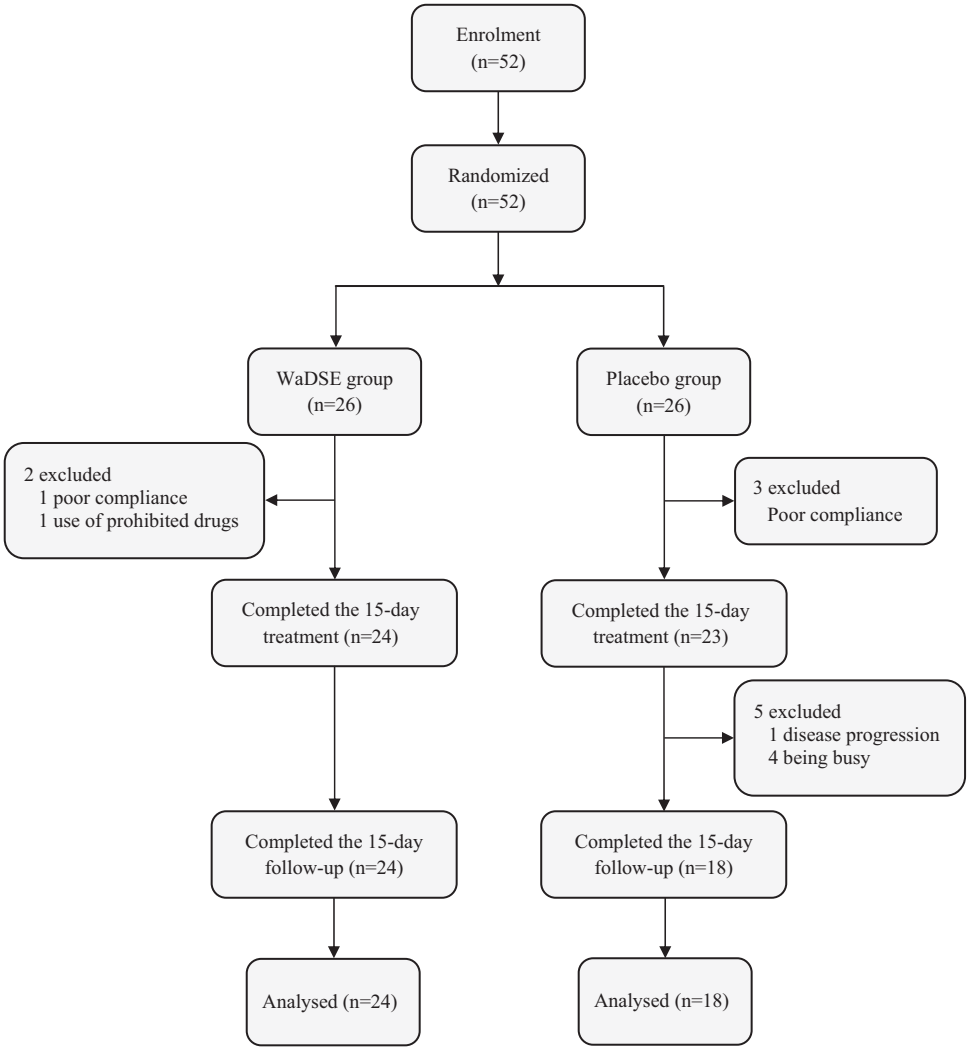

Fig. 1. Enrolment, randomization and treatment flowchart.

Table 1
Baseline characteristics of patients.

Variable	WaDSE	Placebo	*p*-Value
Gender (female)[a]	20 (83.3)	16 (88.8)	0.621
Age (years)[b]	28.62 ± 2.30	24.33 ± 1.50	0.155
Duration of AD (years)[b]	13.45 ± 1.82	12.77 ± 2.09	0.760
Positive familial history of AD[a]	11 (45.8)	8 (44.4)	0.931
Skin moisture[b]	13.43 ± 2.08	19.72 ± 2.59	0.063
Skin elasticity[b]	56.04 ± 5.32	61.73 ± 5.76	0.476
Skin pigmentation[b]	22.66 ± 1.64	23.15 ± 2.42	0.864
Skin surface pH[b]	5.80 ± 0.10	5.70 ± 0.11	0.546
Skin sebum[b]	0.87 ± 0.25	1.03 ± 0.41	0.725
Pruritus[b]	5.70 ± 0.45	4.72 ± 0.39	0.122
Sleep disturbance[b]	2.41 ± 0.57	1.61 ± 0.24	0.255

Abbreviations: WaDSE, whey associated with dodder seed extract; AD, atopic dermatitis.

[a] Data presented as number of patients (percentage).
[b] Data presented as mean ± SEM.

the placebo group ($p < 0.001$). Moreover, with regards to within-group comparisons, within the group receiving WaDSE, the skin moisture and elasticity from the baseline values to the end of treatment significantly increased ($p < 0.001$). While, there was no significant change in terms of skin pigmentation between the two groups ($p = 0.158$), in the WaDSE group skin pigmentation was reduced quite significantly with time ($p < 0.001$). There was no significant difference in skin surface pH and sebum between the two groups (p-Values are 0.757 and 0.443, respectively). Regarding the itching as a secondary outcome, after 15 days of receiving the medicine or the placebo a significant difference between the two groups was created ($p < 0.05$), which was also significant at the end of thirty days ($p < 0.001$). Comparison of sleep disturbance showed significant changes between two groups ($p < 0.05$), and at the end of the study a considerable improvement in subjective sleep disturbance was demonstrated in the WaDSE group ($p < 0.001$).

3.3. Safety Profile

In the WaDSE group, 13 patients (54.1%) reported anorexia, and four patients (16.6%) reported mild gastrointestinal problems, such as dyspepsia and a feeling of heaviness in the stomach after administration of the drug. It is worth noting that all these side effects were temporary. Other important side effects were not reported. Abnormality in liver and kidney function tests, blood cell count, as well as changes in blood pressure and body weight were not observed.

4. Discussion

The current study indicated the prescription of whey associated with dodder seed extract to cause a clear and considerable increase of skin moisture and elasticity, decrease of pigmentation, reduced itching and improvement of sleep disturbance in patients with atopic dermatitis. Comparisons of mean ± SEM of patients receiving WaDSE revealed degrees of skin moisture and elasticity to be enhanced by approximately 100% and 40%, respectively.

An increase in elasticity, decrease in pigmentation, reduced itching and improvement of sleep disturbance occurring subsequent to reduced itching may be considered as a direct result of skin moisture enhancement. Notably, it can be said that although the patients received WaDSE only within the first 15 days of the study, skin moisture and elasticity continued to increase during the second half of the study (follow-up period). This result highlights that the effect of WaDSE is not transient; moreover, the drug actually contributes to the reconstruction of the skin barrier and is therefore effective in terms of the skin parameters by accelerating the trend of skin repair. Additionally, a decrease of skin pigmentation in patients consuming WaDSE proposes the efficacy of this drug in the improvement of post-inflammatory hyperpigmentation.

Skin barrier malfunctions caused by genetic and environmental factors, as well as immune system dysregulation is of the main pathophysiologic aspects of atopic dermatitis (Leung et al., 2004). Ceramide deficiency as the major component of stratum corneum lipids and the main retaining factor of extracellular space water leads to epidermal water loss. Consequently, skin dryness occurs, which involves numerous pores and cracks, and enables the penetration of pathogens, antigens and irritants, subsequently leading to infection and inflammation (Cork et al., 2006).

A wide range of essential and non-essential amino acids, minerals, lipids and biologically active proteins such as lactoferrin, beta-lactoglobulin, alpha-lactalbumin, glycomacropeptide and immunoglobulins exist in whey, giving it a high nutritional value (Walzem et al., 2002). Due to its rich protein content, whey provides the possibility for better skin repair and proper skin barrier function (MacKay and Miller, 2003). On the other hand, lactoferrin present in whey is involved in bacteriostatic, bacteriocidal and anti-fungal activities (Farnaud and Evans, 2003; Orsi, 2004), and indicates that whey consumption in AD patients can reduce secondary bacterial and fungal infections in skin lesions.

Studies demonstrated that the consumption of whey is associated with an increase in serotonin level, leading to an increased ability for coping with stress (Markus et al., 2002). This in turn can influence the promotion of psychological health among AD patients whose quality of life has been negatively impacted as a result of the long-term tendency of the disease and its complications

Table 2
Change in variables during the study period.

Variable	Week 3			Week 5		
	WaDSE Mean ± SEM	Placebo Mean ± SEM	*p*	WaDSE Mean ± SEM	Placebo Mean ± SEM	*p*
Skin moisture	20.97 ± 2.02	19.44 ± 2.44	0.629	29.91 ± 1.68	17.66 ± 2.20	< 0.001**
Skin elasticity	70.97 ± 4.29	63.48 ± 4.95	0.261	79.01 ± 2.96	59.30 ± 4.99	< 0.001**
Skin pigmentation	20.75 ± 1.63	23.31 ± 2.47	0.375	19.81 ± 1.54	23.82 ± 2.47	0.158
Skin surface pH	5.66 ± 0.10	5.74 ± 0.11	0.619	5.62 ± 0.07	5.66 ± 0.09	0.757
Skin sebum	1.20 ± 0.33	1.03 ± 0.40	0.753	1.22 ± 0.36	1.08 ± 0.41	0.799
Pruritus	2.75 ± 0.41	4.83 ± 0.45	0.002*	2.04 ± 0.32	5.38 ± 0.45	< 0.001**
Sleep disturbance	0.79 ± 0.26	1.50 ± 0.30	0.086	0.66 ± 0.20	1.77 ± 0.32	0.005*

Abbreviations: WaDSE, whey associated with dodder seed extract; SEM, standard error mean.

** $p < 0.001$.
* $p < 0.05$.

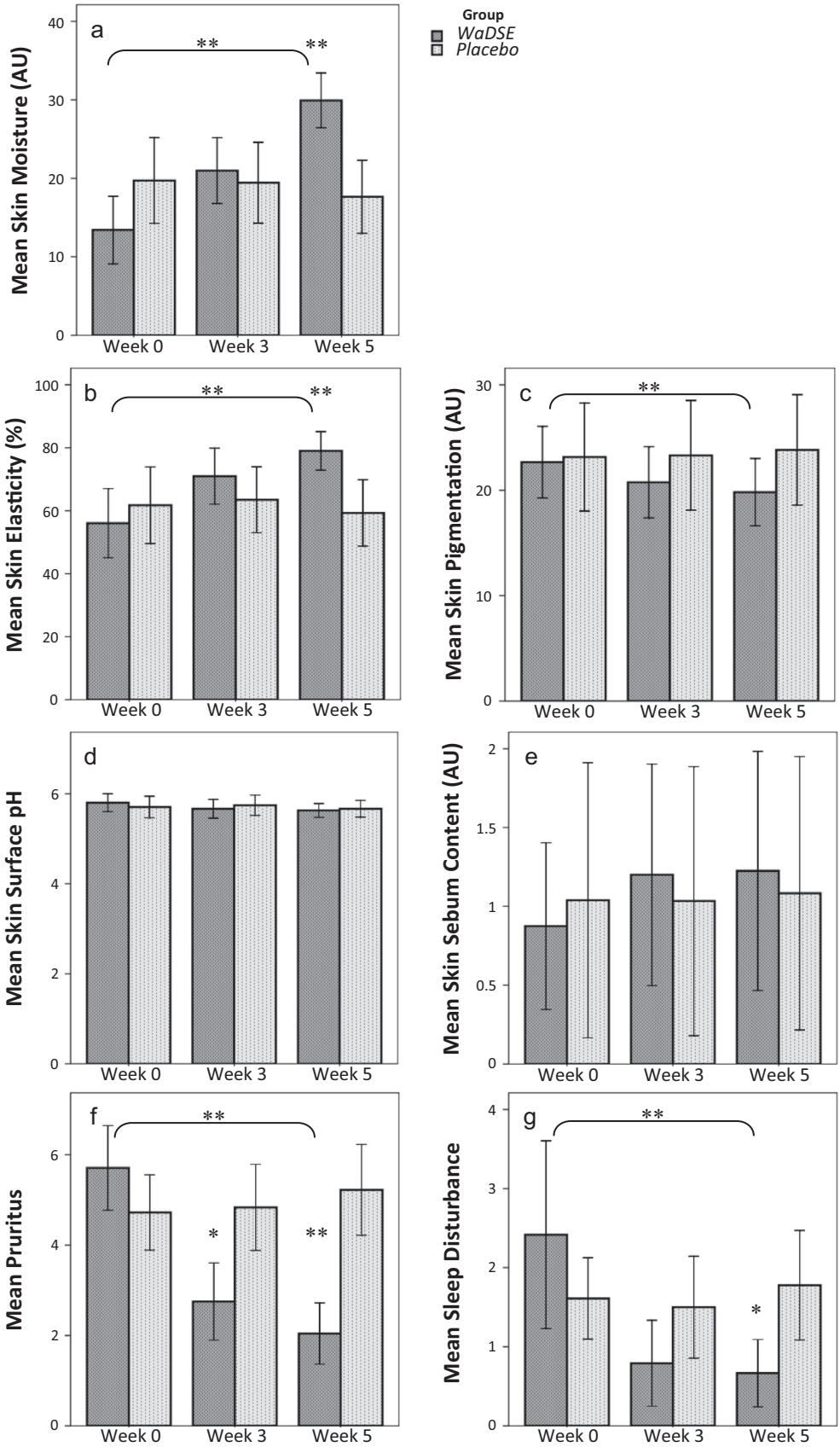

Fig. 2. Change in all the variables in the treatment (WaDSE) group from baseline (week 0) to weeks 3 and 5, compared to the placebo group. (a). Skin moisture. (b). Skin elasticity. (c). Skin pigmentation. (d). Skin surface pH. (e). Skin sebum content. (f). Pruritus. (g). Sleep disturbance. $^{*}p < 0.05$; $^{**}p < 0.001$.

(Hashiro and Okumura, 1997; Kawana et al., 2010). In addition, serotonin is an immune modulator and plays a role in reducing itching by suppressing T cells (Kim, 2012).

Studies have shown that whey intake, even in infants with a positive family history, compared to standard formulas can reduce the risk of atopic dermatitis in the future (Alexander et al., 2010).

One whey component called milk basic protein (MBP) stimulates the proliferation and differentiation of osteoblasts. Hence, the authors theorize that the administration of whey in patients with moderate-to-severe atopic dermatitis that are predisposed to decreased bone mineral density, due to the inflammatory nature of the disease and the effects of long term use of corticosteroids, can benefit by reducing the risk of osteoporosis and osteopenia (Aalto-Korte and Turpeinen, 1997; Haeck et al., 2009).

Although the use of traditional medicines has been highly regarded in the treatment of atopic dermatitis, few studies exist to assess the efficacy of these drugs within the framework of a double-blind, placebo-controlled clinical trial (Chen et al., 2015; Hon et al., 2011; Tan et al., 2013). Whey associated with dodder seed extract, which is applied in the treatment of chronic and severe atopic dermatitis in traditional medicine, is in fact a functional food widely used as a nutritional supplement. Various clinical trials have been conducted that have proven its useful effects on the treatment of cancer, HIV, hepatitis B, cardiovascular diseases, osteoporosis and microbial diseases, while no serious side effects have been reported (Marshall, 2004).

The field dodder seed, the decoction of which is used in traditional medicine in the treatment of atopic dermatitis, possesses anti-inflammatory and anti-proliferative properties due to the flavonoids quercetin, kaempferol and rutin (Hämäläinen et al., 2007; Lee et al., 2011). One of the main pathophysiologic aspects of AD is immune system dysregulation, especially related to the two main subgroups of CD4+ T cells, i.e., T-helper 1 and T-helper 2 (Leung et al., 2004). Quercetin can have a considerable anti-inflammatory role through the inhibition of cytokine production by T-helper cells (Yu et al., 2008). Quercetin blocks substances involved in allergies and has the ability to act as an inhibitor of mast cell secretion, which is critically involved in the pathogenesis of AD (Shaik et al., 2006). Recent studies have shown that heat processing causes a considerable increase of quercetin within field dodder seeds compared to unprocessed seeds, consequently intensifying its anti-inflammatory and anti-proliferative properties (Lee et al., 2011). In addition, the flavonoids quercetin and kaempferol show anti-inflammatory effects by modulating the pro-inflammatory factors, such as inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) (García-Mediavilla et al., 2007). Nitric oxide (NO) derived from inducible NO synthase (iNOS) is involved in the pathogenesis of allergic rhinitis and exacerbation of atopic dermatitis symptoms like scratching (Orita et al., 2011). Thus, it is concluded that consuming the aqueous extract of field dodder seeds can be helpful for the improvement of AD lesions due to decrease of inflammation. Its consumption produces no hepatic or renal complications, but in cases of overdose, intestinal colic and diarrhoea may occur (Gruenwald et al., 2004).

5. Conclusions

It can be said that WaDSE is efficient in the treatment of atopic dermatitis through the functioning of different mechanisms. Focusing on skin barrier dysfunction and immune system dysregulation, WaDSE can satisfy the main purpose of treatment, which is reducing the severity and flare-ups of the disease. The results of this study demonstrate that WaDSE can provide a suitable treatment for moderate-to-severe AD with the lowest incidence of complications and could even be posed as an alternative for systemic and highly morbid treatments. Despite short-term prescription of the mentioned drug in this study, skin moisture and elasticity underwent considerable enhancement.

Since changes in skin pH and sebum content displayed a long-term trend, other controlled trials over longer periods of time and with larger sample sizes should be performed on the parameters related to the assessment of the drug efficacy. Moreover, implementation of other clinical trials with longer follow-up periods will be able to evaluate the effects of this drug on the relevant atopies, such as asthma and allergic rhinitis.

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References

Aalto-Korte, K., Turpeinen, M., 1997. Bone mineral density in patients with atopic dermatitis. Br. J. Dermatol. 136, 172–175.
Agha, A.M., Abdel Sattar, E., Galal, A., 1996. Pharmacological Study of *Cuscuta campestris* Yuncker. Phytother. Res. 10, 117–120.
Aghili Khorasani, M.H., 2011a. Makhzan al-Advieh, Second ed. Sabzarang Publications, Tehran (in Persian).
Aghili Khorasani, M.H., 2011b. Qarabadin-e Kabir, First ed.Vol. 2. Norouhi Publications, Qom (in Persian).
Alexander, D.D., Schmitt, D.F., Tran, N.L., Barraj, L.M., Cushing, C.A., 2010. Partially hydrolyzed 100% whey protein infant formula and atopic dermatitis risk reduction: a systematic review of the literature. Nutr. Rev. 68, 232–245.
Avicenna, 2005. First ed.The Cannon of Medicine Vol. 4. Alaalami Library, Tehran (in Arabic).
Bieber, T., 2008. Atopic dermatitis. N. Engl. J. Med. 358, 1483–1494.
Boirie, Y., Dangin, M., Gachon, P., Vasson, M.P., Maubois, J.L., Beaufrère, B., 1997. Slow and fast dietary proteins differently modulate postprandial protein accretion. Proc. Natl. Acad. Sci. USA 94, 14930–14935.
Boneberger, S., Rupec, R.A., Ruzicka, T., 2010. Complementary therapy for atopic dermatitis and other allergic skin diseases: facts and controversies. Clin. Dermatol. 28, 57–61.
Chen, H.Y., Lin, Y.H., Wu, J.C., Hu, S., Yang, S.H., Chen, J.L., Chen, Y.C., Lo, S.S., 2015. Use of traditional Chinese medicine reduces exposure to corticosteroid among atopic dermatitis children: a 1-year follow-up cohort study. J. Ethnopharmacol. 159, 189–196.
Cork, M.J., Robinson, D.A., Vasilopoulos, Y., Ferguson, A., Moustafa, M., MacGowan, A., Duff, G.W., Ward, S.J., Tazi-Ahnini, R., 2006. New perspectives on epidermal barrier dysfunction in atopic dermatitis: gene-environment interactions. J. Allergy Clin. Immunol. 118, 3–21.
Farnaud, S., Evans, R.W., 2003. Lactoferrin–a multifunctional protein with antimicrobial properties. Mol. Immunol. 40, 395–405.
Fernald, M.L., 1970. Gray's Manual of Botany, 8th ed. D. Van Nostrand Company, New York.
Fivenson, D., Arnold, R.J., Kaniecki, D.J., Cohen, J.L., Frech, F., Finlay, A.Y., 2002. The effect of atopic dermatitis on total burden of illness and quality of life on adults and children in a large managed care organization. J. Manag. Care Pharm. 8, 333–342.
García-Mediavilla, V., Crespo, I., Collado, P.S., Esteller, A., Sánchez-Campos, S., Tuñón, M.J., González-Gallego, J., 2007. The anti-inflammatory flavones quercetin and kaempferol cause inhibition of inducible nitric oxide synthase, cyclooxygenase-2 and reactive C-protein, and down-regulation of the nuclear factor kappaB pathway in Chang Liver cells. Eur. J. Pharmacol. 557, 221–229.
Goyal, N., Gandhi, D.N., 2009. Comparative analysis of indian paneer and cheese whey for electrolyte whey drink. World J. Dairy Food Sci. 4, 70–72.
Gruenwald, J., Brendler, T., Jaenicke, C., 2004. PDR for Herbal Medicines, Third ed. Thomson PDR, Montvale, NJ.
Haeck, I.M., Hamdy, N.A., Timmer-de Mik, L., Lentjes, E.G., Verhaar, H.J., Knol, M.J., de Bruin-Weller, M.S., Bruijnzeel-Koomen, C.A., 2009. Low bone mineral density in adult patients with moderate to severe atopic dermatitis. Br. J. Dermatol. 161, 1248–1254.
Hämäläinen, M., Nieminen, R., Vuorela, P., Heinonen, M., Moilanen, E., 2007. Anti-inflammatory effects of flavonoids: genistein, kaempferol, quercetin, and daidzein inhibit STAT-1 and NF-kappaB activations, whereas flavone, isorhamnetin, naringenin, and pelargonidin inhibit only NF-kappaB activation along with their inhibitory effect on iNOS expression and NO production in activated macrophages. Mediat. Inflamm., 45673.

Hanifin, J.M., Rajka, G., 1980. Diagnostic features of atopic dermatitis. Acta Derm.-Venereol. Suppl. 92, 44–47.
Harborne, J.B., 1998. Phytochemical Methods, Third ed. Chapman and Hall Ltd., London.
Hashiro, M., Okumura, M., 1997. Anxiety, depression and psychosomatic symptoms in patients with atopic dermatitis: comparison with normal controls and among groups of different degrees of severity. J. Dermatol. Sci. 14, 63–67.
Holm, L., Doll, J., Holm, E., Panch, J., Herberger, J., 1997. World weeds: Natural histories and distribution. J. Wiley, New York.
Hon, K.L., Chan, B.C., Leung, P.C., 2011. Chinese herbal medicine research in eczema treatment. Chin. Med. 6, 17.
Hong, J., Buddenkotte, J., Berger, T.G., Steinhoff, M., 2011. Management of itch in atopic dermatitis. Semin. Cutan. Med. Surg. 30, 71–86.
Howell, M.D., Kim, B.E., Gao, P., Grant, A.V., Boguniewicz, M., DeBenedetto, A., Schneider, L., Beck, L.A., Barnes, K.C., Leung, D.Y.M., 2009. Cytokine modulation of atopic dermatitis filaggrin skin expression. J. Allergy Clin. Immunol. 124, R7–R12.
Kawana, S., Kato, Y., Omi, T., 2010. Efficacy of a 5-HT1a receptor agonist in atopic dermatitis. Clin. Exp. Dermatol. 35, 835–840.
Kim, K., 2012. Neuroimmunological mechanism of pruritus in atopic dermatitis focused on the role of serotonin. Biomol. Ther. 20, 506–512.
Kim, K.H., 2013. Overview of atopic dermatitis. Asia Pac. Allergy 3, 79–87.
Knor, T., Meholjić-Fetahović, A., Mehmedagić, A., 2011. Stratum corneum hydration and skin surface pH in patients with atopic dermatitis. Acta Dermatovenerol. Croat. 19, 242–247.
Lee, M.S., Chen, C.J., Wan, L., Koizumi, A., Chang, W.T., Yang, M.J., Lin, W.H., Tsai, F.J., Lin, M.K., 2011. Quercetin is increased in heat-processed *Cuscuta campestris* seeds, which enhances the seed's anti-inflammatory and anti-proliferative activities. Process Biochem. 46, 2248–2254.
Leung, D.Y.M., Boguniewicz, M., Howell, M.D., Nomura, I., Hamid, Q.A., 2004. New insights into atopic dermatitis. J. Clin. Investig. 113, 651–657.
MacKay, D., Miller, A.L., 2003. Nutritional support for wound healing. Altern. Med. Rev. 8, 359–377.
Markus, C.R., Olivier, B., de Haan, E.H., 2002. Whey protein rich in alpha-lactalbumin increases the ratio of plasma tryptophan to the sum of the other large neutral amino acids and improves cognitive performance in stress-vulnerable subjects. Am. J. Clin. Nutr. 75, 1051–1056.
Marshall, K., 2004. Therapeutic applications of whey protein. Altern. Med. Rev. 9, 136–156.
Orita, K., Hiramoto, K., Kobayashi, H., Ishii, M., Sekiyama, A., Inoue, M., 2011. Inducible nitric oxide synthase (iNOS) and α-melanocyte-stimulating hormones of iNOS origin play important roles in the allergic reactions of atopic dermatitis in mice. Exp. Dermatol. 20, 911–914.
Orsi, N., 2004. The antimicrobial activity of lactoferrin: current status and perspectives. Biometals 17, 189–196.
Rhazes, 1990. First ed.Al-Havi (Liber Continent) Vol. 7. Pharmaceutical Company Press, Tehran, in Arabic.
Roekevisch, E., Spuls, P.I., Kuester, D., Limpens, J., Schmitt, J., 2014. Efficacy and safety of systemic treatments for moderate-to-severe atopic dermatitis: a systematic review. J. Allergy Clin. Immunol. 133, 429–438.
Sator, P.G., Schmidt, J.B., Hönigsmann, H., 2003. Comparison of epidermal hydration and skin surface lipids in healthy individuals and in patients with atopic dermatitis. J. Am. Acad. Dermatol. 48, 352–358.
Shah, N.P., 2000. Effects of milk-derived bioactives: an overview. Br. J. Nutr. 84, S3–S10.
Shaik, Y.B., Castellani, M.L., Perrella, A., Conti, F., Salini, V., Tete, S., Madhappan, B., Vecchiet, J., De Lutiis, M.A., Caraffa, A., Cerulli, G., 2006. Role of quercetin (a natural herbal compound) in allergy and inflammation. J. Biol. Regul. Homeost. Agents 20, 47–52.
Smithers, G.W., 2008. Whey and whey proteins—From 'gutter-to-gold'. Int. Dairy J. 18, 695–704.
Tan, H.Y., Zhang, A.L., Chen, D., Xue, C.C., Lenon, G.B., 2013. Chinese herbal medicine for atopic dermatitis: a systematic review. J. Am. Acad. Dermatol. 69, 295–304.
The European Task Force on Atopic Dermatitis, 1993. Severity scoring of atopic dermatitis: the SCORAD index. Dermatology 186, 23–31.
Vasey, C., 2006. The Whey Prescription: The Healing Miracle in Milk. Healing Arts Press, Rochester, VT.
Walzem, R.L., Dillard, C.J., German, J.B., 2002. Whey components: millennia of evolution create functionalities for mammalian nutrition: what we know and what we may be overlooking. Crit. Rev. Food Sci. Nutr. 42, 353–375.
Yu, E.S., Min, H.J., An, S.Y., Won, H.Y., Hong, J.H., Hwang, E.S., 2008. Regulatory mechanisms of IL-2 and IFNgamma suppression by quercetin in T helper cells. Biochem. Pharmacol. 76, 70–78.