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A non-inferiority randomized controlled clinical trial comparing Unani formulations and PUVAsol in non-segmental vitiligo

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Abstract

Objectives: Greco-Arab medicine is an ancient system of medicine with greater treasure on therapeutics of vitiligo. The trial Unani formulations have not been scientifically explored for their safety and efficacy, but have been repeatedly prescribed by the great Unani physicians in the management of *Baraṣ* (vitiligo). Hence, these interventions were selected for the trial.

Methods: In this randomized, controlled, open-label clinical trial, 82 participants with non-segmental vitiligo aged 18–40 years were block randomized to either receive Unani interventions or control for 16 weeks. Out of 82 participants, 42 were randomized to the Unani group and 40 were randomized to the control group. The primary outcome measure was change in vitiligo area scoring index (VASI), which was assessed on weeks 4, 8, 12 and 16. The secondary outcome measures included the patient's global assessment on VAS and investigator's global assessment based on photographic evaluation at baseline and after the treatment. Safety parameters included hemogram, LFTs, RFTs, CXR, ECG, urine, and stool examinations, which were evaluated at baseline and after the treatment.

Results: The per-protocol analysis was done on 30 participants in each group and the response in Unani group was not inferior to those receiving control group. The mean ± SD of vitiligo area scoring index (VASI) decreased from 4.09 ± 2.87 and 5.50 ± 5.73 at baseline to 3.13 ± 2.20 and 4.29 ± 4.95 at the end of the trial in both the Unani and control groups respectively.

Conclusions: The study inferred that both the interventions are equally effective and well-tolerated in patients with non-segmental vitiligo.

Keywords: *Baraṣ*; *Habb-i Baras*; *Habb-i Hindi*; non-segmental vitiligo; PUVAsol; VASI.

Introduction

Baraṣ (vitiligo) is an acquired chronic, organ-specific autoimmune pigmentary disorder which results due to loss of melanocytes, characterized by hypopigmented, sharply demarcated macules and sometimes, whitening of the hairs [1]. It is considered a cosmetic and untreatable disorder by several physicians; some other physicians are of the opinion that it's treatable by various treatment modalities, but due to the exhaustive treatment duration and certain complications, most people think that there is no treatment of vitiligo [2, 3].

Vitiligo affects approximately 0.5–2% of the world population [4]. However, it is quite difficult to achieve the true picture of the prevalence. It is a psychologically devastating and frequently recalcitrant condition [5]. It is mainly classified into segmental and non-segmental vitiligo. Non-segmental vitiligo is more common as it comprises 85–90% of the overall cases [6], whereas segmental vitiligo accounts only for 30% cases, and less especially in the childhood [7].

The etiology of vitiligo is still unclear. Although a number of hypotheses have been propounded by the scholars including autoimmune, environmental factors, neural defects, melatonin receptor dysfunction, impaired melanocyte migration, genetic susceptibility, and biochemical defects, etc. [1, 8, 9].

The eminent Unani physicians have given a detailed account of etiopathogenesis, clinical and diagnostic features, and treatments of *Baraṣ* (vitiligo). Zakariyya Rāzī (865–925 AD), in his most famous book "*Kitāb al-Ḥāwī*" described that if the skin turns reddish on rubbing, then

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vitiligo is curable; if on pricking the affected skin, whitish fluid oozes, then there is the least possibility of a cure. He also reported that Sun exposure post topical application of medication activates the process of pigmentation [10]. The etiopathogeneses of *Baraṣ* described by the Unani physicians are *Ḍu'f-i Quwwat-i Mughayyira Badan* and *Mushabbiha-i Badan* (weakness of transformative and resemblance faculties) [11–15]. These are the powers that mould the nutrients into tissues [16]. The *Ḍu'f* (weakness) of these powers occurs due to accumulation of *Balgham-i Ghalīz* (viscous phlegm), *Fasād al-Dam*, or *Burūdat-i Dam* in the body [13, 15, 17].

Currently, no effective treatment is available for vitiligo. Although several interventions have been tried with partial success along with undesired effects, such as topical corticosteroids, immunomodulators, ultraviolet A (UVA), narrow and broadband ultraviolet B (UVB), psoralen with UVA (PUVA), excimer laser, and monochromatic excimer light (MEL). In the surgical approach, grafting, melanocyte transplantation, and micro-pigmentation have been tried to cure this disease with dismal outcome [18]. Among these, photochemotherapy (PUVA) is an evidence-based therapeutic modality for vitiligo wherein the systemic or topical drug, such as psoralen is used followed by exposure of the affected area to ultraviolet light; but it also has systemic and dermatological complications [19, 20].

Alternatively, Unani medicine may play a pivotal role in this regard. Some of the commonly recommended Unani drugs for vitiligo include *Atrilāl* (*Ammi majus* L.), *Bābchī* (*Psoralea corylifolia* L.); *Khardal* Safed (*Brassica alba* L.); *Post Beikh-i Kibr* (*Capparis spinosa* L.); *Būrāh-i Armani* (*Armeniac bole*); *Gandhak* (*Sulphur*), and compound formulations, such as *Safūf Baraṣ*; *Safūf Bābchi*; *Habb-i Baraṣ*; *Ḥabb-i Farfiyūn*; *Ayārij Loghāziyāh*; *Dawā-i Hindi*; *Ma'jūn Suqrāt*; *Ma'jūn Ḥabbal-Fīl*; *Marham-i Baraṣ*; *Ṭilā-i Hindi*, etc. [21, 22]. But, very few of them have been evaluated on scientific parameters [23]. The trial interventions "*Ḥabb-i-e-Hindi*" and "*Ḥabb-i-Baraṣ*" also have not been evaluated scientifically for their efficacy as well as safety.

Materials and methods

Site and time

It was a non-inferiority randomized, active-controlled, clinical trial which was conducted from 01/07/2018 to 25/07/2019 at Central Research Institute of Unani Medicine, Hyderabad after getting approval from the Institutional Ethics Committee (38-18/2015-16/CRIUM/Hyd/IEC/02/M) and registration with the Clinical Trials Registry-India (CTRI/2017/12/010998).

Inclusion criteria

Participants aged 18–40 years with non-segmental vitiligo and chronicity of >6 months and <2 years with the body surface area (BSA) of ≥2% or the vitiligo area severity index (VASI) of ≥2; or participants having <5 new lesions in the last month or <15 new lesions in the last three months were included in the trial.

Exclusion criteria

Patients younger than 18 years or older than 40 years of age; those with segmental vitiligo or lip-tip or universal or mixed vitiligo or vitiligo with leukotrichia; pregnant and lactating women; patients with the previous history of photosensitivity; photo-exaggerated dermatoses or connective tissue diseases; those with significant pulmonary/cardiovascular/hepato-renal comorbidities, and participants with personal or family history of immunocompromised states (HIV/AIDS, etc.), and malignancies (cutaneous or internal) were excluded from the study. Similarly, those who had received systemic therapy for vitiligo in the previous month were also excluded.

Method of preparation of *Habb-i Hindi*

Tukhm-i Bābchī [treated with *Āb-i Zanjabīli (Zingiber officinale* rhizome water) for seven consecutive days in ratio of 1:1] [24], *Katomarī, Post Beikh-i Nīm, Post Shākh-i Nīm*, and *Barg-i Nīm* were powdered and sieved through sieve no. 85. The wood of *Khair* was boiled in water (weighing two times of *Khair*) till it became half (Table 1). Lastly, it was mixed with powdered drugs to prepare the tablet [25].

Method of preparation of *Habb-i Baras*

Tukhm-i Bābchī were treated with *Āb-i Zanjabīli* (*Zingiber officinale* rhizome water) for seven consecutive days in ratio of 1:1 [24] and all three ingredients were powdered separately. *Geru*, was ground in

Table 1: Composition of *Habb-i Hindi* and *Habb-i Baraṣ*.

Composition of *Habb-i Hindi*		
Ingredients	**Part used**	**Quantity**
Bābchī Mudabbar (*Psoralea corylifolia*)	Seeds	250 g
Katomarī (*Ficus hispida*)	Root pulp	250 g
Post Beikh-i Nīm (*Azadirachta indica*)	Root bark	250 g
Post Shākh-i Nīm (*Azadirachta indica*)	Stem bark	250 g
Barg-i Nīm (*Azadirachta indica*)	Leaves	250 g
Khair ki Lakdi (*Senegalia catechu*)	Heartwood	1 kg 250 g
Composition of *Habb-i Baraṣ*		
Bābchi (*Psoralea corylifolia*)	Seed	500 g
Gerū (*Red soil*)	Soil	250 g
Gandhak Amlā Sār (*Purified sulphur*)	Powder	125 g

mortar and pestle with water, then *Bābchi* powder was added to *Geru* powder, and both were ground in mortar and pestle, and lastly, *Gandhak Āmla Sār* powder was added to it, and now all three ingredients were ground in mortar and pestle, and tablets were prepared (Table 1) [25].

Treatment allocation

The participants were allocated into two parallel groups using computer-generated block randomization codes. The randomization was done with the help of sequentially numbered, sealed, opaque envelopes supplied by the Institute's Statistics Department.

Participants in the Unani group received *Habb-i Hindi* orally in the dose of six tablets of 500 mg twice a day. The topical application of *Habb-i Baraṣ* paste made by rubbing 1 tablet in 5 mL of plain water was advised in the morning on the depigmented skin lesion(s) on alternate day after 1½–2½ hours of oral drug intake followed by sun exposure between 7 and 8 A.M. in summer season and 8–9 A.M. in winter season for 5 min initially; the duration was extended by another 5 min every 4th week up to the maximum of 20 min.

Participants in the control group received 8-methoxypsoralen (methoxsalen) in a single dose of 0.6 mg/kg (20 mg for 31–40 kg; 30 mg for 41–60 kg, and 40 mg for >60 kg of body weight) on alternate days after breakfast followed by 1½–2½ hours later sun exposure between 7 and 8 A.M. in summer and 8–9 A.M. in winter seasons starting from 5 min and gradually increased by another 5 min every 4th week, up to a maximum of 15 min or till the development of mild erythema, whichever was reached earlier. All the participants of control group were also advised to apply mometasone furoate cream daily at night.

Efficacy assessment

The response to the treatment was assessed using the vitiligo area scoring index (recorded by two independent clinicians) at weeks 4, 8, 12, and 16. The patient's global assessment (PGA) was done on the 0–100 mm Visual Analogue Scale (VAS) score. Participants were asked to place the X mark on the scale corresponding to the disease severity at each clinical visit, and the corresponding reading was recorded. Disease severity was assessed on a 6-point severity scale, where no change was marked as 0; minimal improvement (1–25%) as 1; moderate improvement (26–50%) as 2; good improvement (51–75%) as 3; very good improvement (76–99%) as 4, and complete improvement (100%) being 5, which was based on a serial photographic record of participants taken by digital zoom camera (Sony IMX398ExmorRSSensor, 16MPf/1.7) with fixed distance and the same place at baseline and 16th week. Concomitant use of any systemic or topical medications was not allowed during the study.

Estimation of VASI

Hamzavi et al. introduced a quantitative parametric scoring system, i.e., vitiligo area scoring index (VASI) for assessment of vitiligo in which the extent of vitiligo is calculated as hand unit, and one hand unit (palm plus the volar surface of all the digits) is calculated about 1% of the total body surface area [8]. The body is divided into 5 separate and mutually exclusive regions: hands; upper extremities (excluding hands); trunk; lower extremities (excluding the feet), and feet. For each body region, VASI is determined as the product of the vitiligo area in hand units and the pattern of depigmentation within each hand-unit-measured patch (possible values of 10, 25, 50, 75, 90, or 100%). VASI is calculated using the following formula (range 0–100):

$$\text{VASI} = \sum_{\text{All Body sites}} [\text{Hand Units}] \times [\text{Residual Depigmentation}]$$

In this study, only patients with >6 months and <2 years of chronicity and >2% affected body surface area (BSA) were included. Then, it was quite difficult to fulfill this criterion as a large number of the patients with 2 years of chronicity did not have >2% affected BSA. Most of the patients had small patches scattered over the body. Thus, to increase the objectivity of VASI, the hand unit of the assessor was divided into 10 parts, where each part regarded as 10% of the hand unit (Figure 1). For smaller patches mostly two fingers unit (index and middle finger) considering 20% of hand unit, i.e., 0.2 hand unit was used, rest of the calculation remained as it was. The body regions were also subdivided in right and left as well as anterior and posterior surfaces.

Safety assessment

Assessment of safety was done based on clinical adverse drug reactions; local dermal tolerability; vital signs at each visit; and routine

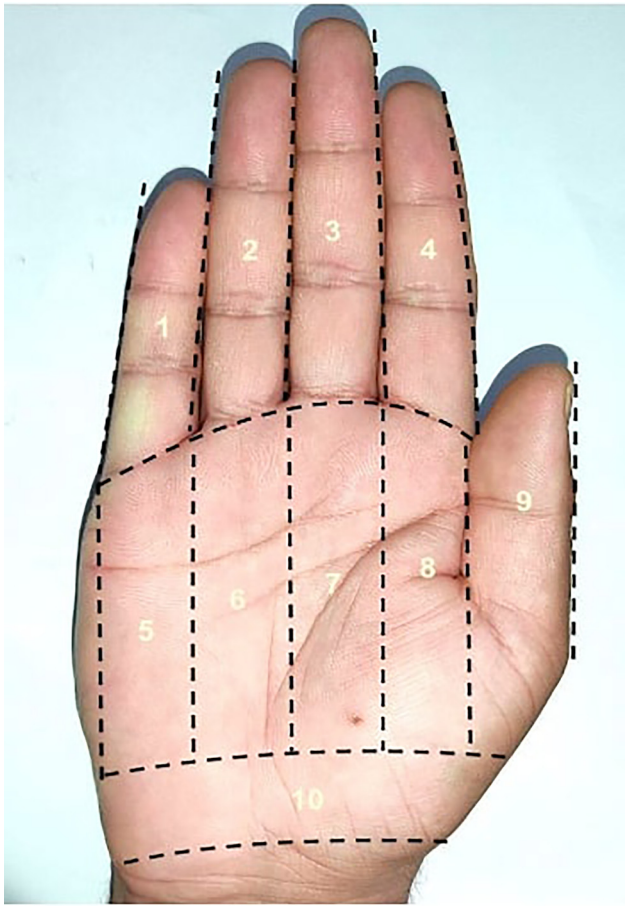

Figure 1: Hand unit of the assessor representing the assumed subdivision.

laboratory investigations such as hemogram (Hb; TLC; DLC; ESR); urine examination (routine and microscopic); liver function tests (SGOT; SGPT; S. Alkaline Phosphatase and S. Bilirubin), and kidney function tests (S. Creatinine and Blood Urea Nitrogen) at baseline and after treatment. The local and systemic adverse effects, if any, were duly recorded in the CRF.

Withdrawal of participants

Participants were withdrawn from the study, if they developed clinical or investigational adverse effects at any time of the study. Patients were also withdrawn, if they missed >2 consecutive treatment sessions in either group.

Statistical analysis

Data were analyzed by per-protocol (PP) analysis. The sample size calculation was based on an earlier study with an assumed power and alpha of 90 and 5% respectively [26]. Thus, a sample size of 30 participants per group was calculated. Considering the 20% loss to follow up, 41 volunteers were allocated to each group.

Statistical analysis was carried out using SPSS 23.0 (Mac version). Data were presented as the proportion (%); mean ± SD or median, wherever appropriate. Baseline as well as after treatment categorical and continuous variables were compared between the groups using Chi-square/Fisher's exact test, Student's t-test and Wilcoxon signed-rank test.

Results

Of 82 participants, 60 patients (30 in each group) completed the 16 weeks duration of treatment; 8 patients from the Unani group and 7 participants from control group dropped out of the study due to loss of follow-up, while 4 and 3 patients were withdrawn respectively due to adverse events. The 22 non-completers were excluded from the analysis as well (Figure 2).

Clinico-demographic profile

The mean age of patients in Unani and control groups was 30.83 ± 6.95 and 29.80 ± 7.18 years respectively. There were 19 males and 11 females in the Unani group, whereas the control group consisted of 13 males and 17 females. The mean of chronicity of disease in Unani and control groups was 16.33 ± 4.61 and 15.77 ± 5.44 months respectively. There was no significant difference ($p>0.05$) in the baseline demographic and clinical characteristics between the two groups (Table2).

VASI (Vitiligo Area Scoring Index)

In the Unani group, the mean ± SD of VASI significantly reduced from 4.09 ± 2.87 at baseline to 3.13 ± 2.20 after 16 weeks of treatment ($p<0.0001$). In the control group, the mean ± SD of VASI significantly reduced from 5.50 ± 5.73 at baseline to 4.29 ± 4.95 after 16 weeks of treatment ($p<0.0001$). The mean percentage reduction in VASI was 23.47 and 22.00% in test and control groups respectively. However, the between-group analysis for Unani and control groups remained statistically insignificant (Table 3).

Patient's Global Assessment (PGA) on VAS

The mean PGA score in both Unani and control groups significantly reduced from baseline 83.00 ± 4.66 to 64.33 ± 11.94 and 84.33 ± 5.68 to 61.33 ± 18.14 respectively at end of the trial ($p<0.0001$). The percentage reduction in PGA score in Unani and control groups was 22.49 and 27.27% respectively. However, the difference in mean and percentage of reduction between Unani and control groups was not significant (Table 4).

Investigator's Global Assessment (IGA) on photographic evaluation

Disease severity was evaluated using a 6-point severity scale based on the serial photographic record at baseline and after treatment. The study inferred the minimal improvement consisting of 21 (70%) cases in test and 20 (66.7%) cases in control groups followed by moderate improvement with 5 (16.7%) cases each in test and control groups (Table 5) (Figure 3).

Discussion

Baraṣ (vitiligo) is a most common, acquired, pigmentary disorder of the skin and mucous membranes, which results in selective destruction of functional melanocytes characterized by well-circumscribed macules and patches [20]. This study was conducted to evaluate the non-inferiority of Unani formulations vs. control in patients with non-segmental vitiligo.

The mean age in both the groups (n=60) was 30.40 ± 6.95 which is similar to the findings reported by Naveen et al. [27] and Krupa Shankar et al. [28] being 31.03 and 32.4 years respectively. This observation supports the claim that vitiligo peaks in the 3rd decade of life [29–31].

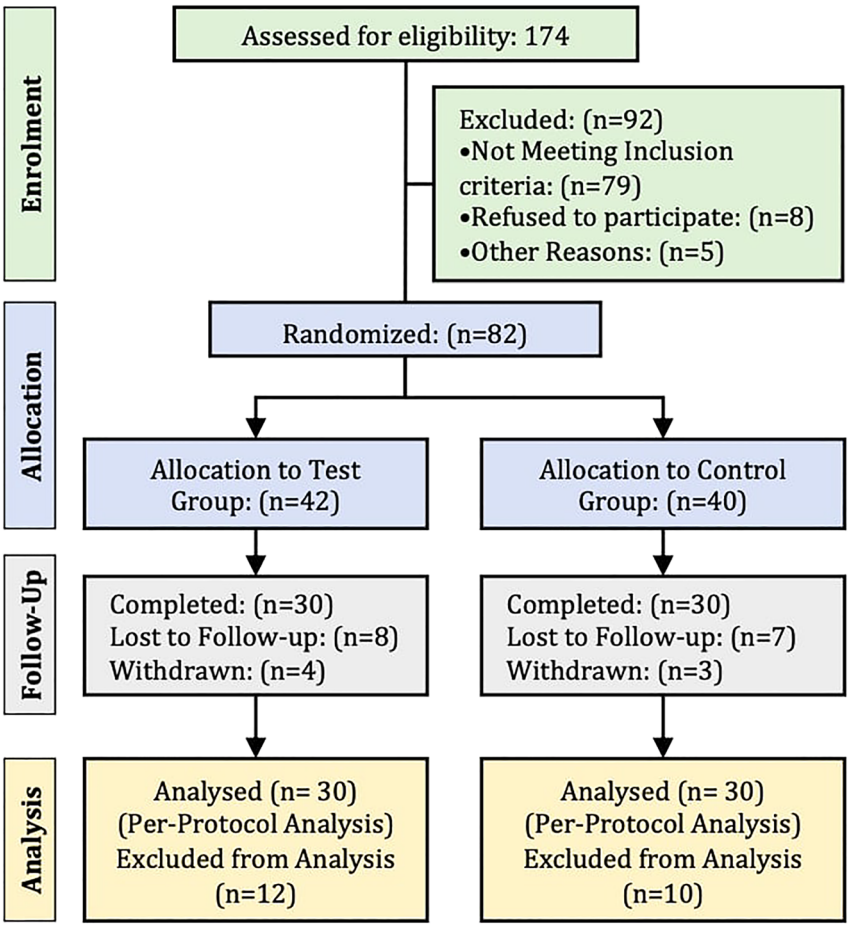

Figure 2: CONSORT flow chart of recruitment and allocation of the patients to Unani and control group.

Gender-wise, there were 32 (53.3%) males and 28 (46.7%) females (Table 3). This data is in conformity with Ali et al. [32]; Krupa Shankar et al. [28], Gopal et al. 54% [33] and Dave et al. [34] who reported marginally increased distribution in males as compared to females. Whereas, no gender variation was reported by Sehgal et al. [31].

In this study, the familial association of vitiligo was 8.3% (Table 3) and this finding is in accordance with Dave et al. [34] and Behl et al. [35]. Conversely, Shajil et al. [36] found no familial association for vitiligo. This familial relation highlights the genetic factors implicated in the causation of vitiligo.

Diet-wise, the majority of participants (76.7%) had mixed diet as compared to the vegetarian diet (23.3%). It underscores the causal relation of vegetarian diet with vitiligo.

The per-protocol analysis revealed that the Unani medications were non-inferior to control in achieving a significant reduction in VASI. Similarly, the percentage reduction in VASI at 12-week was comparable in both the groups. However, less than 30% of the participants in both the groups achieved >25% reduction in VASI at 16-week,

Table 2: Demographic and clinical profile of vitiligo patients in Unani vs control groups.

	Unani group (n=30)	Control group (n=30)	p-Value
Demographic profile			
Age, year (mean ± SD)	30.83 ± 6.95	29.80 ± 7.18	p=0.618 (t-test) Not sig.
Gender			
Males, n (%)	19 (63.3%)	13 (43.3%)	p=0.098
Females, n (%)	11 (36.7%)	17 (56.6%)	(Fisher exact test) not Sig.
Disease profile			
Chronicity, month (mean ± SD)	16.33 ± 4.61	15.77 ± 5.44	p=0.647 (t-test)
Median (range)	18 (12–24)	16.5 (6–24)	Not sig.
Family history number, %	2 (3.33%)	3 (5.0%)	
Disease severity			
Body surface area, % Median (range)	3 (2–11.8)	3.5 (2–29.4)	p=0.238 (t-test) Not sig.

Table 3: Percentage reduction in Vitiligo Area Scoring Index (VASI).

Percentage reduction in VASI after treatment (within the group comparison)				
Group	**Baseline (mean ± SD)**	**After treatment (mean ± SD)**	**Mean %age reduction**	**p-Value[a]**
Unani group	4.09 ± 2.87	3.13 ± 2.20	23.47%	t=5.09, p<0.0001
Control group	5.50 ± 5.73	4.29 ± 4.95	22.00%	t=3 0.99, p<0.0001

Reduction in VASI at 1st follow-up, 2nd follow-up, 3rd follow-up, and final visit (between the group comparison)				
Visit	**Tendencies**	**Unani group (n=30)**	**Control group (n=30)**	**p-Value[b]**
Baseline	Mean ± SD, Median	4.09 ± 2.87, 2.75	5.50 ± 5.73, 3.3	0.233
After 4 weeks (1st follow-up)	Mean ± SD, Median	3.93 ± 2.68, 2.75	5.28 ± 5.55, 3.1	0.235
After 8 weeks (2nd follow-up)	Mean ± SD, Median	3.72 ± 2.60, 2.68	5.14 ± 5.57, 2.96	0.211
After 12 weeks (3rd follow-up)	Mean ± SD, Median	3.49 ± 2.33 2.55	4.46 ± 4.77 2.6	0.321
After 16 weeks (final visit)	Mean ± SD, Median	3.13 ± 2.20 2.09	4.29 ± 4.95 2.41	0.246

[a]Paired sample t-test, [b]Independent sample t-test.

indicating that 16-week may not be an adequate duration of therapy, both with control and Unani formulations.

The improvement in the Unani group may be attributed to the ingredients inherent in the Unani formulations, especially *P. corylifolia*. Psoralen, an active ingredient derived from *P. corylifolia* has potent anti-vitiligo activity as Sultan et al. reported that psoralen stimulates cholinergic-like psoralen receptors and causes stimulation of melanocytes [37]. Li Yin et al. found that the psoralen induced melanin synthesis through intracellular cAMP accumulation, melanogenesis-related signalling pathway, and tyrosinase activity in a concentration-dependent manner as well as significantly activated the expression of melanogenic proteins such as tyrosinase [38].

In a meta-analysis on *Baraṣ*, it was concluded that *Bābchī* being an important constituent had better anti-vitiligo effects [23].

The second important ingredient is *Azadirachta indica* L., which has extensively been studied for its anti-inflammatory, anti-microbial, and antioxidant activities [39]. Limited data are available on its anti-vitiligo effect. Contrary to that, Jadhav et al. in a case series of vitiligo found that the de-pigmentation on oral and mucosal lesions is caused by Neem [40]. *Ficus hispida* has anti-neoplastic, cardioprotective, neuroprotective, and anti-inflammatory effects and the anti-vitiligo effect may be attributed to these actions [41]. *Zingiber officinale* is an

Table 4: Patient's Global Assessment on VAS (within the group and between the group comparison).

Within the group comparison							
Group	**Baseline (mean ± SD)**		**After treatment (mean ± SD)**		**Percentage reduction in mean PGA score, %**		**p-Value[a]**
Unani group	83.00 ± 4.66		64.33 ± 11.94		22.49		p<0.0001
Control group	84.33 ± 5.68		61.33 ± 18.14		27.27		p<0.0001
Between the group comparison							
Time points	**Group**	**Mean rank**	**U**	**W**	**p-Value[b]**	**Mean ± SD of VAS**	**p-Value[c]**
VAS-baseline	Test	28.35	385.5	850.5	0.264	83.00 ± 4.66	0.325
	Control	32.65				84.33 ± 5.68	
VAS-after treatment	Test	31.07	433.0	898	0.796	64.33 ± 11.94	0.452
	Control	29.93				61.33 ± 18.14	

[a]Paired sample t-test, [b]Wilcoxon signed-rank test, [c]Independent sample t-test. U=Mann–Whitney U test, W=Wilcoxon sign rank test.

Table 5: Percentage reduction in vitiligo lesions based on Photographic evaluation.

Reduction	Unani group (n=30)	Control group (n=30)	Total
<1%	2 (6.6%)	3 (10%)	5
1–25%	21 (70%)	20 (66.7%)	41
26–50%	5 (16.7%)	5 (16.7%)	10
51–75%	2 (6.7%)	0	2
76–90%	0	2 (6.7%)	2
>90%	0	0	0

important plant of Unani medicine indicated for vitiligo. It has antioxidant, anti-inflammatory, immuno-modulator, and anti-tumour activities [42]. Similarly, the response in both groups was non-inferior in terms of patient's global assessment and investigator's global assessment.

There were some side effects like nausea and vomiting in the control group (26.7%) as compared to the Unani group (10.0%), and this difference was statistically significant (p=0.001). A total of 6 (20.0%) patients in the control group had gastrointestinal side effects vs. 1 (3.3%) in the Unani group. As far as the topical medications were concerned, side effects like hyperaemia, itching, and bullae formation were higher in the Unani group (20%) as compared to the control group (3.3%).

The evaluation of safety was made in both groups by hemogram, LFTs, KFTs, ECG, and Chest X-ray at baseline and after completion of the treatment, and all the safety parameters were within normal limits. The limitations of the study were the use of sunlight as a source of UV radiation, which may vary with regard to time, place, season, and atmospheric conditions. The sample size was less and the duration of therapy was also not adequate for both treatment groups.

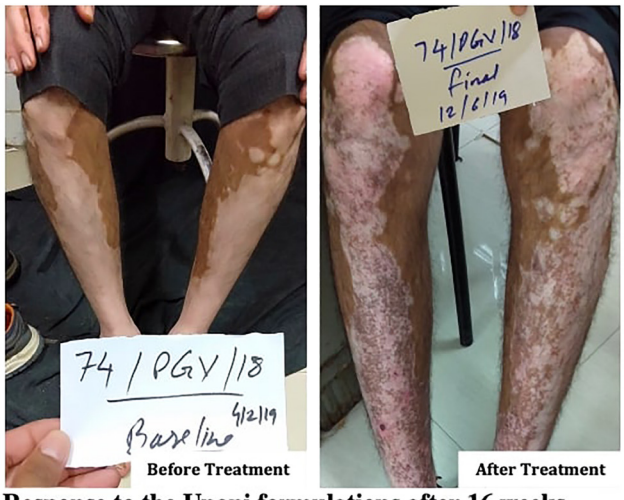

Figure 3: Response to the treatment after 16 weeks.

Conclusions

The study inferred that Unani formulations are effective, safe, and well-tolerated in the patients with non-segmental vitiligo. The trial drugs are worth investigating further as an alternative treatment in non-segmental vitiligo, but rigorously designed, double-blinded, placebo-controlled trials with larger sample size, longer duration of therapy, and validated scientific parameters are needed to reinforce the scientific evidence.

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Ethical approval: Approval taken from Institutional Ethics Committee, CRIUM, Hyderabad.

Trial registration: Clinical Trial Registry of India (www.ctri.nic.in) registration number CTRI/2017/12/010998.

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