Original Article

Evaluating the efficacy and safety of *Ātrilāl (Ammi majus* L.*)* against Psoralen in Vitiligo: a single-blind, parallel-group randomized controlled trial

Mozakkir Husain[1], Qamar Uddin[1], Mohammad Nawab[1], Younis Iftikhar Munshi[2]

ABSTRACT

Objectives

Vitiligo is a common skin disorder characterized by focal failure of pigmentation due to the destruction of melanocytes mediated by immunological mechanisms. Ātrilal (*Ammi majus* **L.**), a plant drug, is used traditionally for the treatment of vitiligo. However, clinical studies showing its safety and efficacy are lacking. This study aimed to evaluate the efficacy and safety of *Ātrilal* against Psoralen on depigmented vitiliginous skin.

Materials and methods

This randomized active controlled study was conducted on the participants diagnosed with vitiligo. The participants in the test group were treated with Ātrilal (1500 mg) thrice daily orally and Ātrilal powder mixed with vinegar applied topically on vitiliginous lesions on alternate days followed by sun exposure for 16 weeks. The participants in the control group received methoxsalen tablets (20-40 mg) orally on alternate days and *Methoxsalen* (1%) solution was applied topically in the morning, followed by sun exposure. The outcome measures were the change in VASI, IGA, and PGA scores from baseline to post-treatment.

Results

In the test group, VASI (mean ± SD) reduced by 48.27% from 2.9±0.65 to 1.5±0.67. In the control group, VASI (mean ±SD) improved by 42.42% from 3.3±1.5 to 1.9±1.5. The difference in VASI in both test and control groups were found statistically and clinically significant. The test drug did not show any adverse drug reaction or change in haematological and biochemical parameters from baseline to post-treatment.

Conclusion

Ātrilal was found safe, effective and tolerable herbal treatment for depigmented vitiliginous skin in vitiligo. *[Registration Number: CTRI/2019/04/018669 dated 18/04/2019].*

Keywords

Ātrilal, Cosmetic, Herbal, Skin Disease, Unani

INTRODUCTION

Vitiligo is a commonly acquired chronic disease characterized clinically by "chalky-white" or "milky-white" patches of skin, and histopathologically by the complete absence of melanocytes in well-developed lesions.[1-6] The lesions of vitiligo may have three colours (trichrome vitiligo) due to the presence of a zone of an intermediate colour (hypopigmented light brown skin) between the perilesional normal skin (dark brown) and the depigmented vitiliginous skin (white). The presence of trichome vitiligo denotes progressive or active disease.[7]

Vitiligo is a multifactorial, polygenic disorder, with a complex pathogenesis, which is not well understood yet.[8] The destruction of melanocytes in vitiligo is the cause of white patches, which clinically represent the disease. The exact cause of melanocyte destruction is unknown. Several hypotheses have been proposed to explain the disease pathogenesis, such as autoimmune, self-destruction (auto cytotoxicity), and neural hypotheses.[4] The most accepted theory of disease pathogenesis, particularly for generalized vitiligo is that genetic and non-genetic factors interact to influence the function

1. Department of Moalajat (Medicine), National Research Institute of Unani Medicine for Skin Disorders, Opp. ESIC Hospital, Eragadda, Hyderabad, India, 500038.
2. National Research Institute of Unani Medicine for Skin Disorders, Opp. ESIC Hospital, Eragadda, Hyderabad, India, 500038.

Correspondence

Mohammad Nawab, Department of Moalajat (Medicine), National Research Institute of Unani Medicine for Skin Disorders, Opp. ESI Hospital, Eragadda, Hyderabad, India, 500038. e-mail: ccrumnawab@gmail.com

Bangladesh Journal of Medical Science Vol. 25 No. 03 July'26

DOI: https://doi.org/10.3329/bjms.v25i3.90530

and survival of melanocytes, ultimately leading to the autoimmune destruction of melanocytes.[8-9] The autoimmune hypothesis holds that selected melanocytes are destroyed by antibody-dependent, cell-mediated cytotoxicity utilizing natural killer cells (cytotoxic lymphocytes).[10-12] The autoimmune hypothesis is more prominent in generalized vitiligo.[13]

The self-destruct hypothesis suggests that melanocytes are destroyed by toxic substances, i.e., melanin precursors formed as part of normal melanin biosynthesis. Vitiligo patients have an intrinsic inability to eliminate these toxic melanin precursors e.g., free radicals that accumulate, leading to melanocyte destruction by apoptosis.[13-14] The neurogenic hypothesis suggests that melanocyte destruction is due to a neurochemical mediator released at nerve endings. This theory holds for segmental vitiligo, which results from the dysfunction of sympathetic nerves in the affected areas.[15] The neural theory is expected in focal and segmental vitiligo.[16] The theory of melanocytorrhagy has also been proposed, which is supported by the lesions observed by the Koebner phenomenon.[17]

Vitiligo is a pigmentary disorder of the skin affecting up to 1% of the population worldwide.[18] In India, the incidence among dermatology outdoor patients is estimated to be between 0.25% and 4%. The incidence of vitiligo is 8.8% in Rajasthan and Gujrat.[18] However, most authors say that its incidence is around 4%, which is more than the world's population of 1%.[19] The white patches of vitiligo may appear on any area of the skin but are generally seen on the sites of pressure and stretch, for example, elbows, knees, dorsum of the hands, and fingers. Macules are frequently rounded to oval in shape, variable in size, without itching and scaling. Borders of the macules are sharply demarcated, often convex towards the margin.[20]

In the Unani System of Medicine, the cause of vitiligo is the excessive accumulation of *Balgham Ghayr Ṭabī'ī / Balgham Mutaghayyir* (abnormal phlegm) in the body. Unani physicians including *Ibn Sīnā* in his treatise *Al-Qānūnfi'l-*Ṭibb[21], *Ḥakīm Akbar Arzānī* in his book *Ṭibb-i Akbar*[22], *Muḥammad Ṭabarī* in his book *Mu'ālajāt al-Buqrāṭiyya*[23], *Sadīd al-Dīn Gāzrūnī* in his book *Sadīdī*[24] and *Ismā'īl Jurjānī* in his book *Dhakhīra Khawārizm Shāhī*[25] described the cause of vitiligo as *Ḍu'f-i-Quwwat-i-Mughayyira* (weakness of transformative faculty), the power that brings changes and shapes the nutrients into tissues and *Ḍu'f-i-Quwwat-i-Mushabbiha* (weakness of faculty of assimilation).[26-27] This *Ḍu'f* (weakness) may be due to the accumulation of *Balgham-i Ghalīz* (viscous phlegm), *Fasād al-Dam* (chronic abnormality of blood affecting cutaneous nutrition), or *Burūdat al-Dam* (coldness in the blood) in the body.[24,27,28]

The term 'vitiligo' may be used as an umbrella term for all forms of non-segmental vitiligo, including, acrofacial, mucosal, generalized, universal, and mixed vitiligo (Vitiligo Global Issue Consensus Conference).[13] Segmental vitiligo is classified separately, as uni-segmental, bi-segmental, or pluri-segmental. Unclassified / Undetermined vitiligo includes focal vitiligo (small isolated depigmented focal lesions that are not segmentally distributed and are not evolved into non-segmental vitiligo after 1-2 years) and mucosal vitiligo (isolated mucosal lesions on one site).[29]

In the classical literature, the therapeutic approach to vitiligo is primarily *Tanqiya'-i-Badan* (cleansing of morbid matter/humour from the body) performed in three steps, including, *Nuḍj* (concoction), *Ishāl* (inducing purgation) and *Tabrīd* (cooling of body). Accordingly, first *Munḍij-i-Balgham* (concoctive of phlegm) drugs are administered till *Nuḍj* (concoction) appears, followed by three *Mushil* (purgative) alternated with three *Mubarrid* (refrigerant) are given.[20,26] After *Tanqiya'-i-Badan*, the digestive system is corrected by consuming easily digestible food.[26,31]

In Unani medicine, various single drugs like *Sudab* (*Ruta graveolens* L.), Bābchī (*Psoralia corylifolia* **L.**), Khardal Safed (*Brassica alba* **L.**), Atrilāl (*Ammi majus* **L.**), Post Beikh-i Kibr (*Capparis spinosa* **L.**), Gandhak (Sulphur), Būrāh-i Armani (Armeniac bole) and compound formulations such as *Habb-i Baraṣ, Ḥabb-i-Farfiyūn, Safūf Baraṣ, Safūf Bābchi, Dawā-i Hindi, Ayārij Loghāziyāh, Marham-i Baraṣ, Ṭilā-i Hindi, Ma'jūn Ḥabbal-Nīl, Ma'jūn Suqrāt* and *Ma'jūn Seer* are effective in the treatment of vitiligo, but very few of them are evaluated clinically on the scientific parameters.[32-35]

Atrilāl (*Ammi majus* L.) has been used orally and locally for the treatment of vitiligo in clinical practice since

ancient times and is claimed to be an effective drug for vitiligo.[36,-39]

But, there are very limited clinical studies to support the efficacy of Atrilāl in vitiligo. In this study, we aimed to study the safety and efficacy of Atrilāl in the participants diagnosed with vitiligo.

MATERIALS AND METHODS

2.1 Study settings and location

This prospective study was conducted in the outpatient department, National Research Institute of Unani Medicine for Skin Disorders (NRIUMSD), Hyderabad, India from May 2019 to August 2020. This research institute provides first-line therapy through Unani medicine to the patients visiting this institute. The average footfall of the patient was 350 patients/day.

2.2 Inclusion criteria

The participants of any sex aged between 18 and 40 years having Non-segmental vitiligo with chronicity of 6 months to 2 years involving ≥2% body surface area (BSA) and fulfilling the following criteria were included in the study.

- Participants with <5 new lesions in the last month
- Participants with <15 lesions in the last 3 months
- Participants who had not taken systemic treatment in the last 4 weeks
- Participants who had not taken topical treatment in the last 2 weeks

The participants having a history of photosensitivity/ photo exaggerated dermatoses, pregnant or lactating women and the participants not having a suitable facility for sun exposure were not included in the study.

2.3 Ethical consideration

Ethics approval for this study was obtained by the Institutional Ethics Committee (IEC) on 27.02.2019 (Ref. No. 38-18/2018-19/CRIUM/Tech/IEC-10/08). This trial was registered with the Clinical Trial Registry-India (Registration Number: CTRI/2019/04/018669 dated 18/04/2019). The participants were enrolled prospectively. This study followed the principles of the Declaration of Helsinki, good clinical practice guidelines for clinical trials in Ayurveda, Siddha and Unani medicine and national ethical guidelines for biomedical and health research involving human subjects, 2017.[40,41] The participants submitted the signed informed consent form before enrollment into the study.

2.4 Study design and randomization

This study was designed as a randomized, active controlled, single-blind (assessor blinded) and parallel group. The randomization of the participants was done using a random sequence generated by online software (www.sealedenvelope.com) with a block size of 4. The random sequence was concealed manually using the methods of sequentially numbered opaque sealed envelopes (SNOSE).[42]

2.5 Sample size estimation

The sample size for this study was calculated using G power software a priori. The required sample size was 50 participants excluding expected dropouts. The allocation ratio was 3:2 (test group: control group). 20% dropouts were expected in this study and the total sample size required was 63 participants.

2.6 Interventions

The participants in the test group received 2 tablets (750 mg each) of *Ātrilal* (*Ammi majus* L.) orally thrice daily with water an hour after meals and, *Ātrilal* powder mixed with Apple vinegar was applied topically on vitiliginous skin lesions on alternate days, 1-2 hours after oral dose of *Ātrilal* in the morning followed by sun exposure. Table 1 displays the dose and mode administration of *Ātrilal.* The participants were exposed to sunlight for 15-30 minutes after topical application of *Ātrilal*. The participants were advised to expose the lesion in the sunlight between 9 a.m. and 10 a.m. during summers and 10 a.m and 11 a.m. during winters, while the control group was given *Methoxsalen* (Melanocyl 10 mg) on alternate days in a dose of 20-40 mg (Table 2) daily orally with water after breakfast, 1-2 hours before exposure to sunlight. Participants were also advised to carefully apply *Methoxsalen* (1%) solution topically on vitiliginous lesions, 1-2 hours after an oral dose of *Methoxsalen* in the morning followed by Sun exposure for 15-30 minutes.[43,44]

Table 1 Dosage and administration of test drug[45]

Study Drug (Scientific name)	Dosage form	Route of administration	Daily Doses	Frequency	Instructions
Ātrilal (*Ammi majus*L.)	Tablet (750 mg)	Oral	4.5 g	Two Tablets thrice daily	Taken with water one hour after meals
Ātrilal (*Ammi majus*L.)	Powder	Topical	Q.S.	On alternate days in the morning 1-2 hrs after an oral dose	Powder mixed with vinegar was applied on the affected skin, which was then exposed to sunlight for 15-30 minutes

2.7 Method of preparation of Unani formulation

The test drug Ātrilal was procured from the cultivar at Aligarh (Uttar Pradesh) and identified and authenticated by Dr. Mohd Kashif Husain, botanist, Survey and Medicinal Plant Unit, NRIUMSD, Hyderabad. A sample of the study drugs was stored in the museum of the institute for future reference. The seeds of Ātrilal were prepared in tablets and powder dosage form in a single batch (Batch No. 1/2019-2020) according to the standard method described in the National Formulary of Unani Medicine (NFUM), at GMP-certified Pharmacy of NRIUMSD, Hyderabad.[46]

Table 2 Dose and administration of Methoxsalen

Patient's Weight	Dose	Dose with Frequency
40-50 kg	20 mg	Two tablets single dose
50-60 kg	30 mg	Three tablets single dose
>60 kg	40 mg	Four tablets single dose

2.8 PUVAsol therapy

2.8.1 Oral Methoxsalen

Methoxsalen (Melanocyl) was given on alternate days in the dose of 20-40 mg orally with water after meals, 1-2 hours before exposure to sunlight.[44] Table 2 displays the dose and frequency of Methoxsalen**.** In participants developing nausea or vomiting, medication was advised to be administered 45 minutes after administration of an anti-emetic. If nausea or vomiting persisted, *Methoxsalen* was administered in 2 divided doses 30 minutes apart.

2.8.2 Topical Methoxsalen

Participants were also advised to carefully apply *Methoxsalen* (1%) solution topically on vitiliginous lesions, 1-2 hours after an oral dose of *Methoxsalen* in the morning followed by sun exposure.[44]

The duration of therapy was 16 weeks in both groups and all the participants were followed up at weeks 4, 8, 12, and 16. The participants were advised to follow the dietary restrictions and recommendations as per the diet chart provided and asked to fill out the chart to confirm participants' compliance with the dietary advice.

2.9 Outcome measures

2.9.1 Vitiligo Area Scoring Index (VASI)

The mean VASI for each group was calculated at 0, 4, 12 and 16 weeks, and the mean percentage reduction from baseline in each group at these visits was calculated and the difference between the two groups was statistically evaluated to assess the relative efficacy and rapidity of response.

The number of participants in each group, who achieved 75% and 90% reduction in VASI at 16 weeks was calculated for each treatment group, and the difference between the 2 groups was statistically evaluated.

2.9.2 Vitiligo Disease Activity (VIDA) Score[47]

Disease activity was evaluated using a 6-point vitiligo activity scale based on the patient's observation of the expansion of existing lesions or appearance of new lesions with the worst being +4 and the best being -1. VIDA was evaluated at baseline and the end of therapy.

2.9.3 Patient's Global Assessment (PGA) on VAS

Participants were asked to evaluate their disease severity at baseline and week 16 using a Visual Analogue Scale (VAS) with worst being 100 and best being 0.

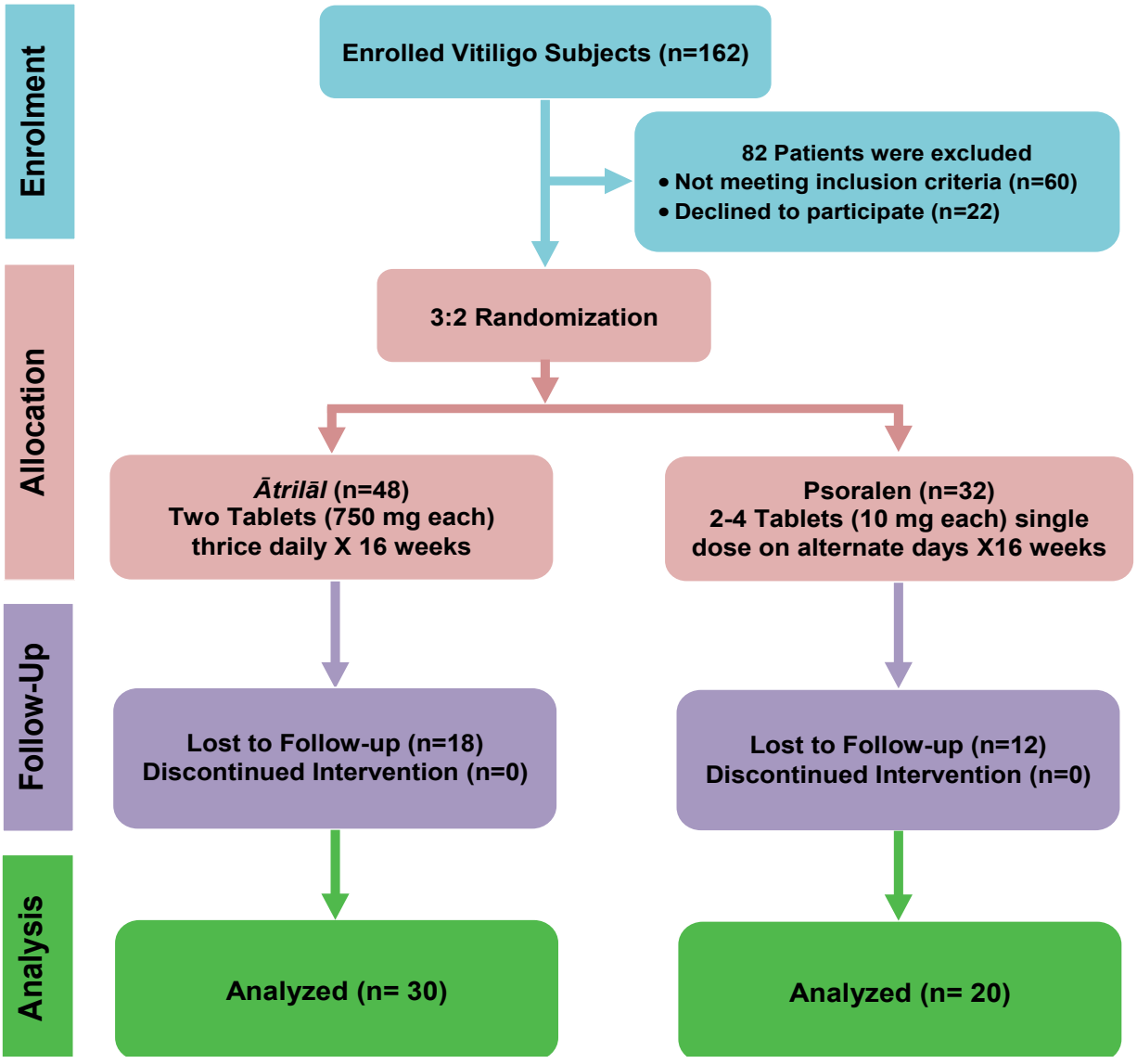
2.9.4 Investigator's Global Assessment (IGA)

Disease severity was evaluated using a 6-point severity scale with the worst being 0 and the best being 5 using a serial photographic record. IGA was done at baseline and 16 weeks. Table 3 displays the Investigator's Global Assessment scale.

Table 3 Investigator's Global Assessment Scale

Grade	%	Response
0	0%	No change
1	1-25%	Minimal improvement
2	26-50%	Moderate improvement
3	51-75%	Good improvement
4	76-90%	Very good improvement
5	91-100%	Complete improvement

Graphical Abstract



2.10 Assessment of safety

The systemic safety was assessed in both test and control groups based on parameters such as haemogram (Hb%, TLC, DLC, ESR), LFTs (SGOT, SGPT, Serum Alkaline Phosphatase), KFTs (Serum Creatinine and Blood Urea), urinalysis, chest X-ray and ECG. The local dermal safety was also assessed.

2.11 Adverse events (AEs)

The adverse effects of therapy (either to Unani formulation or Psoralen) were recorded at each clinical assessment visit (4, 8, 12 and 16 weeks), both as complained by the participants, and as found on examination by the physician, and also by investigations (done at 8 weeks and 16 weeks).

2.12 Statistical Analysis

The data were analyzed as per protocol. The continuous data were measured in mean (± S.D) and categorical data were measured in frequency distribution. The continuous data were compared for statistical significance using paired t-test and unpaired t-test. The chi-square test was used to compare categorical variables. Microsoft Excel 2016 was used to calculate the mean, standard deviation, t-value and p-value. Microsoft Word 2016 was used to prepare charts and tables. P-value ≤ 0.05 was considered as significant.

RESULTS

3.1 Participants' flow in the study

A total of 162 participants were screened for this study. Of them, 80 participants with *Non-Segmental Vitiligo* (NSV) were enrolled after obtaining written informed consent. They were randomly allocated into the test (n=48) and control (n=32) groups in a ratio of 3:2. In total 50 participants, 30 in the test group and 20 in the control group, completed the study. Figure 1 shows the flow of the participants in the study.

3.2 Baseline characteristics of the participants

In the test group, there were 18 (60%) males and 12 (40%) females whereas there were 16 (80%) males and 4 (20%) females in the control group. The age of the participants ranged between 18 to 40 years in the test group and 19 to 40 years in the control group. The minimum chronicity was 8 months and the maximum was 24 months in both test and control groups. Gender difference with male and female ratio was analyzed using the Chi-Square Test, and it was found statistically significant (P<0.05). The baseline characteristics of the participants have been displayed in Table 4.

Table 4 Baseline characteristics of the participants

S. No.	Variables	Test Group (n=30)	Control Group (n=20)	p-value
	Male, n (%)	18 (60)	16 (80)	p<0.05*
	Female, n (%)	12 (40)	4 (20)	
	Age (years)			
	Mean (±SD)	27.6 ± 7	28.1 ± 6.6	p>0.05**
	Range	18 - 40	19 - 40	
	Chronicity (months)			
	Mean ± SD	18 ± 6.65	16.6± 5.8	p>0.05
	Range	8-24	8-24	
	Positive Family History	3 (10)	2 (10)	p>0.05*
	Dietary Habit			
	Non-Vegetarian, n (%)	19 (63.3)	16 (80)	p>0.05*
	Vegetarian, n (%)	11 (36.7)	4 (20)	
	Marital Status			
	Married, n (%)	12 (40)	10 (50)	p>0.05*
	Unmarried, n (%)	18 (60)	10 (50)	
	Temperament			
	Balghami, n (%)	7 (23.3)	6 (30)	p>0.05*
	Damawi, n (%)	15 (50)	7 (35)	
	Safrawi, n (%)	6 (20)	3 (15)	
	Sawdawi, n (%)	2 (6.7)	4 (20)	
	Religion			
	Christian, n (%)	1(3.3)	2 (10)	p>0.05*
	Hindu, n (%)	21 (70)	13 (65)	
	Muslim, n (%)	8 (26.7)	5 (25)	

*=Chi-square test; **=Independent t-test

3.3 Efficacy of the intervention

3.3.1 Effect on Vitiligo Area Scoring Index (VASI)

In the test group, the mean (± SD) VASI at baseline was 2.9 ± 0.65 [range: 0.25 – 4.5]. It reduced to 1.5 ± 0.67 [range 0.3–3.25] post-treatment leading to a 48.27% reduction in mean VASI. Whereas, in the control group, the mean ± SD VASI calculated at baseline was 3.3 ± 1.5 [range: 2.25 – 7.4], and it reduced to 1.9 ± 1.5 [range 0.55 – 6.75] leading to 42.42% change in mean VASI. Table 5 displays the mean VASI of the participants. The reduction in mean VASI from baseline to post-treatment in each group was found statistically significant.

Table 5 Effect of the intervention on VASI Score

Study group	Baseline	1st Follow-up	2nd Follow-up	3rd Follow-up	Post-treatment	P – Value	Mean Reduction (%)
Test group, Mean ± SD (Range)	2.9 ± 0.65 (0.25 – 4.5)	2.8 ± 0.66 (1.75 – 4.4)	2.5 ± 0.66 (1 – 4.4)	2.18 ± 0.64 (0.75 – 3.9)	1.5 ± 0.67 (0.3 – 3.25)	p<0.01*	48.27
Control group, Mean ± SD (Range)	3.3 ± 1.5 (2.25 – 7.4)	3.23 ± 1.5 (2.25 – 7.4)	2.9 ± 1.5 (1.75 – 7.25)	2.5 ± 1.6 (1.10 – 6.75)	1.9 ± 1.5 (0.55 – 6.75)	p<0.01*	42.42

*paired t-test

3.3.2 Changes in Patient's Global Assessment (PGA) on VAS

In the test group, the PGA score (mean ± SD) was 84.6 ± 6.3 at baseline and 51 ± 15 after 16 weeks of treatment; whereas in the control group, the PGA score was 85 ± 6 at baseline and 46.5 ± 15 after treatment. The PGA is shown in Table 6. The changes in PGA Score on VAS from baseline to post-treatment were statistically significant (p<0.01) in both test and control groups.

Table 6 Effect of the intervention on PGA

Study group	Baseline (Mean ± SD)	Post-treatment (Mean ± SD)	Mean Difference	p - Value
Test group	84.6 ± 6.3	51 ± 15	33.6	<0.01*
Control group	85 ± 6	46.5 ± 15	38.5	<0.01*

*paired t-test

3.3.3 Improvement in Investigator's Global Assessment (IGA)

This study showed 51-75% repigmentation (good improvement) in 20 cases (n_1=12 and n_2=8), followed by 26-50% repigmentation (moderate improvement) in 18 cases (n_2=10 and n_2=8). A minimal improvement, i.e., 1-25% repigmentation was seen in 6 cases. Of them, the test group had 4 (13.3%) cases and the control group had 2 (10%) cases. Very good improvement, i.e., 76-90% repigmentation was seen in 3 cases. Of them, there were 2 (6.7%) cases in the test group and 1 (5%) case in the control group. There were 2 (6.7%) cases in the test group and 1 (5%) case in the control group who did not respond to the treatment. The changes in the IGA Score from baseline to post-treatment were statistically analyzed. The overall mean percentage improvement in IGA in the test group was 45.13% and in the control group, it was 46%.

3.4 Photographic assessment

The photograph of the lesion taken at baseline was compared with the post-treatment photograph to assess the efficacy of the treatment. The change in the depigmented area after treatment was considered significant. Figure 2 shows the clinical photographs of a participant taken at baseline and after 16 weeks of treatment.

3.5 Assessment of safety

The systemic safety of the test and control drugs was assessed using parameters such as haemogram (Hb%, TLC, DLC, ESR), LFTs (SGOT, SGPT, Serum Alkaline Phosphatase), KFTs (Serum Creatinine and Blood Urea), urinalysis, chest X-ray and ECG. This study demonstrated no significant difference in the safety parameters before and after treatment.

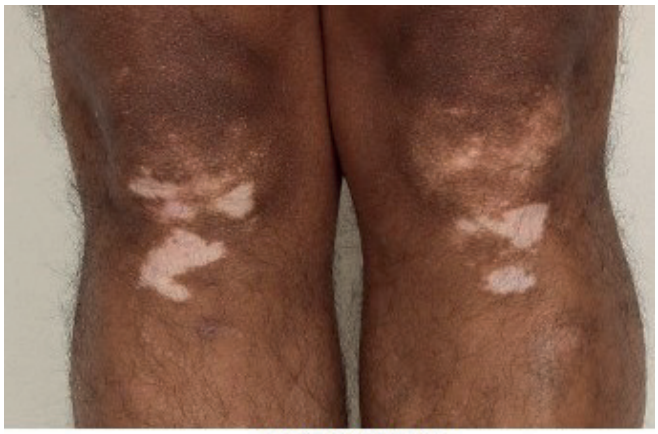


Figure 2 Photographs of depigmented lesion at baseline and post-treatment

Any participants did not report local irritation, redness, itching and eruptions in the area where interventions were applied.

3.6 Adverse events

During the study, only two participants reported the adverse effects of topical methoxsalen (solution 1%) drug, i.e., the occurrence of blisters at the area where the drug was applied, which was relieved after 10 days by stopping the drug and applying olive oil on the affected area.

DISCUSSION

In the present study, we evaluated the efficacy and safety of the Unani drug *Ātrilal* (*Ammi majus* L.) in vitiligo and compared its efficacy with that of the standard drug recommended for the treatment of vitiligo. This study showed that *Ātrilal* (*Ammi majus* L.) used orally and topically reduced the severity of the disease in terms of reduction in mean VASI, PGA and IGA scores. The reduction in mean VASI, PGA and IGA scores at the end of 16 weeks of treatment was found clinically as well as statistically significant. The overall improvement in mean IGA in the test group was 45.13% and in the control group, 46% was observed.

The Unani drug *Ātrilal* was found comparatively more effective than several other formulations reported in the recent past.[34,36] In addition, there are two clinical studies which reported that the Unani formulations UNIM-004 + UNIM-005 and UNIM-001 + UNIM-003 had a parallel response to the Unani drug *Ātrilal* and a study assessing the efficacy of PUVA sol had a parallel response as completed in the control group in our study.[31,34,48] But, all of these studies had a larger treatment duration than our study.

Vitiligo is a cosmetic disorder, but it has a significant impact on the quality of life of the patient. It is still considered as incurable in conventional medicine. This study showed the efficacy of *Ātrilal* in vitiligo. *Ātrilal* has demonstrated analgesic, anti-inflammatory, antipyretic, antihyperlipidemic, anti-microbial, anti-viral, insecticidal, antioxidant, larvicidal, hepatoprotective, and nephroprotective activities in various pre-clinical studies.[36] It's rich source of furanocoumarins, flavonoids, terpenoids, proteins, and essential oil could be responsible for alleviating vitiligo.36

Vitiligo is an acquired clinical condition of skin and hair. In this disease, the formation of white macules due to the absence of melanocytes is generally reported clinically. The destruction of melanocytes results in macule formation in the skin. This study showed that vitiligo can be treated effectively by *Ātrilal.* It contains active principle xanthotoxin which is also reported to be effective in Vitiligo.[36] Systemic and local uses of some other medicinal plants have also been reported to be effective in vitiligo along with sunlight exposure. [49]

4.1 Merits and demerits

This is an active controlled clinical trial. In this study, the efficacy and safety of *Ātrilal* were compared with a standard control. The permuted block randomization method was adopted to randomize participants in two different treatment arms. This design could minimize the selection bias in the outcomes,

However, this study had several limitations, too. The sample size was small and the duration of treatment for this chronic disease was comparatively short. The

outcomes of this study may be influenced by recall bias due to the unmasking of the study. The strict inclusion and exclusion criteria could reduce the generalizability of the outcomes to the general population.

4.2 Recommendations

A randomized controlled clinical trial with a large sample size may be conducted to scientifically validate the efficacy and safety of the Unani drug *Ātrilal* in the treatment of *Baraṣ*. The herb-drug interaction may be studied to understand the synergistic action of *Ātrilal* in vitiligo.

CONCLUSION

This study concludes that *Ātrilal was* an effective and safe treatment for vitiligo. *Ātrilal* showed no issues of tolerability and noncompliance to the therapy. The safety and efficacy of *Ātrilal* was comparable to methoxsalen. The small sample size and short duration of therapy may be considered as the limitations of this study. It is, therefore, clinical studies with a larger sample size and longer duration of therapy may be conducted to confirm the safety and efficacy of *Ātrilal*.

Acknowledgements: We are thankful to the Central Council for Research in Unani Medicine, Ministry of AYUSH, Government of India, New Delhi for providing the necessary financial support for this study.

Research Funding: This study was sponsored by the Central Council for Research in Unani Medicine, New Delhi, Ministry of AYUSH, Government of India as an academic activity required for submission of postgraduate dissertation.

Author contributions: Mozakkir Husain designed the study, developed the protocol and case record form and conducted the study. Qamar Uddin designed the study, developed the protocol and case record form and supervised the study. Yunis Iftikhar Munshi edited the manuscript. Mohammad Nawab evaluated the outcome, analysed the data and edited the manuscript.

Competing interests: Authors declare that there is no conflict of interest.

Informed consent: Informed consent was obtained from all individuals included in this study

Ethical Statement: Institutional Ethics Committee of the NRIUMSD, Hyderabad, India approved the ICF, protocol and CRF of the study on 27.02.2019 (Ref. No. 38-18/2018-19/CRIUM/Tech/IEC-10/08) and registered in CTR-India with registration no. CTRI/2019/04/018669 dated 18/04/2019.

REFERENCES

1. Koranne RV, Sachdeva KG. Vitiligo. Int J Dermatol1988;27:676-681. doi:10.1111/j.1365-4362.1988.tb01260.x https://doi.org/10.1111/j.1365-4362.1988.tb01260.x
2. Nordlund JJ, Lerner AB. Vitiligo. It is important. Arch Dermatol1982;118:5-8. doi:10.1001/archderm.118.1.5 https://doi.org/10.1001/archderm.118.1.5
3. Sharquie KE. Vitiligo. Clin Exp Dermatol1984;9:117-126. doi:10.1111/j.1365-2230.1984.tb00772.x https://doi.org/10.1111/j.1365-2230.1984.tb00772.x
4. Kovacs SO. Vitiligo. J Am Acad Dermatol1998;38:647-668. doi:10.1016/s0190-9622(98)70194-x https://doi.org/10.1016/S0190-9622(98)70194-X
5. Xia Q, Zhou WM, Liang YH, Ge HS, Liu HS, Wang JY,et al. MHC haplotypic association in Chinese Han patients with vitiligo. J EurAcad Dermatol Venereol2006;20:941-946. doi:10.1111/j.1468-3083.2006.01686.x https://doi.org/10.1111/j.1468-3083.2006.01686.x
6. Sehgal VN. Textbook of Clinical Dermatology, 5th ed., Chapter 24: Vitiligo. New Delhi: Jaypee Brothers Medical Publishers (P) Ltd; 2011. https://doi.org/10.5005/jp/books/11454_24
7. Hann SK, Kim YS, Yoo JH, Chun YS. Clinical and histopathologic characteristics of trichrome vitiligo. J Am Acad Dermatol. 2000;42:589-596. doi:10.1016/s0190-9622(00)90170-1 https://doi.org/10.1016/S0190-9622(00)90170-1
8. Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Wolff K. Fitzpatrick's Dermatology in General Medicine, 8th ed., Vol. 1, US: The McGraw-Hill Companies, Inc.; 2012.
9. Spritz RA. The genetics of generalized vitiligo. Curr Dir Autoimmun. 2008;10:244-257. doi:10.1159/000131501 https://doi.org/10.1159/000131501
10. Badri AM, Todd PM, Garioch JJ, Gudgeon JE, Stewart DG, Goudie RB. An immunohistological study of cutaneous lymphocytes in vitiligo. J Pathol. 1993;170:149-155. doi:10.1002/path.1711700209

https://doi.org/10.1002/path.1711700209
11. Yee C, Thompson JA, Roche P, Byrd DR, Lee PP, Piepkorn M, et al. Melanocyte destruction after antigen-specific immunotherapy of melanoma: direct evidence of t cell-mediated vitiligo. J Exp Med2000;192:1637-1644. doi:10.1084/jem.192.11.1637 https://doi.org/10.1084/jem.192.11.1637
12. Farrokhi S, Hojjat-Farsangi M, Noohpisheh MK, Tahmasbi R, Rezaei N. Assessment of the immune system in 55 Iranian patients with vitiligo. J EurAcad Dermatol Venereol2005;19:706-711. doi:10.1111/j.1468-3083.2005.01295.x https://doi.org/10.1111/j.1468-3083.2005.01295.x
13. Ezzedine K, Lim HW, Suzuki T, Katayama I, Hamzavi I, Lan CC, et al. Revised classification/nomenclature of vitiligo and related issues: the Vitiligo Global Issues Consensus Conference. Pigment Cell Melanoma Res 2012;25:E1-E13. doi:10.1111/j.1755-148X.2012.00997.x https://doi.org/10.1111/j.1755-148X.2012.00997.x
14. Maresca V, Roccella M, Roccella F, Camera E, Del Porto G, Passi S, et al. Increased sensitivity to peroxidative agents as a possible pathogenic factor of melanocyte damage in vitiligo. J Invest Dermatol1997;109:310-313. doi:10.1111/1523-1747.ep12335801 https://doi.org/10.1111/1523-1747.ep12335801
15. Koga M, Tango T. Clinical features and course of type A and type B vitiligo. Br J Dermatol 1988;118:223-228. doi:10.1111/j.1365-2133.1988.tb01778.x https://doi.org/10.1111/j.1365-2133.1988.tb01778.x
16. Mohammed GF, Gomaa AH, Al-Dhubaibi MS. Highlights in pathogenesis of vitiligo. World J Clin Cases2015;3:221-230. doi:10.12998/wjcc.v3.i3.221 https://doi.org/10.12998/wjcc.v3.i3.221
17. Boisseau-Garsaud AM, Garsaud P, Calès-Quist D, Hélénon R, Quénéhervé C, Claire RC. Epidemiology of vitiligo in the French West Indies (Isle of Martinique). Int J Dermatol2000;39:18-20. doi:10.1046/j.1365-4362.2000.00880.x https://doi.org/10.1046/j.1365-4362.2000.00880.x
18. Mahajan VK, Vashist S, Chauhan PS, Mehta KIS, Sharma V, Sharma A. Clinico-Epidemiological Profile of Patients with Vitiligo: A Retrospective Study from a Tertiary Care Center of North India. Indian Dermatol Online J. 2019;10(1):38-44. doi: 10.4103/idoj.IDOJ_124_18. https://doi.org/10.4103/idoj.IDOJ_124_18
19. Dutta AK, Mandal SB. A clinical study of 650 vitiligo cases and their classification. Indian J Dermatol1969;14:103-111. PMID: 5362324.
20. Njoo MD, Westerhof W. Vitiligo. Pathogenesis and treatment. Am J Clin Dermatol2001;2:167-181. doi:10.2165/00128071-200102030-00006 https://doi.org/10.2165/00128071-200102030-00006
21. Ibn Sīnā AAHA. Al-Qānūnfi'l Ṭibb. (Translation by Kinturi GH). Lahore: Shaikh Muhammad Basheer and Sons; Year of publication not known.
22. Arzānī HA. Ṭibb-i Akbar. Deoband: Faisal Publications; Year of publication not known.
23. Ṭabarī AHAM. Al-Mu'ālajāt al-Buqrāṭiyya, Vol. II. New Delhi: Central Council for Research in Unani Medicine, Govt. of India, Ministry of Health and Family Welfare; 1997:199p.
24. Gāzrūnī. Sadīd al-Dīn. Sadīdī (Arabic). Lucknow: Maṭba Munshi Nawal Kishor; year of publication not known:61p.
25. Jurjāni SIH. Dhakhīra Khawārizm Shāhī. New Delhi: Idara Kitab-us-Shifa;2010:8p.
26. Anonymous. WHO International Standard Terminologies on Unani Medicine. Geneva: World Health Organization; 2022.
27. Anonymous. Standard Unani Medical Terminology. New Delhi: Central Council for Research in Unani Medicine, Govt. of India, Ministry of Health and Family Welfare;2012:32p.
28. Rāzī ABMZ. Kitāb al-Manṣūrī (Urdu translation). New Delhi: Central Council for Research in Unani Medicine, Govt. of India, Ministry of Health and Family Welfare; 1991:207p.
29. Griffiths CEM, Barker J, Bleiker T, Chalmers R, Creamer D. Rook's Textbook of Dermatology, 9th Ed., Volume 3, Part 8 (Skin Disorders Associated with Specific Cutaneous Structure), Chapter 88 (Acquired Pigmentary Disorders).UK: John Wiley & Sons, Ltd.;2016. https://doi.org/10.1002/9781118441213
30. Anonymous. Standard Unani Treatment Guidelines for Common Diseases, Vol. I. New Delhi: Central Council for Research in Unani Medicine, Govt. of India, Ministry of Health and Family Welfare; 2014:180-82.
31. Ali MI, Khan MMA, Shakera AR. Seminar on Bars (Leucoderma), Hyderabad. In Hyderabad: New Delhi: Central Council for Research in Unani Medicine; 2014.
32. Anonymous. National Formulary of Unani Medicine. New Delhi: Central Council for Research in Unani Medicine, Govt. of India, Ministry of Health and Family Welfare; 2006.
33. Anonymous.The Unani Pharmacopoeia of India, Part-I, Vol. IV. New Delhi: Central Council for Research in Unani Medicine, Govt. of India, Ministry of Health and Family Welfare; 2007.
34. Husain N, Qamar Uddin, Kazmi MH. Clinical Studies on the Treatment of Baraṣ (Vitiligo) in Unani System of Medicine - a Systematic Review. Eur J Biomed Pharm Sci. 2018:5;1088-94.
35. Kabīr al-Dīn H. Al-Qarābādīn Taba'Sāni. New Delhi: Central Council for Research in Unani Medicine;2006.
36. Usmani QI, Jahan N, Aleem M, Hasan SA. Aatrilal (Ammi majus L.), an important drug of Unani system of medicine: A review. J Ethnopharmacol2021;276:114144. doi:10.1016/j.jep.2021.114144 https://doi.org/10.1016/j.jep.2021.114144
37. Rahman SZ. Risalah Atrilāl by Imaduddin Maḥmud ibn Mas'ud Shirazi. Aligarh: Publication Division, Aligarh Muslim

University; 1993.

38. Khan NA, Rahman SZ, A Study on Atrilal (A. Majus linn.): A Traditional Drug for Leucoderma, Nagarjun, 1985;29 (3): 4-8.
39. Ashiq K, Bajwa MA, Khokhar R, Abid F, Tanveer S, Qayyum M, et al. A cross-sectional analysis of knowledge, beliefs and practices regarding traditional medicine use among pharmacy students of different private and government universities of lahore, Pakistan. Bangladesh J Med Sci. 2022;21(2):323-34. https://doi.org/10.3329/bjms.v21i2.58065
40. Anonymous. Good Clinical Practice Guidelines for clinical trials in Ayurveda Siddha and Unani Medicine. New Delhi: Department of AYUSH, Ministry of Health & Family Welfare Government of India; 2013.
41. Mathur, R., Swaminathan, S. National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, 2017: A commentary, Indian journal of medical ethics, 2018. https://doi.org/10.20529/IJME.2018.065 https://doi.org/10.20529/IJME.2018.065
42. Ismail BA, Nawab M, Fatima SH, Minhajuddin A, Naikodi MA. Evaluation of the efficacy and safety of Unani Formulations in Pityriasis Versicolor: A randomized controlled trial. Journal Ethnopharmacol 2022; 298:115603. https://doi.org/10.1016/j.jep.2022.115603 https://doi.org/10.1016/j.jep.2022.115603
43. Godse KV. Comparison of two diluents of 1% methoxsalen in the treatment of vitiligo. Indian J Dermatol Venereol Leprol. 2008; 74: 298-9. https://doi.org/10.4103/0378-6323.41405
44. Tripathi KD. Essentials of Medical Pharmacology, 8th edition, New Delhi: Jaypee Brothers Medical Publishers; 2019.
45. Anonymous. Quality Standards of Indian Medicinal Plants, Vol. 5. New Delhi: Indian Council of Medical Research; 2008:54-62.
46. Anonymous.The Unani Pharmacopoeia of India, Part-I, Vol. IV. New Delhi: Central Council for Research in Unani Medicine, Govt. of India, Ministry of Health and Family Welfare; 2007.
47. Lakhani DR, Prakash DC, Tiwari DS, Purohit DS, Paliwal DV, Mathur DD, Bhargava P. Scoring system in dermatology: a review. IOSR J Dent Med Sci 2016;15:89-99. https://doi.org/10.9790/0853-150798999
48. Jalel A, Hamdaoui MH. Study of total antioxidant status and glutathione peroxidase activity in Tunisian vitiligo patients. Indian journal of dermatology 2009 Jan 1;54:13-16. doi: 10.4103/0019-5154.48978. https://doi.org/10.4103/0019-5154.48978
49. Glynn J, Bhikha R. Herbal products and conventional drugs - an uneasy alliance. Bangladesh J Med Sci. 2018 Dec. 30;18(1):24-9. https://doi.org/10.3329/bjms.v18i1.39542