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The efficacy of topical Marham-e-Akbar in chronic atopic dermatitis – an open-label interventional study

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Abstract

Objectives: Chronic atopic dermatitis (AD) is an inflammatory skin condition marked by intense pruritus, dry skin, and severe impact on the life quality of the patients. Conventionally, it is managed by using emollients, calcineurin inhibitors, and topical corticosteroids. In Unani medicine, eminent scholars advocated many drug formulations including topical Marham-e-Akbar for effective healing of AD but scientific evidence is scarce. Hence, this study was designed.

Methods: This was a single-arm clinical trial conducted on 30 participants aged 18–65 years suffering from chronic AD after obtaining written informed consent. The trial intervention was Marham-e-Akbar consisting of *Murdār Sang* (*Plumbi oxidum)*; *Sindūr* (red lead); olive oil (*Olea europaea* oil); *Kath* (*Acacia catechu* extract); *Safeda Kāshgari* (*Zinc oxide*); *Sirka (vinegar);* and *Phitkirī* (*alum*) to be applied twice daily for 42 days. The objective parameters were SCORAD and DLQI, while the subjective parameters included itching, scaling, and erythema assessed on a customized VAS scale and 4-point Likert scale.

Results: The pre-post analysis inferred statistically significant attenuation in subjective parameters (itching, scaling, and erythema) and objective scales (SCORAD) and (DLQI) with $p<0.001$.

Conclusions: The study findings deduced that Marham-e-Akbar is effective in the amelioration of chronic atopic dermatitis and quality of life of the patients as well.

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Introduction

Atopic dermatitis is an inflammatory disease of the skin that generally manifests in early childhood but may also extend to adulthood in chronic conditions [1]. The prevalence reports of AD vary from 3% to 20.5% worldwide [2]. Although prevalence decreases with the increasing age [3], it is more prevalent in patients aged above 18 years in some countries [4]. The symptoms of AD include pruritus, erythema, dry skin, and vesicle formation. The etiology of AD is not completely understood but genetic predispositions and exogenous as well as endogenous triggers are stated to play a role [5]. Increased sensitization to cutaneous antigens due to impaired skin barrier is pondered as the major factor in its pathophysiology [6]. Impairment in skin barrier function results from filaggrin gene mutations [7]. If inflammation and scratching persist for a longer period, it can ultimately result in chronic AD, characterized by thick and lichenified skin [8]. The treatment approach of AD consists of patient education to avoid triggers and proper use of topical treatment [9], including emollients like calcineurin inhibitors and corticosteroids [10]. However, treatment-resistant dermatitis requires systemic immunosuppressants and ultraviolet (UV) light therapy [10, 11]. But many reports claimed that steroids, tacrolimus, and biological drugs have various unwanted effects including atrophy, thickness, and darkness of skin, metabolic derangement, etc. [12].

In Unani medicine, AD simulates with *Nār Fārsi* which has extensively been described by Unani scholars. It is a type of itch related to very severe non-bearable burning and vesicles filled with liquid. The prime cause of *Nār Fārsi* is considered increased *Hiddat-i Khilt-i Dam* (heat of sanguineous matter) [13]. The treatment is based on the evacuation of morbid matter through venesection, leeching, purgation, *Tasfiya-i Dam* (blood purification), and local applications of *Tila* and ointments possessing *Jāli* (detergent); *Mujaffif* (desiccant); and *Muḥallil* (resolvent) actions [14]. The

most commonly recommended drugs in Unani medicine include *Unnāb (Ziziphus jujuba* fruit), *Shāhatra (Fumaria officinalis* herb); *Sarphūka (Tephrosia purpurea* herb); *Murdār Sang* (*plumbi oxidum*); *Sindūr* (*red lead*); olive oil (*Olea europaea* oil), etc. The selected intervention "Marham-e-Akbar" is taken from *Qarabādīn Najmul Ghani* which contains *Murdār Sang* (*Plumbi oxidum)*; *Sindūr* (red lead); olive oil (*O. europaea* oil); *Kath* (*Acacia catechu* extract); *Safeda Kāshgari* (*Zinc oxide*); *Sirka* and *Phitkirī* (*alum*) [15]. These ingredients possess *Jāli* (detergent); *Mujaffif* (desiccant); *Muḥalil* (resolvent); *Musaffi-i Dam* (blood purifier), and *Munbit-i Laham* actions [15]. Because of these pharmacological actions, the selection of intervention was justified.

Materials and methods

Trial design

This was a single-arm clinical trial with pre and post-analysis conducted on 30 eligible participants in Vijayapura (Bijapur), Karnataka, India.

Participants

Participants in the age bracket of 18 to 65 years with mild to moderate chronic atopic dermatitis fulfilling Hannifin and Rajka's criteria for AD and patients of both genders were included in the trial. Pregnant and lactating women, participants with the history or presence of skin cancer or suspicious lesions, significant renal, hepatic, endocrine, cardiac, pulmonary, pancreatic, neurologic, and hematologic dysfunction were excluded from the study. Similarly, those who were allergic to any of the investigational ingredients were also excluded.

Withdrawal of participants

Participants, who developed adverse effects either clinical or investigational, at any time of the study, were withdrawn from the study.

Study setting

The study took place at PG Department of Moalajat (medicine), Luqman Unani Medical College, Hospital and Research Centre, Vijayapura (Bijapur), Karnataka, India from March 2020 to March 2021.

Intervention

Participants received Marham-e-Akbar (semisolid paste) to be applied on the affected area of the skin (quantity sufficient to cover the lesions) twice daily for 42 days.

Dosage regimen and quantitative description

At baseline and every follow-up, 1 or 2 container(s) of *Marham-e-Akbar* paste, 15 g each were provided to the participants based on affected body surface area. The paste was advised to be applied on the affected body area in the morning and at night daily.

Qualitative testing and preparation of Marham-e-Akbar

The ingredients of Marham-e-Akbar were provided by the Unani pharmacy of LUMC, Bijapur, India, and identified and authenticated in the department of pharmacology LUMC by the chief pharmacologist. *Safeda Kāshgarī* (*zinc oxide*) 7 g, *Sindūr* (*red lead*) 7 g, *Murdār Sang* (*Plumbi oxidum)* 10 g, *Phitkiri* (*alum*) 7 g, and *Kath* (*A. catechu extract)* 7 g were powdered and sieved through sieve No. 80 and mixed with *Sirka* (acetic acid) 10 g, *Roghan Zaytūn* (*O. europaea* oil) 10 g, and 'Asl (honey) in sufficient quantity to make a homogenous paste [15].

Outcomes

***Efficacy outcome measures*:** The primary outcome measure was the SCORAD score which is a semi-objective scale to measure the severity of AD, in which a score below 25 denotes mild severity; a score between 25 and 50 denotes moderate severity, whereas a score above 50 indicates higher severity. The secondary outcome measures were itching, scaling, redness, and DLQI. The severity of itching was measured on a visual analog scale customized as 0 to 10; where 10 indicated extremely severe and 0 stood for no complaint. The severity of scaling was measured on an arbitrary scale of 0 to 3; where 3 indicated extremely severe and 0 stood for no complaint. The severity of redness was measured on an arbitrary scale of 0 to 3; where 3 indicated extremely severe and 0 stood for no complaint. All the assessments were executed at baseline and end of the trial.

***Safety assessment*:** Safety assessment was done on clinical adverse drug reaction records and local dermal tolerability at each visit. The local and systemic adverse effects, if any, were duly recorded in the case report form.

Study duration and follow-up

The protocol therapy duration was 42 days. The follow-up was done every week. At every visit, participants were enquired about the progression or regression in their symptoms and were subjected to the clinical assessment, and findings were duly recorded in the case report form.

Statistical analysis

Data were analyzed statistically by using SPSS 23.0 (Mac version) and presented as proportion (%), mean and standard deviation. Pre- and post-treatment variables were analyzed using paired sample *t*-test.

Ethical approval and trial registration

This study was initiated only after ethical approval by the institutional ethics committee (Ref. No. BJP/LUMC/PG/IEC/04/2018–19/MOALIJAT/03) and registration with Clinical Trial Registry-India (CTRI/2020/03/024360). The patients were informed about all aspects of the study and written informed consent was obtained from all individuals included in this study.

Results

Participant flow

A total of 46 participants having clinical features of chronic AD were screened for eligibility, of which 36 eligible participants were included in the trial of which 30 participants completed 6 weeks treatment duration; 4 participants dropped out of the study while 2 patients were withdrawn due to protocol deviation (Figure 1).

Clinico-demographic profile

The mean ± SD age of participants was 33.40 ± 11.78 years in which maximum; 15 (50%) cases were in the 18–30 years age group, 8 (26.67%) were in 31–40 years age group, 5 (16.7%) were in 41–50 years age group, and only 2 (6.67%) were in 50–60 years age group. Gender wise 17 (56.7%) males and 13 females (43.3%) were there, of whom 22 were married whereas 8 were unmarried. Socio-economic status, based on the modified Kuppuswamy scale, was lower middle class in all participants. Temperament-wise, 21 (70%) participants had *Safrāwi Mizāj* followed by 8 with *Sawdāwi Mizāj* and 1 with *Damawi Mizāj* (Table 1). The data conforms with the basic concept of *Nār Fārsi* in Unani medicine. Ibn Sina has described that *Nār Fārsi* results from *Hād Akhlāt* mixed with *Khilt-e-Raqīq* i.e., *Safra'* [16]

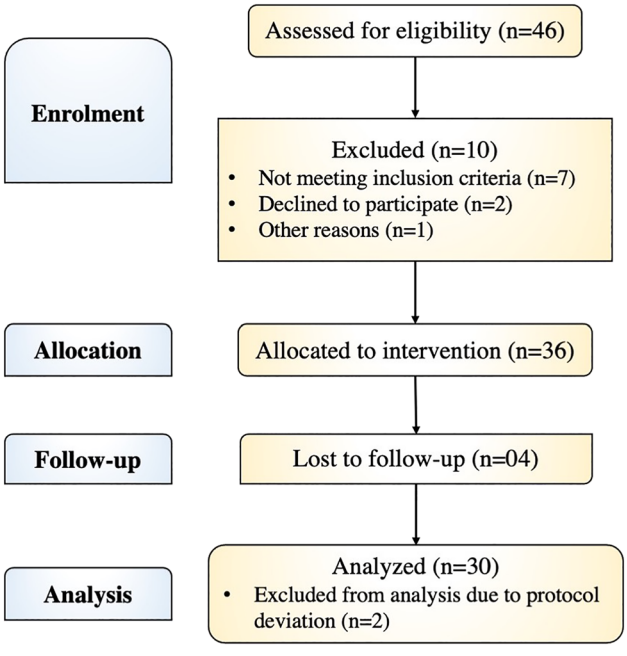

Figure 1: Flow diagram of the participants studied.

Table 1: Demographic and clinical profile of *Nār Fārsi* (AD) patients with Mizaj distribution of patients studied.

Variables	Characteristics	Descriptive
Gender (n=30)	Male	17 (56.67%)
	Female	13 (43.33%)
Age (years) (n=30)	Age (mean ± SD)	33.40 ± 11.78 years
	Minimum–maximum	18–65
Marital status (n=30)	Married	22 (73.33%)
	Unmarried	8 (26.67%)
Mizāj (temperament) (n=30)	*Damawi*	1 (3.33%)
	Safrawi	21 (70.00%)
	Sawdawi	8 (26.67%)

Primary outcome measures

Change in SCORAD score

The baseline mean ± SD of SCORAD was 70.24 ± 7.90 which significantly reduced to 19.81 ± 4.68 at the end of the trial with ($p<0.001$). Moreover, all the participants had SCORAD > 50 at baseline which significantly reduced to mild grade i.e., <25 in 26 participants while 4 had moderate severity after treatment (Table 2).

Secondary outcome measures

Change in severity of itching on VAS

The baseline mean ± SD of itching on VAS was 7.73 ± 0.98 which significantly reduced to 2.43 ± 0.73 at the end of the trial with $p<0.001$ (Table 2).

Change in severity of scaling on VAS

The baseline mean ± SD of scaling on VAS was 2.23 ± 0.57 which significantly reduced to 0.87 ± 0.51 at the end of the trial with $p<0.001$ (Table 2).

Change in severity of redness on VAS

The severity of redness was measured on an arbitrary scale of 0 to 3; where 3 indicated extremely severe and 0 stood for no complaint. 27 (90%) participants had erythema of moderate severity i.e., 2 followed by 3 (10%) with a very severe grade at baseline which significantly reduced to mild grade in 28 participants while 2 had no complaint of redness at all after treatment. The baseline mean ± SD was

Table 2: Effect of intervention on the itching, scaling, redness, SCORAD, and DLQI.

Outcome	Before treatment (mean ± SD)	After treatment (mean ± SD)	Mean difference	t-Value	p-Value
Itching	7.73 ± 0.98	2.43 ± 0.73	5.300	28.400	<0.001[a]
Scaling	2.23 ± 0.57	0.87 ± 0.51	1.367	15.272	<0.001[a]
Redness	2.10 ± 0.31	0.93 ± 0.25	1.167	13.857	<0.001[a]
SCORAD	70.24 ± 7.90	19.81 ± 4.68	50.428	36.872	<0.001[a]
DLQI	25.80 ± 3.35	12.00 ± 2.59	13.800	22.586	<0.001[a]

[a]paired t-test.

2.10 ± 0.31 which significantly reduced to 0.93 ± 0.25 at the end of the trial with p<0.001 (Table 2).

Change in quality of life (DLQI)

The baseline mean ± SD of DLQI was 25.80 ± 3.35 which significantly reduced to 12.00 ± 2.59 at the end of the trial with p<0.001 (Table 2).

Discussion

Chronic atopic dermatitis (AD) is an inflammatory skin condition marked by intense pruritus, dry skin, and a severe impact on the life quality of the patients. In Unani medicine, it simulates with *Nār Fārsi* which is marked by a very severe nonbearable burning sensation, itching, and vesicles filled with liquid. Being increased *Hiddat-i Khilt-i Dam* (heat of sanguineous matter) its primary cause [13], it is treated with ointments possessing *Jali* (detergent); *Mujaffif* (desiccant); and *Muhallil* (resolvent) actions besides evacuation of morbid matter through venesection, leeching, purgation, and blood [14]. The trial intervention "Marham-e-Akbar" contains *Murdār Sang* (*Plumbi oxidum)*; *Sindūr* (red lead); olive oil (*O. europaea* oil); Kath (*A. catechu* extract); *Safeda Kashgari* (*Zinc oxide*); and *Sirka* and *Phitkiri* (*alum*) which exhibit *Jali* (detergent); *Mujaffif* (desiccant); *Muhallil* (resolvent); and *Munbit-i Laham* actions [15]. Hence, this study was performed to investigate the efficacy and safety of *Marham-e-Akbar* in chronic AD.

The mean ± SD of the age of the participants was 33.40 years. Kanwar et al. found that the occurrence of AD is more common in adulthood starting after 18 years of age as compared to children of 5–7 years [17]. There were 17 (56.7%) males and 13 females (43.3%) (Table 1). The data does not agree with the reported gender difference as females are more susceptible to AD. Mollerup et al. found that women are more susceptible to hand AD as compared to men [18]. Similarly, Osman et al. reported that female predominance of AD presentation was seen in the reproductive period of 15–49 years [19]. Johannisson et al. found that the one-year prevalence of hand AD was 15.8% (females 20.3% and males 10.0%, p<0.001) [20].

All the participants had mixed dietary patterns. The data is confirmatory with the Unani concept as meat, spicy and oily foods are implicated in the causation of AD [14]. The epidemiological data on food relevance with AD is highly consistent. Foods like peanuts, tree nuts, cow's milk, eggs, soy, wheat, seafood, and shellfish are largely implicated in the causation of AD [21]. IgE-mediated food sensitization is also linked with egg and cow's milk [22].

All the participants had no prior family history of atopy. This data is not confirmatory with epidemiological studies. Uehara et al. examined the descendant family history of AD in 529 children of 270 adults with AD. Of the 529 cases, 316 (60%) had a history of AD, especially the first-degree family members [23].

The per-protocol analysis unveiled that *Marham-e-Akbar* significantly reduced SCORAD score in participants with AD. Similarly, scaling, redness, itching, and DLQI were also reduced significantly which infers that the test drug has a good effect in amelioration of signs and symptoms of AD also. The mechanism of action of this formulation is ingrained in the actions of its ingredients. *Phitkiri* has *Qābiz* (astringent); *Muhalil-i Waram* (anti-inflammatory); *Dāfi-i Taʿaffun* (antiseptic); *Hābis* (hemostyptic); *Musakkin* (a drug which helps in neutralizing the heat of humors); *Mujaffif* (desiccant); *Mundamil-i Qūrūh* (cicatrizant), *Muqawwi-e-Dandān wa Lissā* (teeth and gums tonic), *Jāli* (detergent) properties [24–27]. The ethnobotanical action such as anti-inflammatory effect [28] gives strength to the therapeutic result as well. *Sirka* has *Muhallil-i Waram* (anti-inflammatory), *Jāli* (detergent), *Dāfi'-i Ta'ffun* (antiseptic), and *Qābiz* (astringent) [26, 29] along with evidence-based antibacterial and antioxidant activities [30–32]. *Safeda Kāshgari* also has *Muhallil* (resolvent), *Mulattif* (demulcent), *Mujaffif* (desiccant), *Mudammil-i Qūrūh* (cicatrizant) [27, 33] along with antifungal, antibacterial and wound healing activities [34]. *Sindur* is *Musakkin*, *Jāli* (detergent), *Munaqqi* (evacuator), *Mudammil-i Quruh* (cicatrizant) [35] along with anti-inflammatory, antioxidant, and cytotoxic

activities [36]. Honey is *Muhallil-i Waram* (anti-inflammatory), *Jāli* (detergent), *Dāfi'-i Ta'ffun* (antiseptic), *Musaffi-i Dam* (blood purifier), *and Mundamil-e-Qūrūh* (cicatrizant) activities [37] and these actions the reduction of symptoms, has been ensued [38]. So far as the route investigations for safety evaluation are concerned, all the parameters were found within their normal range. No side effect was reported by the participants. Thus, it is concluded that Marham-e-Akbar has statistically as well as clinically significant effects in the amelioration of AD.

Conclusions

The study inferred that Marham-e-Akbar is statistically as well as clinically significant in the amelioration of signs and symptoms of AD. It may be further evaluated with larger sample size, longer study duration, and standard control. The study also inferred that the adults in the age group of 20 to 30 are more affected with AD and advancing age is assessed with less occurrence of AD relation.

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Ethical approval: The local Institutional Review Board approved the study protocol.

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