

ORIGINAL CONTRIBUTION

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Impact of *Althaea Officinalis* extract in patients with atopic eczema: a double-blind randomized controlled trial

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Abstract

Background: *Althaea Officinalis* introduced as an emerging anti-inflammatory agent with immunomodulatory effects that may suppress the symptoms of atopic eczema. In this study, we aimed to investigate the impact of liposomal formulation of *Althaea Officinalis* flower extract compared with steroids for atopic eczema treatment.

Methods: In this randomized, double-blind controlled trial phase II, forty patients with moderate to severe allergic atopic eczema confirmed by skin prick test were enrolled in the study from October 2018 to January 2019. Steroids on the lesions of the left side of the body and topical *Althaea Officinalis* extract (intervention) or eucerin as a topical placebo on the lesions of the right side of the body were tested. SCORAD (SCORing Atopic Dermatitis) was assessed at the baseline, and two, and four weeks after completing the trial. Data were analyzed by SPSS version 22.

Results: In the active treatment group, after two weeks, the SCORAD was significantly lower in the left side (recovery with steroid treatment) ($p < 0.001$), and after 4 weeks the SCORAD was lower on both sides, and there were no significant differences between two sides (similarity between *Althaea Officinalis* and steroid effects). In the control group, the SCORAD score was significantly lower on the left side (steroid) after two and four weeks ($p < 0.001$). There was no side effect and reaction to drugs.

Conclusions: Considering the potential side effects of steroids, and the similar efficacy of *Althaea Officinalis* flower extract, using this component may be accompanied by higher benefits in patients with atopic eczema.

Trial registration: IRCT2016102323235N5.

Keywords: *Althaea Officinalis* extract, Atopic eczema, SCORing Atopic Dermatitis

Introduction

Atopic eczema is one of the most prevalent diseases worldwide with a wide age distribution that is a debilitating medical condition affecting psychological and somatic functions [1, 2]. Current data support the use of systemic therapies such as novel monoclonal antibodies and Janus kinase inhibitors beside systemic corticosteroids and

antidepressants and topical therapies and topical treatments such as topical corticosteroids, antibiotics, and different eucerin in the treatment of atopic eczema with various severity indices [3]. Recently, alternative medicine using traditional herbal medicines has gained great interest, especially in refractory and severe cases in different age groups with or without the supervision of clinicians [4, 5]. Components such as honey, beeswax, olive oil, and marshmallow (*Althaea Officinalis*) showed promising results on dermatologic disorders with autoimmune and/or inflammatory basis [6–8].

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Althaea officinalis, (common name: Marshmallow), which showed in Fig. 1, is a perennial species indigenous to Europe, Western Asia, and North Africa, which is used in alternative medicine and as an ornamental plant [9]. Its active compounds modulate the immune system through stimulation of monocytes leading to secretion of interleukin-6 and tumor necrosis factor (TNF) [10, 11]. *Althaea Officinalis* introduced as an emerging anti-inflammatory agent [12] with immunomodulatory effects that may suppress the symptoms of atopic eczema. Therefore, it might suppress the symptoms of atopic eczema.

The prevalence of atopic dermatitis is increasing with the industrialization of communities. Regarding the effects of severe pruritus in patients, which is especially children, its mental health problems on the patients and parents, the side effects of topical steroids in high consumption and increasing the systemic absorption, the resistance and fear of parents in using topical steroids, and vice versa overuse and its side effects, we decided to find a suitable and low-risk solution to control the disease and itching. Due to the anti-inflammatory and itching effects of marshmallows, we aimed to investigate the efficacy and safety of topical liposomal formulation of *Althaea officinalis* flower extract for treating atopic eczema.



Fig. 1 *Althaea Officinalis* plant [13]

Methods

This was a randomized, double-blind controlled trial phase II in forty patients with atopic eczema. The trial was conducted from October 2018 to January 2019, at Qaem Educational Hospital; the largest tertiary referral hospital in Mashhad, Iran. This study is a pilot which considering of the other similar articles, 20 people in each group were selected and each patient had both intervention and control (two Body side selected) to prevent sensory effects (severity of itching that depends on the individual).

The active treatment group included 20 patients with moderate to severe allergic atopic eczema confirmed by skin prick test were received steroids (Hydrocortisone acetate ointment (1%) or Triamcinolone, depending on the age of the patient) on the lesions of the left side of the body and topical *Althaea officinalis* extract (intervention) of the right side of their body.

In the control group, 20 patients with moderate to severe allergic atopic eczema confirmed by skin prick test were received steroids on the lesions of the left side of the body, and eucerin as a topical placebo on lesions of the right side of their body. To make all patients uniform and occurs no mistakes in completing the questionnaire, the left side was chosen for steroids (constant side).

Patients with simultaneous dermatologic disorders including bacterial infection, the patient using systemic immunosuppressive drugs, and patients who missed follow-up sessions showing poor compliance of them, were excluded. Also, before the randomization, all patients were tested for hyper-reactive responses and were excluded if they had them. The online random generator was used to generate random choices (<https://www.random.org/>).

The Intervention group received topical formulation of *Althaea officinalis* 10%. In the summer of 2018, we bought the herb from the validated centers of medicinal herbs in Mashhad. The herbal extract was encapsulated in liposomes to improve its penetration through the skin. The active control group received topical steroids with a similar prescription pattern.

For the effect of these compounds and their comparison with steroids, it is necessary to remove confounding factors such as lesion severity, patient tolerance, skin thickness, and nutrition, etc. therefore, to achieve this goal, the effects of both drugs (marshmallow and hydrocortisone) were examined in each person. This means that both groups were prescribed topical steroids.

Patients or parents were asked to use the new formulation in half of the body (right) and steroids ointment in the second half (left). The duration of treatment was one month. Comparison of the *Althaea Officinalis* flower extracts liposomal formulation with steroids

Table 1 Demographic data between two groups of case and control

| Variable | | Active treatment group | Active control group | P-value |
|-------------------|--------|------------------------|----------------------|---------|
| Subjects enrolled | | 20 | 20 | - |
| Sex | Male | 18 (45 %) | 16 (40 %) | 0.651 |
| | Female | 22 (55 %) | 24 (60 %) | |
| Age (months) | | 34.00 (15.75-90.00) | 31.00 (16.50-72.00) | 0.787 |

ointment in the relieving symptoms (itching, redness, bumps, scaling, and fissures) were done every 2 weeks (twice) after treatment by the therapist with patient history and the SCORAD questionnaire.

Herbal medicine formulation

In the summer of 2018, we bought the herb from the validated centers of medicinal herbs in Mashhad. To produce topical liposomal formulation of *Althaea Officinalis*, first, the hydroalcoholic extract of the *Althaea Officinalis* flowers were obtained by maceration method, in which the dried flowers were powdered then macerated in hydroalcoholic solvent (70 % ethanol, 30 % water) for 72 h. After removing the solvent, the extract was collected.

Then, the extract is encapsulated in liposomes. To make a 20 cc liposomal solution, 200 mg cholesterol and 600 mg lecithin were dissolved in chloroform. After the solvent was removed, the extract suspension in water was added to the bottom lipid layers of the balloon and the resulting suspension was homogenized. This suspension was then added to the topical base of Eucerin. The percentage of extract in this product was 10 %. The acute median lethal dose (LD50) of *A. officinalis* in mice was greater than 5,000 mg/kg [14], so the amount of extract that each patient used (less than 3 g) is very less than the LD50, besides the patient used this product topically not orally.

SCORing Atopic Dermatitis

SCORAD (SCORing Atopic Dermatitis) was assessed at the baseline, and two and four weeks after completing the trial. All patients were evaluated for pruritus,

redness, bulge, scaling, and fissure. The objective SCORAD is a scoring system based on the assessment of extent and intensity in a standardized manner. The extent of lesions is scored by applying the rule of nine after drawing the lesions on an evaluation form. The intensity is determined by grading the 6 items on a scale from 0 to 3 (erythema, edema/population, oozing/crusts, excoriation, lichenification, and dryness).

Data were analyzed by SPSS 25 using chi-square and independent-sample t-tests at the level of 0.05.

Ethics approval and consent to participate

The protocol of the study was approved by the ethics committee of Mashhad University of Medical Sciences (code: IR.MUMS.fm.REC.1394.543). Written informed consent and verbal assent were obtained from patients involved before enrolment when data were collected.

Results

Twenty patients with atopic eczema in each group completed the trial. In this study, 34 (42.5 %) of all subjects were male (18 and 16 patients in treatment and control groups, respectively) and 46 (57.5 %) of them were female (22 and 24 patients in treatment and control groups, respectively). The distribution of age was non-parametric which in treatment and control group was 34 (15.75 -90) and 31 (16.50-72), respectively. According to the Table 1, both groups were similar in terms of age and distribution of gender.

The results of Table 2 shows mean SCORAD in active treatment group. Before the study, for both groups severity of atopic eczema in terms of SCORAD score had been determined, which was similar in the right and left

Table 2 Mean scoring of Atopic Dermatitis (SCORAD) in the active treatment group

| Time | Scores (Mean ± SD) | | Between right and left half-body P-value |
|-------------------|---|--|--|
| | Right half-body <i>Althaea Officinalis</i> | Left half-body Hydrocortisone acetate ointment (1 %) or Triamcinolone | |
| 0 (baseline) | 14.55 ± 2.21 | 14.55 ± 2.21 | - |
| Week 2 | 9.55 ± 2.19 | 5.90 ± 1.97 | < 0.001** |
| P-value weeks 0-2 | < 0.001** | < 0.001** | |
| Week 4 | 1.00 ± 1.34 | 1.05 ± 1.19 | 0.716 |
| P-value weeks 2-4 | < 0.001** | < 0.001** | |
| P-value weeks 0-4 | < 0.001** | < 0.001** | |

Table 3 Mean scoring of Atopic Dermatitis (SCORAD) in the active control group

| Time | Scores (Mean \pm SD) | | Between right and left half-body P-value |
|-------------------|----------------------------|--|--|
| | Right half-body Placebo | Left half-body Hydrocortisone acetate ointment (1 %) or Triamcinolone | |
| 0 (baseline) | 14.40 \pm 1.90 | 14.40 \pm 1.90 | - |
| Week 2 | 13.05 \pm 2.04 | 6.05 \pm 2.31 | < 0.001 |
| P-value weeks 0–2 | 0.287 | < 0.001 | |
| Week 4 | 11.75 \pm 1.94 | 1.10 \pm 0.85 | < 0.001 |
| P-value weeks 2–4 | 0.003 | < 0.001 | |
| P-value weeks 0–4 | < 0.001 | < 0.001 | |

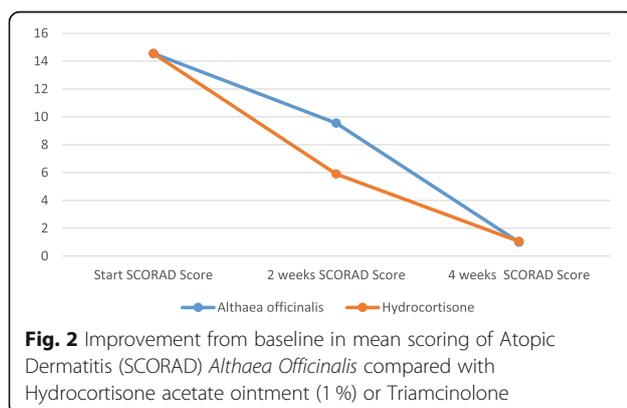
side in each patient. After that, SCORAD had been estimated in each group for left and right lesions every two weeks. In the active treatment group, after two weeks, the SCORAD was significantly lower on the left side (recovery with steroid treatment) ($P < 0.001$), and after four weeks the SCORAD was lower on both sides and there were no significant differences between the two sides (P -value = 0.716). This results shows that *Althaea Officinalis* decreased SCORAD as well as topical triamcinolone after 4 weeks.

The results of Table 3 shows mean SCORAD in active control group. In the control group, the SCORAD score was significantly lower on the left side (steroid) than right side (placebo) after two and four weeks ($P < 0.001$). This results indicate that topical triamcinolone had a better effects in decreasing SCORAD than placebo. There was no side effect and reaction to drugs.

Figure 2 shows improvement from baseline in mean scoring of Atopic Dermatitis (SCORAD) *Althaea Officinalis* compared with Hydrocortisone acetate ointment (1%) or Triamcinolone. Accordingly, topical triamcinolone had a better results than *Althaea Officinalis* in two weeks but the final result after 4 weeks was same.

Discussion

Our study showed that topical liposomal formulation of *Althaea Officinalis* flower extract had a similar effect to



hydrocortisone acetate ointment (1%) or topical triamcinolone in reduction of symptoms of patients suffering from atopic eczema with no remarkable side effects. Previous studies support the use of alternative medicine in the treatment of allergic skin conditions.

Hon et al. studies the role of herbal medicine for the treatment of atopic dermatitis and showed that prescription of traditional Chinese herbal medicine in these patients with atopic dermatitis improves the quality of life of patients and decreases the dose of corticosteroids [15]. Al-Waili used topical honey, beeswax, and olive oil mixture for treatment of atopic dermatitis or psoriasis and they reported its clinical efficacy [6]. In a review by Thandar et al., the topical herbal medicines for atopic eczema were reviewed, they found that current evidence is insufficient to make a general recommendation for using the herbal medicine in the treatment of allergic skin conditions [16].

Previous studies showed that *Althaea Officinalis* has several effects on the human body including its immunomodulatory effects by inhibiting the cytokine and interferon production and anti-complement activity [17–19]. Besides the immunomodulatory effects of *Althaea officinalis*, its extract can influence the proliferation of epithelial cells [20]. In vivo studies showed that this extract has protective effects against ultraviolet radiation, promotes wound healing, and suppresses the symptoms of latex allergic reactions [21–23]. Our results showed that the prescription of liposomal formulation of *Althaea Officinalis* flower extract is as efficient as hydrocortisone acetate ointment (1%) or triamcinolone in the long-term in the controlling of symptoms of patients with atopic eczema.

In a study conducted by Naseri V et al. at [24], the effect of topical marshmallow in children with atopic dermatitis (AD) were examined. The efficacy of *Althaea officinalis* 1% ointment in a decrease of disease severity is more than Hydrocortisone 1% in children with AD. The results of our study was same as this study, but the main difference between these studies is the formulation of the drug. We formulated the liposomal form of herbal

medicine that is the key point in topical drug dosage forms which increase the absorption, significantly.

In another recent study by Bonaterra GA et al. anti-inflammatory and anti-oxidative effects of Phytohusstil and Root Extract of *Althaea officinalis* (REAO) on Macrophages in vitro were studied. This in vitro investigation indicate protective, i.e., anti-oxidative and anti-inflammatory effects of REAO and Phytohusstil. These anti-inflammatory effects were similar or even better than diclofenac [12].

The main constituents responsible for pain reduction and the inflammation suppression are known to be polyphenols, flavonoids, anthocyanins, dioxybutyric acid and terpenoids [25, 26]. Allergic reactions may occur as an adverse effects. We have not enough studies regarding to the bioavailability, although our product is topical, not oral.

As a limitation of the present study, we did not assess the pharmacokinetic and pharmacodynamic effects of *Althaea officinalis*. Therefore, and conclusion regarding understanding the mechanism of action of the drug cannot be derived. In future studies, authors recommend assessing the bioavailability of the liposomal formulation of *Althaea Officinalis* flower extract and the effect of its coadministration with corticosteroids on reducing topical corticosteroid dose.

Conclusion

Our results showed that although the standard treatment for atopic dermatitis lesions, which includes the use of steroid pads, can improve symptoms in a short time, but the liposomal formulation of *Althaea Officinalis* flower extract is clearly effective as steroids in a long time. Also, there was no side effect in the *Althaea Officinalis* flower group. Considering the potential side effects of steroids in a long-term use and similar efficacy of *Althaea Officinalis* flower extract, using this component may be accompanied by higher benefits in patients with atopic eczema.

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Authors' contributions

Roshanak Salari: Conceptualization, Project administration, Supervision, Writing – Review & Editing, Validation. Negar Khalighi: Writing – Original Draft. Farahzad Jabbari-Azad: Project administration, Supervision, Writing – Review & Editing, Validation. Maral Barzegar-Amini: Software, Formal analysis, Writing – Review & Editing, Visualization. Jalil Tavakkol-Afshari: Investigation, Resources, Writing – Review & Editing. Pouran Layegh: Investigation. The author(s) read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were following the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The protocol of the study was approved by the Ethics Committee of Mashhad University of Medical Sciences (IR.MUMS.fm.REC.1394.543).

Consent for publication

All Authors All authors are fully satisfied with the submission of the article for publication and the article was approved by them. Their personal information included:

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Competing interests

There is no conflict of interest.

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