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Treatment of chronic plaque psoriasis with herbal Unani formulations: A randomized control trial of efficacy and safety

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ABSTRACT

Ethnopharmacological relevance: Psoriasis, despite modern therapeutic options, is incurable and recurrent. In Unani (Greco-Arab) medicine, many medications and formulations have been prescribed by eminent scholars for conditions clinically similar to psoriasis, though empirical evidence is sparse. Hence, the experimental formulations *Itrīfal Shāhtra and Marham Ḥina* were chosen to be compared to the standard therapies PUVAsol and petrolatum for their safety and efficacy.

Materials and methods: This open-label, randomized control clinical trial was conducted on 66 male and female participants with chronic plaque psoriasis, ranging in age from 18 to 65 years. In each group, 33 participants were block randomized to either receive Unani formulations or control drugs for 12 weeks. The Unani group received oral *Itrīfal Shāhtra* (a semisolid paste) and topical *Marham Ḥina* (an ointment) twice daily, and the control group received oral 8-methoxypsoralen and topical petroleum jelly for local application. Participants of both groups were advised to get daily sunlight exposure for 5–15 min. The primary outcome measure was the change in psoriasis area and severity index (PASI) assessed at each visit. Secondary outcome measures were patient global assessment on a 100 mm VAS applied at baseline and after 12 weeks of treatment and change in subjective parameters including erythema, induration, scaling, and itching, assessed on a 5-point scale at every visit. Hemogram, LFTs, RFTs, CXR, ECG, urine, and stool tests were all assessed at baseline and after treatment for the safety of the drugs.

Results: The per-protocol analysis was done on 25 participants in each group. The mean ± SD of the psoriasis area severity index (PASI) significantly decreased from 27.88 ± 12.01 and 23.61 ± 9.79 at baseline to 5.01 ± 4.59 and 9.85 ± 7.16 after completion of the trial therapies in both Unani and control groups, respectively. Also, the test formulations outperformed the control drugs on clinically significant endpoints, PASI 50 and PASI 75, with all 25 participants achieving PASI 50 and 76% achieving PASI 75.

Conclusion: The trial formulations, *Itrīfal Shāhtra* and *Marham Ḥina* may be superior to control drugs PUVAsol and petrolatum in terms of safety, efficacy, and tolerability in the treatment of chronic plaque psoriasis. Thus, the Unani formulations may further be evaluated in a well-designed multicentric superiority trial with an adequate sample size.

1. Introduction

Psoriasis is a chronic, relapsing-remitting, immune-mediated, papulosquamous inflammatory skin disease that can affect the joints, nails, heart, blood vessels, kidneys, and liver (Arora et al., 2021). It affects 0.51 percent to 11.43 percent of adults and up to 1.37 percent of children worldwide (Michalek et al., 2017). The lesions are well-defined, scaly (silvery-white), inflammatory, and pruritic plaques that most commonly develop on the extensor surfaces of the elbow and knee, but

Abbreviations: HPTLC, High-performance thin-layer chromatography; HPLC, High-performance liquid chromatography.

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Abbreviations:

CCRUM	Central Council for Research in Unani Medicine,
CRI	Central Research Institute
CRIUM	Central Research Institute of Unani Medicine,
CTRI	Clinical Trial Registry – India
CUE	Complete Urine examination
CXR	Chest X-ray
DLC	Differential leucocyte count
ECG	Electrocardiography
FBS	Fasting blood sugar
Hb	Hemoglobin
HYD	Hyderabad
IEC	Institutional ethics committee
IGA	Investigator's global assessment
IMQ	Imiquimod
KFTs	Kidney function tests
LFTs	Liver function tests
NRIUMSD:	National Research Institute of Unani Medicine for Skin Disorders
PUVA	Psoralen + ultraviolet light A
PUVAsol	Psoralen + ultraviolet light A obtained by solar light
SD	Standard deviation
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SMPU	Survey of medicinal plants unit
TLC	Total leucocyte count
UVB	Ultraviolet B radiation
VAS	Visual Analogue Scale

can also occur on the scalp and back (Marks and Miller, 2013). Patients with psoriasis experience mild to severe itching, as well as a small amount of pinpoint blood, referred to as the Auspitz sign, although the sign is not sensitive enough for this condition (Bernhard, 1990). Psoriasis is genetically predisposed through polygenic inheritance, but the manifestation largely depends on other factors such as infection, mechanical irritations, psychosomatic factors, and drugs (Huffmeier et al., 2009; Sacchidanand et al., 2015). The pathophysiology of psoriasis includes keratinocyte hyperproliferation, acanthosis, parakeratosis, and a T-cell-mediated inflammatory response, but the specific mechanism is still unknown (Lowes et al., 2014). There are several types and varieties of psoriasis, the most common of which is plaque psoriasis, which is characterized by red, inflammatory, thick, and scaly lesions that are scattered symmetrically (Sacchidanand et al., 2015).

The treatment strategy of psoriasis is usually determined by the severity of the disease and the extent of the affected body surface area. Mild psoriasis is treated with a topical corticosteroid and vitamin D analogues (Samarasekera et al., 2013) whereas moderate to severe forms of the disease are treated with phototherapy, systemic therapy such as methotrexate, acitretin, or cyclosporine, apremilast, and biologic therapy (Gisondi et al., 2017). Despite these treatment options, the disease remains incurable and recurrent. Additionally, several adverse effects associated with these treatment modalities have been identified, including carcinogenicity, hepatotoxicity, and exacerbation of symptoms and disease (Papadakis et al., 2017). As a result, the development of novel alternative therapies is urgently required.

In Unani classical literature, different scholars reported clinically similar conditions to psoriasis under different terms; *Taqashshur al-Jild* by *Zakariyya Rāzī* (Rāzī, 1970), *Baraṣ-i Aswad* by *Ibn Hubal Baghdādī* (Hubal, 2007), a type of *S'afa-i-Yābis* by *Ibn* Sīnā (1981), and a type of *Qūbā-i Yābisā* by *Rabban Ṭabarī* (Ṭabarī, 2010). All of them described sloughing of fish-like scales (*Fālūs-i Samak*), husk-like peeling of the skin, roughness, itching, desquamation, and pustules as its major features (Arzāni, 2009). Deranged *Khilṭ-i Sawdā; Hirrīf wa Lādhi' Sawda' Muḥtariq* (acute and irritating burnt black bile) caused by *Ḥiddat* (excess heat) and *Fasād-i Dam* wa *Ṣafrā* (impairment of blood and bile) and *Khushk Būraqi Madda* (dry alkaline matter) are believed to be the primary causes (Anonymous, 2016; Tabarī, 1997). The underlying pathology of *Taqashshur al-Jild* is considered the accumulation of the excess amount of *Khilṭ-i-Ghalīẓ; Sawdā* and weakening of *Quwwat-i Ghādhiya* (nutritive faculty) resulting in dead skin that shreds off in the form of scales (Majūsī, 2010; Zuhr, 1986). The treatment is generally prescribed based on *Talyīn-i Jild* (softening of the skin by emollient), *Tasfiya-i Dam* (blood purification), and *Tanqiya-i Badan* (evacuation of morbid matter from the body) (Anonymous, 2016). Based on these therapeutic principles, various single and compound formulations are used as systemic and topical agents in the treatment of psoriasis by Unani physicians; accordingly, a combination of two Unani formulations – *Itrīfal Shāhtra* (as systemic agent) and *Marham Ḥina* (as topical agent) were selected for this study as *Itrīfal Shāhtra* possesses *Muṣaffī-i Dam* (blood purifier), *Munḍij wa Mushil-i Sawdā'* (concoctive and purgative of melancholic humor) and *Muraṭṭab-i 'Umūmi* (emollient) actions, and *Marham Ḥina* possesses emollient, *Dāfi'-i 'Ufunat* (disinfectant), *Musakkin-i Maqāmī* (local analgesic), *Dāfi'-ī Sozish* (antipruritic), and *Dāfi'-ī Waram* (anti-inflammatory) actions (Khān, 2005; Anonymous, 2011). But scientific evidence supporting their effectiveness or efficacy in psoriasis is limited. Thus, the purpose of this study was to determine whether there is a difference between the mean response rates of the Unani interventions (*Itrīfal Shāhtra* and *Marham Ḥina*) and the control drugs (PUVAsol and petroleum jelly) in terms of the proportion of patients whose psoriasis area and severity index score decreased by 75% or more from baseline (PASI 75). The hypotheses were H_0: $\mu_{PT} = \mu_{PC}$ versus H_a: $\mu_{PT} \neq \mu_{PC,}$ where μ_{PT} and μ_{PC} are the mean response rates of Unani and control groups with respect to PASI 75.

2. Methods and materials

2.1. Trial design

This prospective, randomized, open-label, active-controlled, parallel-group clinical trial was conducted from 03 March 2020 to 04 April 2021 at the National Research Institute of Unani Medicine for Skin Disorders (formerly Central Research Institute of Unani Medicine) in Hyderabad, Telangana, India.

2.2. Participants

Participants aged 18–65 years with clinically diagnosed plaque psoriasis and a psoriasis area severity index (PASI) of 10% or greater were enrolled in the trial. However, participants with significant pulmonary, cardiovascular, or hepato-renal dysfunction, immunocompromised states (HIV/AIDS, etc.), or those unwilling to adhere to the treatment schedule on a consistent basis were excluded from the trial. Similarly, pregnant and lactating mothers were excluded from the trial.

Diagnostic criteria of plaque psoriasis were the presence of typical lesions, i.e., red plaques well-demarcated from unaffected skin, with the features including, silvery-white scales, symmetry of lesions, and Auspitz's sign (Freedberg et al., 2003; Griffiths et al., 2007).

2.3. Study settings

The trial took place at Department of Medicine (Unani), National Research Institute of Unani Medicine for Skin Disorders (previously Central Research Institute of Unani Medicine), Hyderabad, Telangana,

India.

2.4. Interventions

Participants were randomly assigned to receive oral administration of *Itrīfal Shāhtra* twice daily with water before food, followed by topical application of *Marham Ḥina* in sufficient quantity to cover the lesion in Unani group, while in the control group, participants received 8-methoxypsoralen on alternate days after breakfast, followed by sun exposure to the affected part. Additionally, all patients in the control group were advised to apply white petroleum jelly at night on a daily basis. Concomitant use of any medication was not allowed during the study. The participants were advised to avoid the use of cow meat, salty fish, and cheese in the diet, as these dietary components may aggravate the disease as per the Unani concept (Ibn Rushd, 1980).

2.5. Herbal medicine product

The trial formulations *Itrīfal Shāhtra* and *Marham Ḥina* were chosen from authentic Unani Pharmacopoeias– *Qarābādīn-ī A'ẓam wa Akmal* (Khān, 2005) and National Formulary of Unani Medicine respectively (Anonymous, 2011). The ingredients and components used in the formulations are listed in Table 1.

2.6. Dosage regimen and quantitative description

Participants in the Unani group were advised to take 6 g semisolid paste of *Itrīfal Shāhtra* orally twice daily with about 200 ml of water before meals followed by the topical application of *Marham Ḥina* on the affected sites twice daily in an amount sufficient to cover skin lesion for a period of 12 weeks. Participants in the control group were given 10 mg tablets of 8-methoxypsoralen and advised to take two tablets for 31–40 kg body weight, three tablets for 41–60 kg body weight, and four tablets for >60 kg body weight on alternate days after breakfast followed by daily application of petrolatum to the affected site at bedtime (Shenoi and Prabhu, 2014). All participants, whether in the test or control group, were advised to expose the lesions to sunlight after 1½ to 2½ hours of taking oral medications.The optimum time for sunlight was 7–8 a.m. in the summer and 8–9 a.m. in the winter seasons, and the duration of sun exposure was 5 min on the 1st sitting, which was gradually increased by 2 min every third sitting until mild erythema developed.

Table 1
Composition of *Itrīfal Shāhtra* (Khān, 2005) and *Marham Hina* (Anonymous, 2011).

Drug (Botanical/scientific name)	Part used	Quantity
Itrīfal Shāhtra		
1. Sana Makki (*Senna alexandrina* Mill.)	Leaf	63.75 g
2. Āmla Khushk (*Phyllanthus emblica* L.)	Fruit	42.50 g
3. Post Halyla Zard (*Terminalia chebula* Retz.)	Half ripe fruit	63.75 g
4. Shāhtra (*Fumaria parviflora* Lam.)	Whole plant	42.50 g
5. Rewand (*Rheum australe* D. Don)	Root	21.25 g
6. Post Halyla Siyāh (*Terminalia chebula* Retz.)	Unripe fruit	42.50 g
7. Roghan-i Badam Shīrīn (*Prunus amygdalus* Batsch)	Kernel Oil	100 g
8. Shahad Khālis (honey)	Honey	830 g
Marham Ḥina		
1. Roghan Ḥina (*Lawsonia inermis* L.)	Oil	15 L
2. Kāfūr (*Cinnamomum camphora* (L.) J. Presl.)	Camphor	1.5 kg
3. Satt-i Pudīna (*Mentha arvensis* L.)	Dried herb extracts	700 g
4. Satt-i Ajwain (*Trachyspermum ammi* (L.) Sprague)	Dried seed-like fruit extracts	700 g
5. Mom Khālis (wax)	Wax	7 kg
6. Vaseline Safaid (petroleum jelly)	Jelly	3 kg

2.7. Qualitative testing and preparation of Unani formulations

All the ingredients of both formulations were sourced entirely from registered Herbalist, and Botanist Dr. Kashif Husain of NRIUMSD, Hyderabad identified and authenticated the plant drugs. The voucher specimens were also deposited in the museum of Survey of Medicinal Plants Unit of NRIUMSD, Hyderabad with voucher specimen numbers, *Senna alexandrina* Mill. (SMPU/CRI-HYD14293), *Phyllanthus emblica* L. (SMPU/CRI-HYD14294), *Terminalia chebula* Retz. (Post Halayla Zard: SMPU/CRI-HYD14295), *Terminalia chebula* Retz. (Halayla Siyāh: SMPU/CRI-HYD14296), *Rheum australe* D. Don (SMPU/CRI-HYD14297), *Cinnamomum camphora* (L.) J. Presl (SMPU/CRI-HYD14298), *Mentha arvensis* L. (SMPU/CRI-HYD14299), *Trachyspermum ammi* (L.) Sprague (SMPU/CRI-HYD14300), *Fumaria parviflora* Lam. (SMPU/CRI-HYD14301), and *Lawsonia inermis* L. (SMPU/CRI-HYD14302). The botanical names of the plants were also verified using two online databases: http://www.theplantlist.org and http://www.worldfloraonline.org. Both formulations were prepared at GMP-certified Pharmacy of National Research Institute of Unani Medicine for Skin Disorders, Hyderabad, following standard methods described in *Qarābādīn-ī A'ẓam wa Akmal* and National Formulary of Unani Medicine (Khān, 2005; *Anonymous*, 2011).

2.7.1. HPTLC fingerprint analysis

2.7.1.1. Instrumentation and chromatographic conditions. All chemicals and solvents used were of HPLC grade. HPTLC instrument of Desaga Sarstedt Gruppe (Germany) was used. TLC development chamber used was a Twin-trough chamber (20 × 10 cm). TLC aluminium plates precoated with silica gel 60 F254 (Merck KGaA, Germany) were used as stationary phase (200 × 100 mm, 0.2 mm thick). Distance of sample applied on TLC plate was kept 10 mm from the bottom and 20 mm from left side. Volume applied was 5 μL; band length was 10 mm; distance between tracks was 20 mm. The development distance of TLC plate or height of mobile phase developed was 80 mm.

2.7.1.2. HPTLC fingerprinting of Itrīfal Shāhtra. **HPTLC analysis of ethanol extract:** *Itrīfal Shāhtra* formulation sample (5 g) was taken in a conical flask and 100 ml ethanol was added. The flask was placed over the laboratory orbital shaker at 130 rpm for 6 h, then it was removed from shaker, and its contents were filtered through the Whatman filter paper no. 1 and the resultant filtrate was concentrated to 5 ml. The extract obtained was subjected to TLC analysis.

The extract was applied in triplicate on silica gel 60 F254 TLC plate and developed the TLC plate in Twin-trough chamber with the mobile phase as toluene: ethyl acetate: methanol (6: 2:1, *v/v/v*). The plate was developed up to the height of 80 mm from bottom edge of the plate. After development, TLC plate was removed from the Twin-trough chamber and dried in air. The TLC plate was detected under UV λ 366 nm, UV λ 254 nm and after derivatization with vanillin sulphuric acid reagent and photographed as shown in Fig. 1. *Itrīfal Shāhtra* upon detection under UV λ 366 nm, ethanol extract showed seven spots at R_f values 0.06 (blue), 0.16 (brown), 0.20 (pale yellow), 0.30 (pink), 0.39 (blue), 0.57 (blue), 0.97 (greenish pink); upon detection under UV λ 254 nm, ethanol extract showed four spots at R_f values 0.07, 0.14, 0.20, 0.46 (all black colour); upon detection after derivatization with vanillin sulphuric acid reagent at 580 nm, ethanol extract showed seven spots at R_f values 0.14, 0.20, 0.43, 0.61, 0.73, 0.86, 0.99 (all grey colour) (Fig. 1).

HPTLC analysis of hydroethanol extract: *Itrīfal Shāhtra* formulation sample (5 g) was taken in a conical flask and 100 ml of ethanol and distilled water (1:1 ratio) was added for hydroethanol (50% ethanol : 50% water) extract. The flask was placed over the laboratory orbital shaker at 130 rpm for 6 h, then it was removed from shaker, and its contents were filtered through the Whatman filter paper no. 1 and the

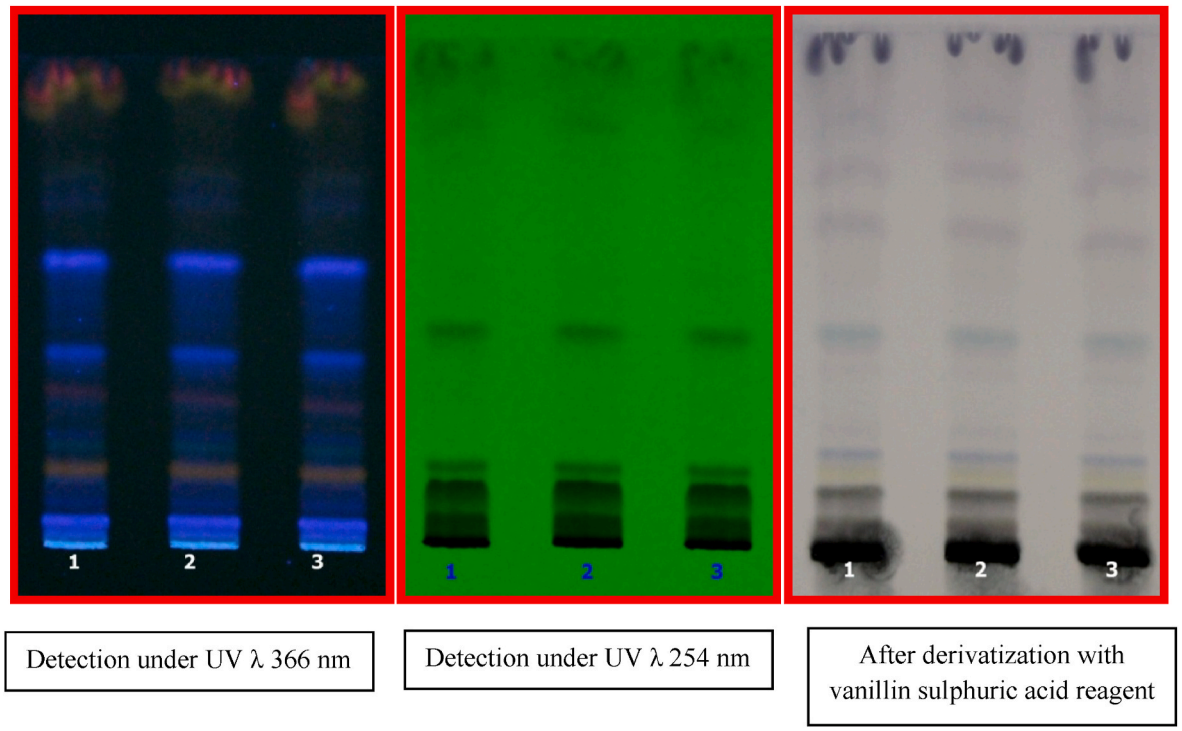

Fig. 1. Developed TLC plate of *Itrīfal Shāhtra* formulation ethanol extract in toluene: ethyl acetate (8:2, *v/v*) applied in triplicate.

resultant filtrate was concentrated to 5 ml. The extract obtained was subjected to TLC analysis.

The extract was applied in triplicate on silica gel 60 F254 TLC plate and developed the TLC plate in Twin-trough chamber with the mobile phase as toluene: ethyl acetate: methanol (7: 2:1, *v/v/v*). The plate was developed up to the height of 80 mm from bottom edge of the plate. After development, TLC plate was removed from the Twin-trough chamber and dried in air. The TLC plate was detected under UV λ 366 nm and UV λ 254 nm and photographed as shown in Fig. 2. *Itrīfal Shāhtra* upon detection under UV λ 366 nm hydroethanol extract showed eight

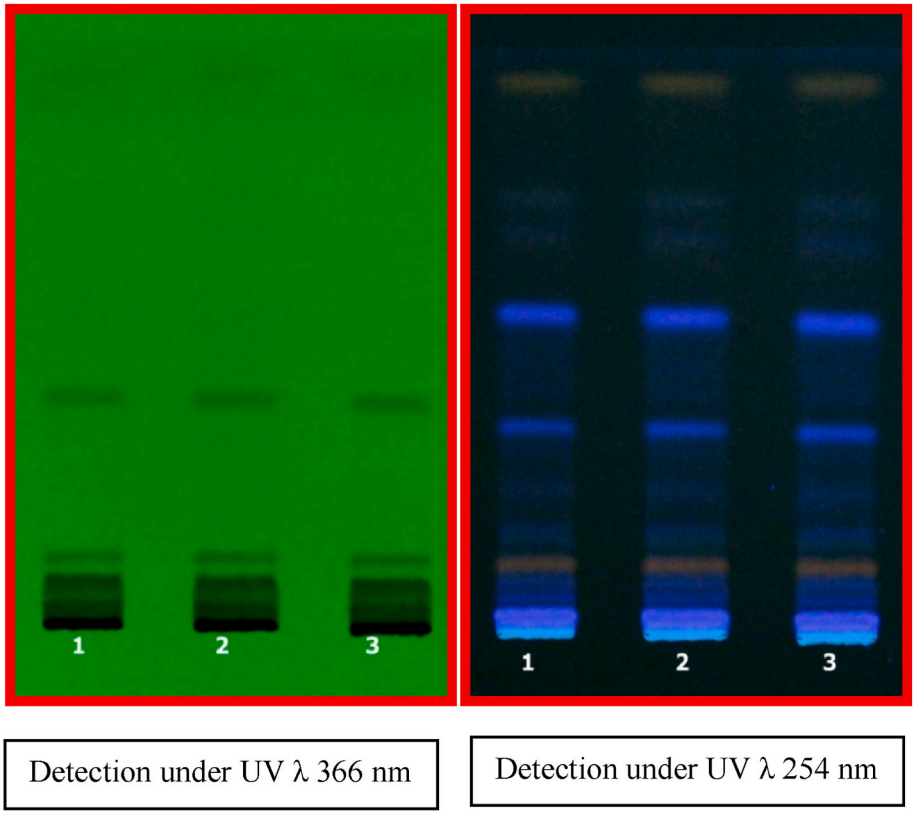

Fig. 2. Developed TLC plate of *Itrīfal Shāhtra* formulation hydroethanol extract in toluene: ethyl acetate: methanol (7: 2: 1, *v/v/v*) applied in triplicate.

spots at R_f values 0.06 (blue), 0.11 (brown), 0.17 (blue), 0.36 (blue), 0.54 (blue), 0.69 (light blue), 0.74 (light blue), 0.97 (brown); upon detection under UV λ 254 nm, hydroethanol extract showed four spots at R_f values 0.03, 0.07, 0.11, 0.36 (all black colour) (Fig. 2).

2.7.1.3. HPTLC fingerprinting of Marham Ḥina. **HPTLC analysis of ethanol extract:** *Marham Ḥina* formulation sample (5 g) was taken in a conical flask and 100 ml ethanol was added. The flask was placed over the laboratory orbital shaker at 130 rpm for 6 h, then it was removed from shaker, and its contents were filtered through the Whatman filter paper no. 1 and the resultant filtrate was concentrated to 5 ml. The extract obtained was subjected to TLC analysis.

The extract was applied in triplicate on silica gel 60 F254 TLC plate and developed the TLC plate in Twin-trough chamber with the mobile phase as toluene : ethyl acetate (8 : 2, *v/v*). The plate was developed up to the height of 80 mm from bottom edge of the plate. After development, TLC plate was removed from the Twin-trough chamber and dried in air. The TLC plate was detected under UV λ 366 nm, UV λ 254 nm and after derivatization with vanillin sulphuric acid reagent and photographed as shown in Fig. 3. *Marham Ḥina* upon detection under UV λ 366 nm, ethanol extract showed five spots at R_f values 0.16, 0.61, 0.71, 0.80, 0.93 (all blue colour); upon detection under UV λ 254 nm, ethanol extract showed three spots at R_f values 0.57, 0.64, 0.71 (all black); upon detection after derivatization with vanillin sulphuric acid reagent at 580 nm, ethanol extract showed seven spots at R_f values 0.07, 0.47, 0.54, 0.64, 0.77, 0.80, 0.99 (all purple colour) (Fig. 3).

In summary, HPTLC fingerprinting was carried out by ethanol and hydroethanol extracts of *Itrīfal Shāhtra* and ethanol extract of *Marham Ḥina*. The fingerprint pattern shown in the TLC plate photographed under UV λ 366 nm, UV λ 254 nm and after derivatization with vanillin sulphuric acid reagent is unique for its identification characters with the obtained R_f values. The developed fingerprint for *Itrīfal Shāhtra* and *Marham Ḥina* will serve as a standard for identification and will also help in the quality control check. Thus, the present study will serve as a reference fingerprint standard for quality control and in future studies.

2.8. Rationale for the type of control used

Photochemotherapy (PUVA) is a well-known and well-studied treatment modality for psoriasis that involves systemic or topical delivery of chemicals known as psoralens, followed by increasing doses of ultraviolet radiation after a time gap (Racz and Prens, 2015). Furthermore, petrolatum was utilized to minimize erythema caused by sun exposure in the control group (Khanna et al., 2018).

2.9. Outcomes

2.9.1. Primary outcome measures

The primary outcome measure was the change in PASI score, a well-established method for determining the severity of psoriasis (Fredriksson and Pettersson, 1978; Lakhani et al., 2016), expressed as mean PASI reduction at each visit. Additionally, the frequency and proportion of participants who attained reductions in PASI scores of 75% and 90% after 12 weeks of treatment were calculated.

2.9.2. Secondary outcome measures

The change in patient global assessment (PGA) was assessed at baseline and 12 weeks after treatment using a 100 mm VAS, in which participants were asked to place a mark on the 100 mm printed scale corresponding to their disease severity level and the distance in millimetres between zero and the participant's mark was measured and recorded (Wewers and Lowe, 1990). Additionally, subjective parameters such as erythema, induration, scaling, and itching were evaluated at each visit using a 5-point scale (Langley et al., 2015).

2.10. Safety and adverse event monitoring

To ascertain the safety of the interventions, local dermal tolerability, changes in vital signs at each follow-up visit, and routine laboratory investigations, such as hemogram (Hb, TLC, DLC, ESR), urine examinations (routine and microscopic), liver function tests (SGOT, SGPT, S. Alkaline Phosphatase, and S. Bilirubin), kidney function tests (S.

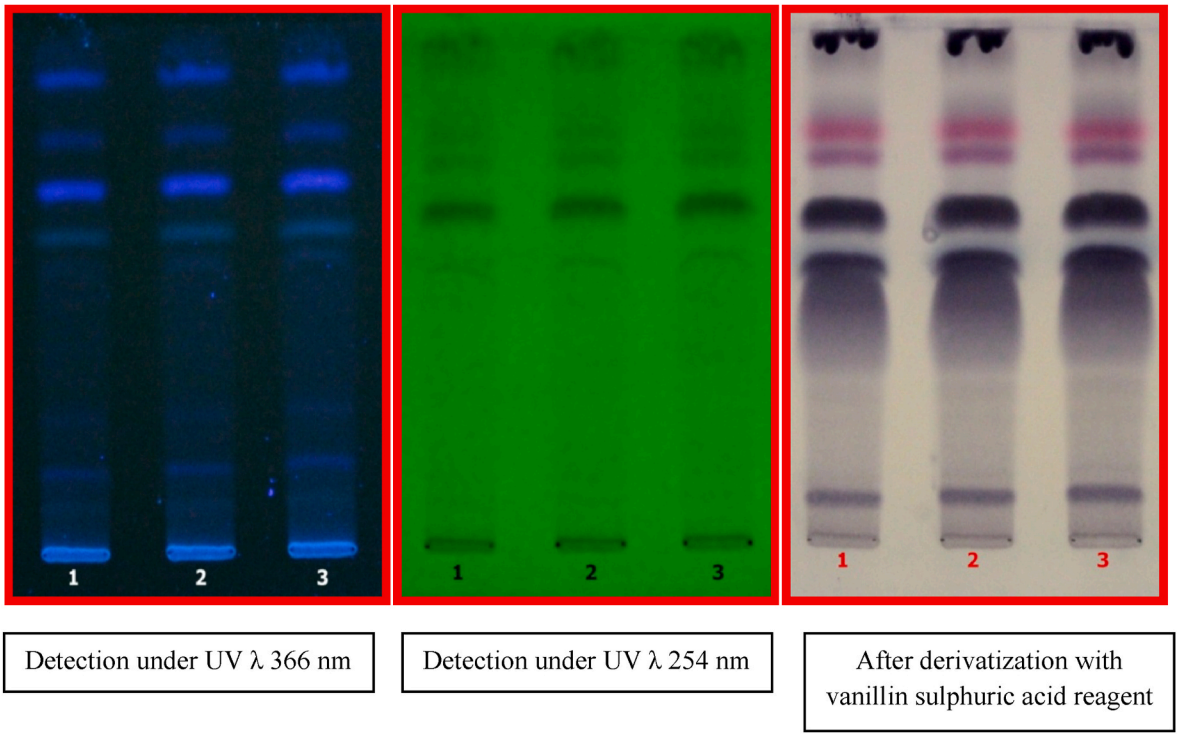

Fig. 3. Developed TLC plate of *Marham Ḥina* formulation ethanol extract in toluene: ethyl acetate (8:2, *v/v*) applied in triplicate.

Creatinine and Blood Urea), ECG and CXR were performed at baseline and after completion of the trial. Any adverse event that occurred during the course of the study was appropriately monitored and documented in the adverse event monitoring form.

2.11. Withdrawal criteria

Participants were withdrawn from the study if they developed adverse effects that necessitated additional therapy, voluntarily withdrew, or missed more than two consecutive treatment sessions.

2.12. Sample size

The sample size was calculated to have at least 80% power to establish the equality of Unani formulations to control drugs for the efficacy comparison of PASI 75 responses at week 12, at a two-sided significance level of 0.05, the ratio of sample size, unexposed/exposed (κ): 1, the proportion of outcome of interest in the control group (p_2): 37.5, the proportion of expected outcome of interest in the Unani group (p_1): 75.0, and the difference between the true mean response rates of Unani and control drugs (ε): 0.375. The following formula was used for the statistical analysis $n_2 = \frac{(z_{\alpha/2}+z_{\beta})^2[p_1(1-p_1)+p_2(1-p_2)]}{\varepsilon^2}$, $n_1 = \kappa n_2$ (Chow et al., 2017). In the original calculation, the total sample size was determined to be 55, with a 10% dropout rate. Since the COVID-19 restrictions have increased dropout rates, our total sample size needed to be increased by 66 participants in order to be adequate. The sample size also provided 80% power to demonstrate the difference between Unani and control groups at week 12.

2.13. Randomization

Participants were assigned to two parallel treatment groups using block randomization. The statistics department of the institute created four-person randomization blocks and delivered them to the investigator in sequentially numbered, sealed, opaque envelopes.

2.14. Statistical methods

The data were entered into spreadsheet software, Microsoft Excel, and analyzed using statistical software, SYSTAT-v12 (by Systat Software Inc. California) and IBM SPSS Statistics v23 (by IBM Corporation). The proportion (percent), mean, and standard deviation (SD) of the data were appropriately represented. The Chi-square test, independent samples t-tests, paired sample t-tests, Friedman tests, and Mann-Whitney U tests, were applied to draw conclusions; $p < 0.05$ was deemed significant for this study.

2.15. Ethical approval

This research complied with all applicable national and institutional regulations, as well as the precepts of the Helsinki Declaration (as revised in 2013), and was approved on 25-11-2019 by the Institutional Ethics Committee (IEC), NRIUMSD, Hyderabad (Ref. No. 38–18/2018-19/CRIUM/Tech/IEC-10/08). Following ethical approval, the trial was prospectively registered with the Clinical Trial Registry - India under the clinical trial registration number CTRI/2020/03/023697 on 02 March 2020. Before patients were enrolled in the study, the trial procedures were explained to them in their native language, and written and informed consent was obtained.

3. Results

3.1. Participant flow

A total of 122 patients were evaluated for eligibility, with 66 people meeting the study requirements being accepted into the study. Of the remaining 56 participants, 32 did not match inclusion criteria, 20 were not willing to come for regular follow-up visits for entire duration of the study due to travel difficulties, and 4 had additional issues that precluded them from participating in the trial. Out of 32 participants who did not match the inclusion criteria, 11 were of plaque psoriasis with PASI <10%, 8 were of other types of psoriasis, 6 were of diabetic mellitus, 4 were of hypertension, 2 had a history of cardiovascular disease, and one was a pregnant woman. Out of the 66 patients that were enrolled, 50 completed the course of treatment and 16 were lost to follow-up, discontinued interventions or excluded from the analysis. A statistical analysis was conducted on 50 participants who had completed the therapy regimen (Fig. 4).

3.2. Clinico-demographic profile

The mean ± SD age of participants in the Unani group was 33.8 ± 9.6 years, with 19 (76%) males and 6 (24%) females while in control group it was 34.2 ± 10.9 years, with 15 (60%) males and 10 (40%) females. The mean ± SD of disease chronicity was 6.6 ± 3.0 years and 7 ± 3.38 years in Unani and control groups respectively. Out of 50 participants, the majority 34 (68%) belonged to lower middle class followed by upper lower class 13 (26%) and upper class 3 (6%) participants. Furthermore, only 19 (38%) participants had relevant family history, whereas 31 (62%) had no prior history. Diet-wise, the majority of participants 41 (82%) followed a mixed diet pattern, while 9 (18%) followed a vegetarian diet. Most of the participant 27 (54%) had BMI of 18.5–24.9 kg/m^2, followed by 15 (30%) had 25.0–29.9 kg/m^2, 6 (12%) had 15.4–18.4 kg/m^2 and 2 (4%) had >30 kg/m^2. Temperament-wise maximum participants 20 (40%) had *Sawdāwī Mizāj*, followed by *Balghamī Mizāj* 15 (30%), *Damwī Mizāj* 8 (16%), and *Ṣafrāwī Mizāj* 7 (14%). In terms of demographic and clinical characteristics, the baseline distribution of individuals in the Unani and control groups was comparable, with statistically insignificant ($p > 0.05$) differences between them (Table 2).

3.3. Change in PASI score

In the Unani group, the mean ± SD of PASI was 27.88 ± 12.01 at baseline, which was reduced to 16.39 ± 8.01 at 1st follow-up, 10.74 ± 6.17 at 2nd follow-up, and 5.01 ± 4.59 after completion of the study. However, in the control group, the mean ± SD of PASI was 23.61 ± 9.79 at baseline, which was reduced to 18.98 ± 8.89 at 1st follow-up, 15.87 ± 8.72 at 2nd follow-up, and 9.85 ± 7.16 after completion of the study. Both groups showed a statistically significant reduction in PASI score ($p < 0.0001$). However, between-group analysis revealed statistically significant differences at the second follow-up ($p = 0.02$) and after the trial completion ($p = 0.006$). (Table 3).

In terms of clinically significant endpoints, 19 (76%) of the 25 patients in the Unani group and 6 (24%) of the 25 patients in the control group obtained a PASI 75 response at 12 weeks. The difference was statistically significant with a p-value of <0.0001, indicating that Unani drugs may be statistically superior to control drugs. Although clinical superiority could not be asserted as the sample size was not calculated with a superiority margin and a one-tailed statistic. In addition, 9 (36%) of 25 patients in the Unani group and 1 (4%) of 25 patients in the control group achieved PASI 90, while 2 (8%) of 25 patients in the Unani group attained PASI 100, although no patient in the control group did so (Table 4) (Fig. 5).

3.4. Improvement in patient's global assessment (PGA)

The mean ± SD PGA score in both Unani and control groups was significantly ($p < 0.0001$) reduced from 74.20 ± 13.97 and 73.60 ± 9.63 at baseline to 9.28 ± 7.41 and 26.28 ± 14.44 after completion of the trial, respectively. However, Unani group may be superior in terms

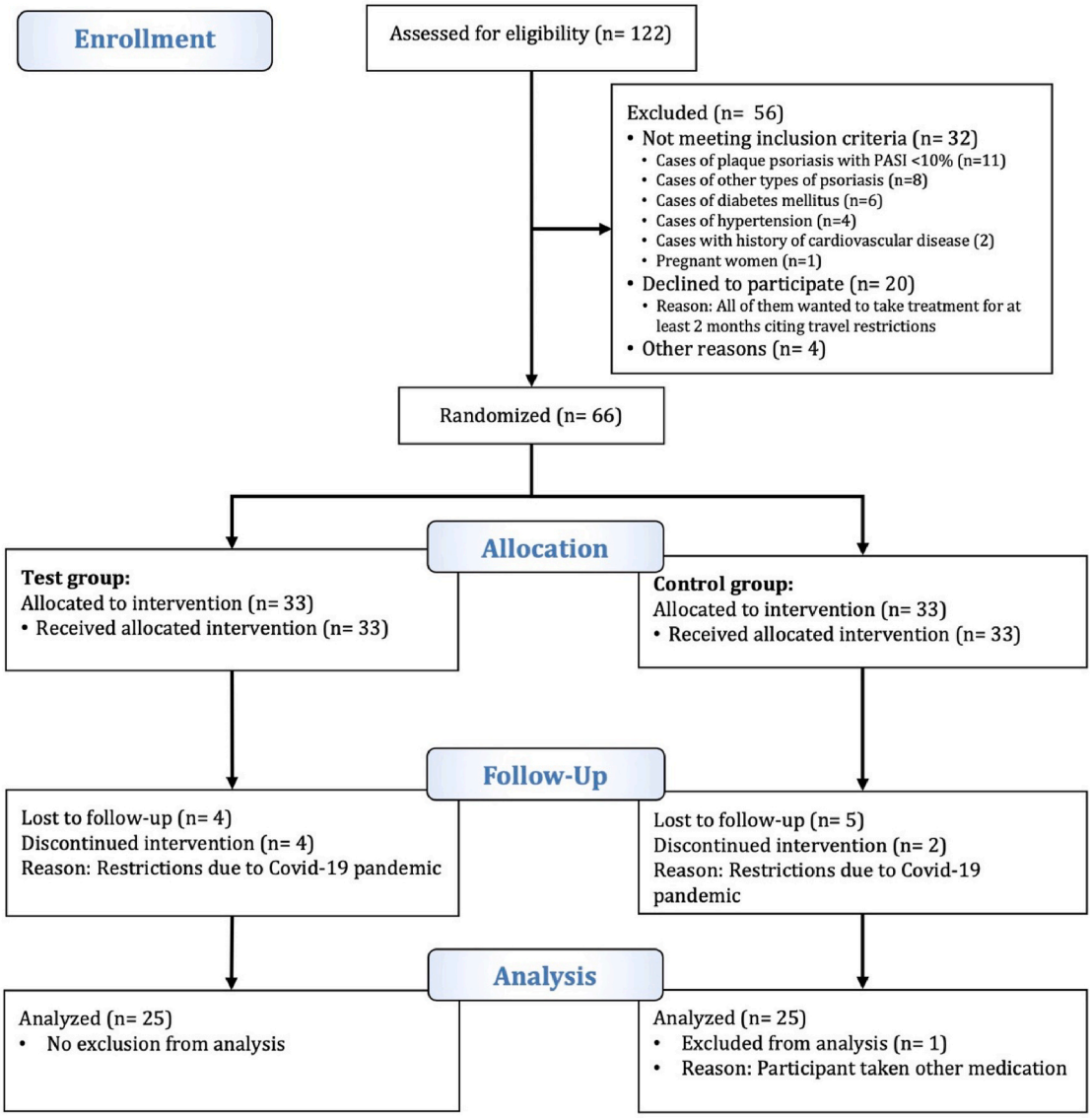

Fig. 4. CONSORT flow diagram of the participant included in the trial.

of efficacy, as between-group analysis revealed a statistically significant difference in after treatment variables ($p < 0.0001$), while baseline variables were statistically equal in both groups ($p = 0.86$) (Table 5).

3.5. Change in subjective parameters

The subjective parameters erythema, induration, scaling, and itching were evaluated on a 5-point scale at each visit and then analyzed using the Friedman test for within-group comparisons and the Mann-Whitney *U* test for between-group comparisons.

The mean rank of erythema in the Unani group was 3.98 at baseline; it decreased significantly to 2.94, 1.94, and 1.14 at the first, second, and third follow-ups, respectively ($p < 0.0001$). Likewise, in the control group, it significantly decreased from baseline 3.84 to 2.90, 2.10, and 1.16, respectively ($p < 0.0001$). The between-group analysis demonstrated a significant difference between the Unani and control groups in the improvement of erythema at the second and third follow-ups with p-values of 0.021 and 0.006, respectively (Table 6).

The mean rank of induration in the Unani group was 3.84 at baseline; it significantly decreased to 2.90, 1.98, and 1.28 at the first, second, and third follow-ups, respectively ($p < 0.0001$). Similarly, in the control group, it decreased significantly from baseline 3.48 to 3.12, 2.04, and 1.36, respectively ($p < 0.0001$). Intergroup analysis demonstrated a statistically significant difference between the Unani and control groups in lowering induration at the first, second, and third follow-ups, with respective p-values of 0.05, 0.01, and 0.003 (Table 6).

The mean rank of scaling in the Unani group was 3.88 at baseline; it significantly reduced to 2.82, 2.00, and 1.30 at first, second, and third follow-ups, respectively ($p < 0.0001$). Likewise, in the control group, it was significantly reduced from baseline 3.60 to 2.86, 2.14, and 1.40, respectively ($p < 0.0001$). The between-group analysis showed a statistically significant difference between the Unani and control groups in the amelioration of scaling at the first, second, and third follow-ups, with respective p-values of 0.038, 0.006, and 0.0001.(Table 6).

The mean rank of itching in the Unani group was 4.00 at baseline; it significantly reduced to 2.76, 2.00, and 1.24 at first, second, and third follow-ups, respectively ($p < 0.0001$). Similarly, in the control group, it significantly reduced from baseline 3.68 to 2.94, 2.12, and 1.26, respectively ($p < 0.0001$). Intergroup analysis demonstrated a statistically significant difference between the Unani and control groups in the reduction of itching at the first, second, and third follow-ups, with respective p-values of 0.003, 0.005, and 0.001 (Table 6).

Table 2
Demographic and clinical profile of the participants in Unani vs control groups.

Characteristics	Unani group	Control Group	p-Value
Age			
Mean ± SD, range, years	33.8 ± 9.6, 36	34.2 ± 10.9, 42	p > 0.05[a]
Chronicity (disease duration)			
Mean ± SD, range, years	6.6 ± 3.0, 9	7.0 ± 3.38, 14	p > 0.05[a]
Gender			
Male, n, %	19 (76%)	15 (60%)	p > 0.05[b]
Female, n, %	6 (24%)	10 (40%)	
Socio-economic status			
Upper, n, %	1 (4%)	2 (8%)	p > 0.05[b]
Lower middle, n, %	14 (56%)	20 (80%)	
Upper lower, n, %	10 (40%)	3 (12%)	
Family history			
Present, n, %	11 (44%)	8 (32%)	p > 0.05[b]
Absent, n, %	14 (56%)	17 (68%)	
Diet			
Vegetarian, n, %	6 (24%)	3 (12%)	p > 0.05[b]
Mixed, n, %	19 (76%)	22 (88%)	
BMI (Kg/m^2)			
15.4–18.4	3 (12%)	3 (12%)	p > 0.05[b]
18.5–24.9	12 (48%)	15 (60%)	
25.0–29.9	8 (32%)	7 (28%)	
30.0–31.7	2 (8%)	0 (0%)	
***Mizāj* (temperament)**			
Damwī (sanguine), n, %	1 (4%)	7 (28%)	p > 0.05[b]
Balghamī (phlegmatic), n, %	9 (36%)	6 (24%)	
Ṣafrāwī(bilious), n, %	5 (20%)	2 (8%)	
Sawdāwī (melancholic), n, %	10 (40%)	10 (40%)	

[a] Independent samples *t*-test.
[b] Chi-square/Fisher exact test.

Table 3
Change in PASI score from baseline to final follow-up.

Within-group analysis				
Group	Follow-up	Mean ± SD	Mean difference	p-Value[a]
Test	Baseline	27.88 ± 12.01	22.87	0.0001
	After treatment	5.01 ± 4.59		
Control	Baseline	23.61 ± 9.79	13.76	0.0001
	After treatment	9.85 ± 7.16		
Between-group analysis				
Follow-up	**Group**	**Mean±SD**	**Mean difference**	**p-Value[b]**
Baseline	Test	27.88 ± 12.01	4.27	0.174
	Control	23.61 ± 9.79		
1st Follow-up	Test	16.39 ± 8.01	−2.59	0.284
	Control	18.98 ± 8.89		
2nd Follow-up	Test	10.74 ± 6.17	−5.13	0.020
	Control	15.87 ± 8.72		
3rd Follow-up	Test	5.01 ± 4.59	−4.84	0.006
	Control	9.85 ± 7.16		

[a] Paired samples *t*-test.
[b] Independent samples *t*-test.

Table 4
The per-protocol analysis of patients who achieved PASI 100, 90, 75 and 50 at 12 weeks in Unani treatment group vs PUVAsol group.

Percentage reduction in PASI	Test (n = 25)	Control (n = 25)	Difference (test vs. control)	p-Value[a]
PASI >50	25 (100.0%)	18 (72.0%)	7 (28%)	0.01
PASI >75	19 (76.0%)	6 (24.0%)	13 (52%)	0.0001
PASI>90	9 (36.0%)	1 (4.0%)	8 (32%)	0.011
PASI 100	2 (8.0%)	0 (0.0%)	2 (8%)	0.49

[a] Fisher Exact test.

3.6. Adverse events

The total number of participants experiencing clinical side effects was significantly greater in the PUVA sol group (20%) than in the Unani group (4%) (p = 0.001). Three (12%) patients treated with PUVA sol experienced gastrointestinal side effects, compared to one (4%) patient treated with Unani. Additionally, 1 (4%) case of phototoxicity and 1 (4%) case of headache were observed in patients treated with PUVA sol, however, none of the participants receiving Unani treatment experienced these adverse events.

4. Discussion

4.1. Interpretation

The mean ± SD age of all 50 participants was 34 ± 10 years, with the majority of individuals being between the ages of 21 and 40, in line with Nevitt et al. findings that psoriasis is more prevalent in the fourth and fifth decades of life (Nevitt and Hutchinson, 1996). Gender wise, the majority of participants were male, with 68% males and only 32% females, which corresponds to Valia's interpretation of male preponderance in psoriasis (Valia RG, 2010). The familial incidence was found only in 38% participants following the report of Freedberg et al. (Freedberg et al., 2003). Out of 50 cases, the majority (68%) were found to be from the lower middle classindicating the highest incidence in the lower middle class, consistent with the report of Mahé et al. (2017). Temperament-wise data complies with *Ibn-i Zuhr* and *Alī Ibn Abbās Majūsī,* who assert that people with *Sawdāwī* (melancholic) dispositions are more prone to this disease. Diet-wise, the majority of individuals (82%) consumed a mixed diet, compared to 18% who consumed a vegetarian diet, which is consistent with traditional Unani medical literature that attributes the development of psoriasis to dietary components such as cattle, cow meat, salty fish, and cheese (Ibn Rushd, 1980). The per-protocol analysis found that the test formulations performed better than the control medications on clinically relevant endpoints, PASI 50 and PASI 75, with all 25 subjects attaining PASI 50 and 76% attaining PASI 75. Similarly, the mean reduction of PASI, patient global evaluation, and subjective parameters were statistically and clinically different from those of the control medications. Several studies published recently demonstrated the efficacy of both traditional and conventional therapies in reducing PASI in psoriasis patients. Khanna et al. in a per-protocol analysis found that PASI 50 was achieved at 12 weeks in 71.4% of patients treated with Unani formulations and 65.2% of patients treated with PUVAsol (Khanna et al., 2018). Gahalaut et al. observed in a per-protocol assessment of 40 patients with psoriasis treated with PUVA sol that 20% attained PASI 75, 40% attained PASI 50, and 10% experienced disease exacerbation at 12 weeks (Gahalaut et al., 2014). Aggarwal et al. found that 75% of patients achieved PASI 50 at 12 weeks in a trial of 36 patients with chronic plaque psoriasis, 20 of whom received PUVA sol (Aggarwal et al., 2013). Kar et al. showed complete clearance of chronic plaque psoriasis in 32% of patients and >50% reduction in 44% of individuals treated for eight weeks with PUVA sol (Kar et al., 1994). Talwalkar et al. observed a 95% reduction in 40.7% of patients and greater than 50% reduction in 22% of patients receiving PUVA sol (Talwalkar et al., 1981).

By comparing the effect of *Itrīfal Shāhtra* and *Marham Ḥina*on psoriasis to the findings of Khanna et al., Gahalaut et al., Aggarwal et al., Kar et al., and Talwalkar et al., it may be concluded that Unani formulations have a greater potential for reducing severity of chronic plaque psoriasis in human participants.

In this study, the dropout was 24.24%, whereas a 10% dropout was assumed while calculating the sample size. As a general rule, a dropout rate >20% raises risk of bias and lowers internal validity. However, there is no certainty that results from a study with a dropout rate of <20% are free from bias (Higgins et al., 2011). The key reason of little higher dropout rate in this study was travel restrictions due to the

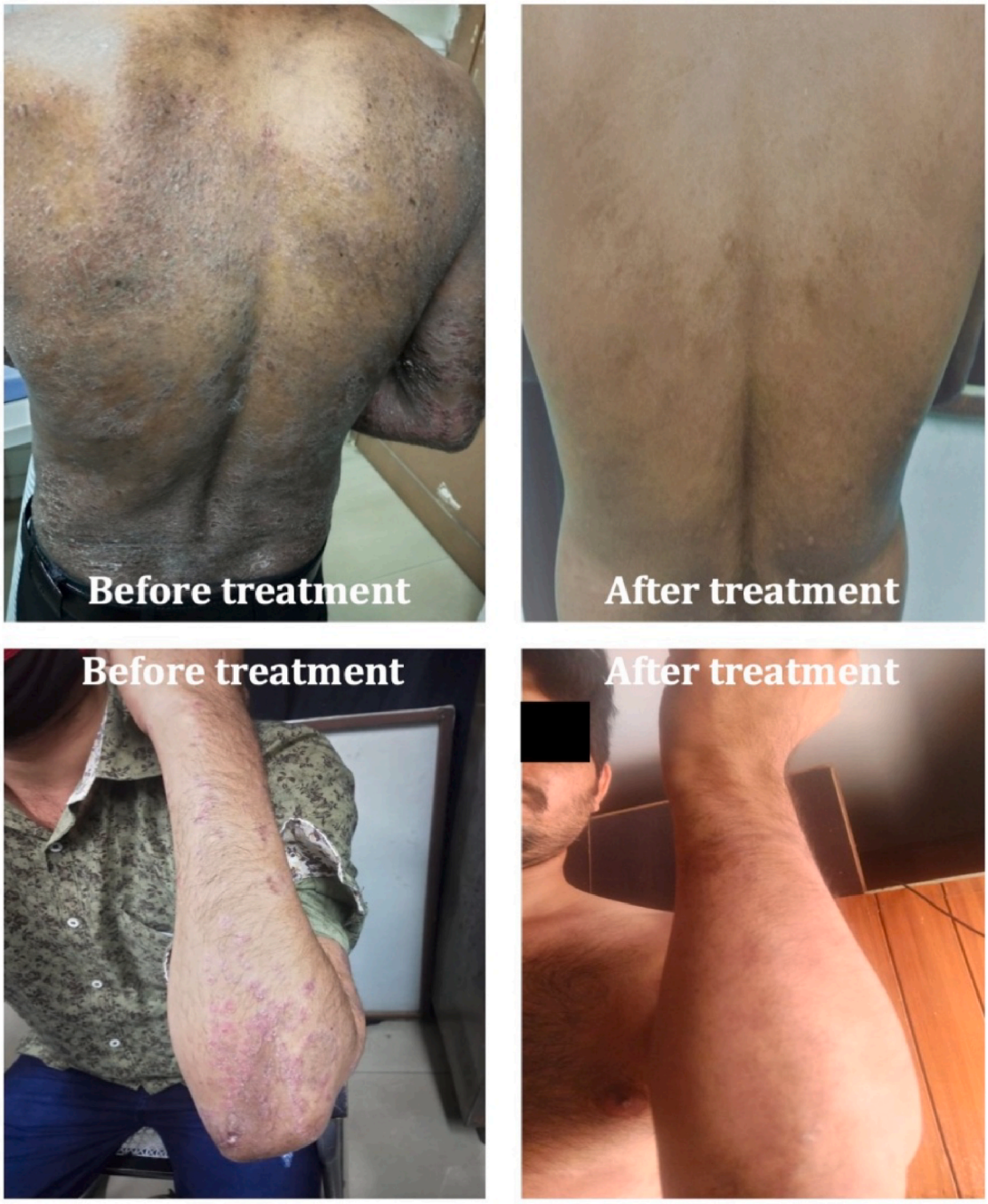

Fig. 5. The response of Unani drugs after a 12-week treatment period.

COVID-19 pandemic; however the dropout rate of present study was lower than that reported in previous studies of psoriasis, which indicated a dropout rate of approximately 28% (Gahalaut et al., 2014; Khanna et al., 2018).

4.2. Overall evidence

The study inferred that both interventions improved the primary and secondary outcomes significantly, but the intergroup difference was statistically significant, indicating that Unani formulations may be statistically superior to the control medications. Although clinical superiority could not be asserted since the sample size was not determined using a superiority margin (clinically meaningful difference) and a one-tailed statistic. Wan et al. determined in a systematic review that the maximum acceptable clinical differences (superiority margin) for systemic psoriasis treatments ranged from 14 to 20% (Wan et al., 2019). Thus, to establish the superiority of the Unani formulations, a sample size of at least 96 is necessary, with 48 participants in each group, assuming the identical assumptions as in the current study and a minimal superiority margin (Chow et al., 2017).

The reduction in disease activity may be attributed to the *Muṣaffi-i Dam* (blood purifier), *Munḍij wa Mushil-i Sawdā'* (concoctive and purgative of melancholic humor), and *Muraṭṭab-i-'Umūmi* (emollient) actions of *Itrīfal Shāhtra,* as well as *Dāfi'-i-Waram* (anti-inflammatory), *Dāfi'-i-'Ufūnat* (disinfectant), *Mumallis* (emollient), and *Musakkin-i Maqāmī* (local sedative) properties of *Marham Ḥina* described in classical Unani literature (Khān, 2005; Anonymous, 2011) and corroborated by pharmacological studies of their ingredients. *Shāhtra* (*Fumaria parviflora* Lam.), the primary ingredient in *Itrīfal Shāhtra,* has been used for a variety of skin disorders since antiquity and has been reported to have

Table 5
Change in patient's global assessment (PGA) from baseline to final follow-up.

Within-group comparison				
Group	Follow-up	Mean ± SD	Mean difference	p-Value[a]
Test	Baseline	74.20 ± 13.97	64.92	0.0001
	After treatment	9.28 ± 7.41		
Control	Baseline	73.60 ± 9.63	47.320	0.0001
	After treatment	26.28 ± 14.44		
Between-group comparison				
Follow-up	**Group**	**Mean±SD**	**Mean difference**	**p-Value[b]**
Baseline	Test	74.20 ± 13.97	6.00	0.860
	Control	73.60 ± 9.63		
After treatment	Test	9.28 ± 7.41	−17.00	0.0001
	Control	26.28 ± 14.44		

[a] Paired samples *t*-test.
[b] Independent samples *t*-test.

anti-inflammatory, analgesic, and smooth muscle relaxant properties (Gupta et al., 2012). Additionally, fumaric acid, which is found in a variety of plants including fumitory, has been reported to have anti-psoriatic properties (Smith, 2017). The second ingredient *Halyla (Terminalia chebula)* has cytoprotective, antiaging, immunomodulatory and anti-inflammatory activities (Nigam et al., 2020). Moreover, Terminalia chebulanin, a polyphenolic component found in *Terminalia chebula*, reduced M5-induced proliferation and inflammation in keratinocytes and alleviated IMQ-induced psoriatic skin lesions in mice (An et al., 2016). Furthermore, topical application of *Terminalia chebula* cream protects rats against developing psoriasis as a result of UVB exposure (Pai et al., 2020). Other ingredients *Āmla Khushk (Phyllanthus emblica)* and *Rewand (Rheum australe)* have anti-inflammatory (Muthuraman et al., 2011) and antioxidant activities (Khopde et al., 2001; Hu et al., 2014), which appear to contribute to the reduction of psoriatic lesions.

Ḥina (*Lawsonia inermis*), the primary active ingredient of *Marham Ḥina*, possesses anti-inflammatory, antioxidant, analgesic, wound healing, and immunomodulatory properties (Singh et al., 2015), making it likely to improve oxidative stress and decrease keratinocyte proliferation. *Kāfūr* (*Cinnamomum camphora*), the second most important ingredient, has antipruritic and antimicrobial properties; it is also used as a skin penetration enhancer, which makes topical drug delivery to plaque psoriatic lesions more feasible (Chen et al., 2013). *Ajwāin* (*Trachyspermum ammi*) is another important ingredient in *Marham Ḥina,* which possesses anti-inflammatory and antioxidant properties (Zarshenas et al., 2014), while *Pudina* (*Mentha arvensis*) has anti-inflammatory and sedative activities (Verma et al., 2003).

To sum up, the anti-inflammatory and antioxidant activity of *Shāhtra* (*Fumaria parviflora* Lam.), *Halyla (Terminalia chebula)*, *Barg-e-Ḥina* (*Lawsonia inermis*), *Kāfūr* (*Cinnamomum camphora*), *Ajwain* (*Trachyspermum ammi*), and *Pudina* (*Mentha arvensis*) as well as the emollient activity of *Ḥina* (*Lawsonia inermis*) and *Kāfūr* (*Cinnamomum camphora*) all appear to contribute to the reduction of psoriatic lesions; the wound healing property of *Ḥina* (*Lawsonia inermis*) appears to be critical in minimizing pin-point bleeding; the antipruritic property of *Kāfūr* (*Cinnamomum camphora*), analgesic & wound healing property of *Ḥina* (*Lawsonia inermis*), and sedative property of *Pudina* (*Mentha arvensis*), may all contribute to the improvement in clinical characteristics of psoriasis. Still, additional studies are required to confirm the efficacy of each component of *Marham Ḥina* in chronic plaque psoriasis.

4.3. Safety and adverse events

All safety parameters, including hemogram, LFTs, KFTs, FBS, and CUE, were within normal limits in both groups at the conclusion of the trial. In addition, neither ECG nor CXR demonstrated any notable alterations after treatment. Concerning adverse events, these are not uncommon with psoralen-based therapies. Khanna et al. reported that 16% of their patients receiving PUVAsol experienced clinical side effects, the majority of which were gastrointestinal in nature, such as nausea and vomiting (Khanna et al., 2018). Husain et al. discovered that 26.7 percent of their vitiligo patients receiving photochemotherapy with psoralens developed clinical side effects, with 20% experiencing gastrointestinal side effects (Husain et al., 2021). We observed that 20% of patients receiving PUVA sol experienced clinically significant adverse events, the majority of which were gastrointestinal in nature. Unani formulations outperformed PUVAsol in this area as well, with least adverse events reported in the Unani treatment group.

4.4. Strength and limitations of the study

This study was meticulously designed and implemented to reduce the possibility of bias and confounding variables, and it reported following the CONSORT extension for herbal medicine interventions. To avoid information bias, the objective parameter PASI was also employed along with the subjective parameter VAS. The investigator analyzed the findings, which were validated by another professional researcher in this domain. The pathology and biochemistry departments independently

Table 6
Changes in the severity of psoriasis symptoms from baseline to treatment completion (within group and between group analysis).

Group	Mean rank at Baseline	Mean rank at 1st follow-up	Mean rank at 2nd follow-up	Mean rank at 3rd follow-up	p-Value[a]
Erythema					
Test	3.98	2.94	1.94	1.14	0.0001
Control	3.84	2.9	2.1	1.16	0.0001
p-Value[b]	0.681	0.35	0.021	0.006	–
Induration					
Test	3.84	2.9	1.98	1.28	0.0001
Control	3.48	3.12	2.04	1.36	0.0001
p-Value[b]	0.801	0.05	0.01	0.002	–
Scaling					
Test	3.88	2.82	2	1.3	0.0001
Control	3.60	2.86	2.14	1.4	0.0001
p-Value[b]	0.833	0.038	0.006	0.0001	–
Itching					
Test	4	2.76	2	1.24	0.0001
Control	3.68	2.94	2.12	1.26	0.0001
p-Value[b]	0.357	0.003	0.005	0.001	–

[a] Friedman Test (non-parametric, k-related samples).
[b] Mann-Whitney *U* test (non-parametric, 2-Independent samples).

submitted laboratory investigation reports. Additionally, Statistics Department received final data of all outcomes with deidentified groups. To minimize the effect of confounding variables, a thorough randomization procedure was used to evenly distribute participants with known or unknown confounding variables.

The limitations of the study include the reliance on sunlight as a source of ultraviolet radiation, which varies according to time, location, season, and atmospheric conditions, a higher dropout rate that reduces the internal validity in general and absence of post-treatment follow-ups. Additionally, the majority of individuals residing far away from the study location were dropped out due to travel limitations imposed by the COVID-19 outbreak, jeopardizing the study's generalizability. However, the observed changes are statistically as well as clinically significant, which are most likely to be a result of the trial formulations, which improved psoriatic lesions. To sum up, the current findings of the study indicate that *Itrīfal Shāhtra* and *Marham Ḥina* may offer a safe and effective alternative treatment for plaque psoriasis. Thus, it is recommended to conduct the future clinical research on these Unani formulations with large sample size and extended therapy duration.

5. Conclusion

Based on the data presented above, it can be concluded that the herbal Unani formulations *Itrīfal Shāhtra* and *Marham Ḥina* may be statistically superior in the treatment of chronic plaque psoriasis than the control drugs PUVAsol and petrolatum, with comparatively least adverse effects. Despite the limitations of the study, which include a small sample size, an open-label study, and a short treatment period, the results are encouraging that may help to establish the efficacy of *Itrīfal Shāhtra* and *Marham Ḥina* in the treatment of chronic plaque psoriasis in clinical practice. However, to reaffirm their effectiveness as an alternative treatment for chronic plaque psoriasis, the Unani formulations may further be evaluated in well-designed multicentric superiority trials with an adequate sample size.

Declaration of interest

Authors declare no conflicts of interest associated with this publication.

Informed consent

Informed consent was obtained from all participants included in this study.

Ethical approval

Approval taken from Institutional Ethics Committee, CRIUM, Hyderabad (Ref. No. 38–18/2018-19/CRIUM/Tech/IEC-10/08).

Trial registration

Clinical Trial Registry of India (www.ctri.nic.in) registration number CTRI/2020/03/023697.

CRediT authorship contribution statement

Faiza Khatoon: Conceptualization, Methodology, Investigation, Data curation, Writing – original draft. **Mohd Azahar:** Conceptualization, Methodology, Validation, Investigation, Data curation. **Arzeena Jabeen:** Validation, Resources, Data curation, Supervision, Project administration, Funding acquisition. **Qamar Uddin:** Validation, Resources, Data curation, Writing – review & editing, Visualization, Supervision, Funding acquisition. **Nazim Husain:** Conceptualization, Methodology, Formal analysis, Writing – review & editing, Visualization. **Mohammed Abdul Rasheed Naikodi:** Quality testing, Validation, Chemical fingerprinting of Unani formulations.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jep.2022.115456.

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