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Original Article

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

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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

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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.

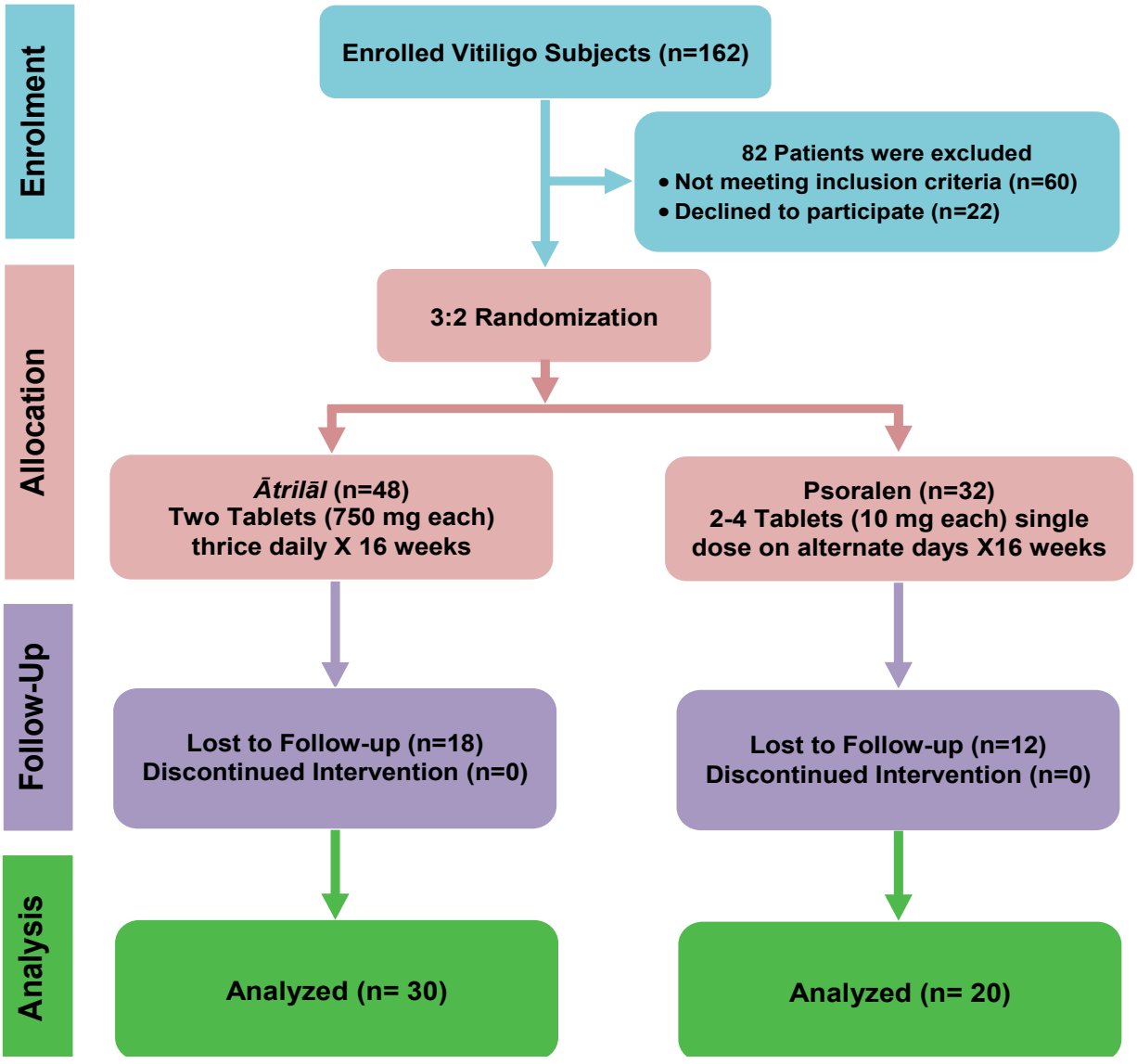
2.9.4 Investigator's Global Assessment (IGA)

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.

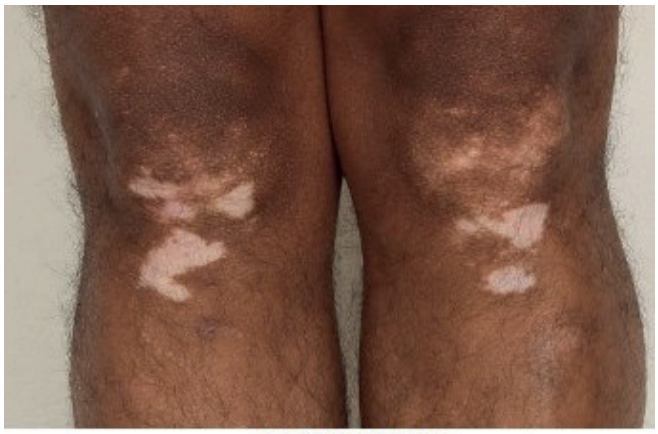


Figure 2 Photographs of depigmented lesion at baseline and post-treatment

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*.

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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.

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BARAṢ (VITILIGO) IN UNANI MEDICINE AND CONVENTIONAL MEDICINE: AN OVERVIEW

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ABSTRACT

Baraṣ (Vitiligo), sometimes referred to as leukoderma (from the Greek words leuco meaning white and derma meaning skin) is an acquired, chronic depigmenting disorder of the skin and/or mucosa, characterized by milky white, non-scaly macules and/or patches with distinct margins, and caused by destruction of melanocytes in lesional skin. According to Unani Medicine, Baraṣ (Vitiligo) is a white discolouration of the skin, which is caused by the weakness of Quwwat Mughayyira (transformative faculty), cold impaired temperament of organs, or it may be congenital. About 1-2% of the world's population, or 40-50 million people, have vitiligo. Vitiligo appears to be more common in people with certain autoimmune diseases. These patches are more common in sun exposed areas, including hands, feet, arms, face, and lips. Other common areas for white patches to appear are the armpits, groin, around mouth, eyes, nostrils, navel, and genitals. Vitiligo generally appears in one of three patterns. In one pattern (focal pattern), depigmentation is limited to one or only a few areas. Some people develop depigmented patches on only one side of their bodies (segmental pattern). But for most people who have vitiligo, depigmentation occurs on different parts of the body (generalized pattern). In addition to white patches on the skin, people with vitiligo may have premature greying of the scalp hair, eyelashes, eyebrows, and beard.

KEYWORDS: Baraṣ, Leukoderma, Unani, Segmental Vitiligo, Non-segmental vitiligo.

INTRODUCTION

Baraṣ (Vitiligo) is a common, acquired, idiopathic discoloration of the skin characterized by well-circumscribed, ivory/ chalky white colored macules, which are flush to the skin surface in contrast to leukoderma. The lesion may be surrounded by a ring of tan intermediate colour around which is the normal skin, 'the trichrome'. The hair over the patch may be either normal or white (leukotrichia).[1] Celsus was the first to use the term vitiligo in his Latin medical classic *De Medicina* during the second century BCE.[2] The name is believed to derive from the Latin *vitium*, meaning defect or blemish[3] rather than *vitellus*, meaning calf.[4] Typical vitiligo lesions can be defined as milky white, non-scaly macules with distinct margins. *Baraṣ* (Vitiligo) occurs worldwide, with a prevalence of 0.1% to 2.0% in the United States, the estimated incidence is 1%.[5] In India, the incidence among dermatology outdoor patients is estimated to be between 3-4%. The incidence of *Baraṣ* (Vitiligo), as reported by various workers in different cities of India can be between 2.9% in Goa to 8.8% in Delhi. However, most authors say that its incidence is around 4%, which is however, definitely more as compared to the world's population of 1%.[6] This is a common condition, in which, completely white patches develop due to melanocyte destruction. It is probably an autoimmune disease.[7] Vitiligo commonly begins in childhood or young adulthood, with peak onset of 10-30 years, but it may occur at any age. All races are affected, and both sexes are equally afflicted. A female preponderance has been reported, but the discrepancy has been attributed to a presumed increase in reporting of cosmetic concerns by female patients. Although familial clustering of cases is commonly seen, inheritance occurs in a non-Mendelian pattern. Approximately 20% of patients with vitiligo have at least one first degree relative with vitiligo, and the relative risk for first degree relatives of vitiligo patient is increase by 7- to 10-fold.[5]

Concept of baraṣ (vitiligo) in unani medicine

Baraṣ (Vitiligo) has been discussed in detail in the classics of Unani Medicine. According to Unani

Medicine, Baraṣ (Vitiligo) is a white discolouration of the skin, which can appear anywhere in the body, but mostly occurs on hands and feet. Sometimes it occurs in few organs, sometimes it affects all organs. When it involves most of the body's skin, it is known as Baraṣ Muntashir (extensive vitiligo). Thus, the whole body becomes white.

According to Ibn Sīnā (Avicenna) (980-1037) in his medical encyclopaedia, Al-Qānūn fi'l Ṭibb, the perfectness of the tissue metabolism depends on four factors, including Quwwat Jādhiba (absorptive faculty), Quwwat Māsika (retentive faculty), Quwwat Mughayyira (transformative faculty) & Quwwat Mushabbiha (power of resemblance), and Quwwat Dāfiʻa (expulsive faculty).[8,9] Quwwat Jādhiba is the power which serves for the absorption of food. Quwwat Māsika is the power that retains the nutrients at tissue level, so that they may be well-integrated with the tissue. Quwwat Mughayyira and Quwwat Mushabbiha are the powers that bring changes and shape the nutrients into tissue power. Quwwat Dāfiʻa is the power that excretes waste material from the tissue level and throws into the bloodstream for final decomposition and excretion from the body. Ibn Sīnā says that depigmentation occurs due to defects in the function of Quwwat Mushabbiha (power of resemblance) at the tissue level.

ʻAli ibn ʻAbbās Majūsī (930-994AD) in his famous book, Kāmil al-Ṣanāʻa al-Ṭibbiyya says[10], Baraṣ occurs due to domination of phlegmatic humour in the blood, and weakness in Quwwat Mughayyira (transformative faculty) in the organ. There is white discolouration of the skin, even the hair also turns white. On puncturing the skin with a needle, if, white fluid oozes in spite of blood, then there is no chance of cure; if blood or reddish fluid oozes, then there is no hopelessness for the cure. When Baraṣ (Vitiligo) becomes chronic, the treatment is difficult. The primary step in the treatment of this disorder is to restrict the intake of phlegm forming foods such as milk, fish and cold and wet foods. Besides, the patients should be given honey and such purgative drugs, which may expel Balgham (phlegm), like Ḥabb-i-Ayārij and Mʻajūn made from Ghāryaqūn, Shaḥm-i-Ḥanzal, Ḥabb al-Nīl, Turbud, etc.

Zakariyya Rāzī (Rhazes) (850-925AD) in his famous book Kitāb al-Ḥāwī fi'l Ṭibb has given a comprehensive description of this disease.[11] According to him, if white patches of Baraṣ (Vitiligo) do not turn red on rubbing or when, instead of blood, white fluid comes out on pricking them, the possibility of recovery is low and vice versa. If white patches are limited and non-extensive and the colour of the patches is yellowish or reddish, then early cure can be expected. Conversely, when Baraṣ (Vitiligo) is extensive and spreading and where the affected areas become bloodless and colour of the patches is cloudy, it is incurable. He also mentioned that the patches on the feet and head do not respond to treatment adequately.

Aetiology and pathogenesis

Vitiligo is a multifactorial, polygenic disorder, with a complex pathogenesis that is not yet well understood. Of various theories of disease pathogenesis, the most accepted is that genetic and nongenetic factors interact to influence melanocyte function and survival, eventually leading to autoimmune destruction of melanocytes. Other suggested explanations have included defects of melanocyte adhesion, neurogenic damage, biochemical damage, auto cytotoxicity and others.[12] According to Unani Medicine, *Baraṣ* (Vitiligo) is caused by the weakness of *Quwwat Mughayyira* (transformative faculty), failure of *Quwwat Mushabbiha* (power of resemblance), cold impaired temperament of organs, or it may be congenital.

Epidemiology

Baraṣ (Vitiligo) is the most common depigmenting disorder. The largest epidemiological study was done in 1977 on the island of Bornholm in Denmark, where vitiligo was described to affect 0.38% of the population.[13] The prevalence of vitiligo is often referred to as 0.5-1% of the world's population.[14] Although the exact prevalence is difficult to estimate, the rates are as high as 8.8% in India, because these data referred to the prevalence of patients with vitiligo within one skin institute in Delhi.[15] This high value could be due to the inclusion of cases with chemically-induced depigmentation. Overall, the highest incidence rates have been recorded in India (up to 8.8%), followed by Mexico (2.6-4%), and then Japan (1.68%). The disparity between prevalence and incidence data could be due to high reporting of data; places where social and cultural stigma are common, forcing patients to seek early consultation, or where lesions are more prominent in dark skinned populations.[16] Adults and children of both sexes are equally affected, although women and girls often present for treatment more frequently, possibly because of the greater negative social effects for affected women and girls than for men and boys.[17] Non-segmental vitiligo (NSV) develops at all ages, but usually occurs in young people between the ages of 10 years and 30 years.[18] Childhood-onset vitiligo (before age of 12 years) is reported to be common and affects 32-37% of patients.[19], compared with previously reported 25%.[20] Non-segmental vitiligo (NSV) can occur at any age, whereas segmental vitiligo (SV) tends to occur at a young age, before the age of 30 years in 87% of cases and before the age of 10 years in 41.3%. Segmental vitiligo accounts for 5-16% of overall vitiligo cases.[21] The proportion of patients with positive family history varies from one part of the world to another. In India, in particular, it ranges from 6.25-18%. In some studies, it is as high as 40%. The mode of transmission of vitiligo is quite complex. It is probably polygenic with a variable penetrance.[22]

Classification of baraṣ (vitiligo)

On the basis of the polymorphic distribution, extension, and number of white patches, vitiligo is classified into

generalized (vulgaris, acrofacial, mixed), universalis, and localized (focal, segmental, and mucosal) types.[23] Vitiligo is also classified as segmental and Non-segmental types, on the basis of distinctive clinical features and natural histories.

1. **Segmental vitiligo (SV):** It is characterized by macules having unilateral dermatomal distribution that does not cross the midline. It generally affects young children and typically remains localized, the depigmented lesions persisting unchanged for many years.[12]
2. **Non-segmental vitiligo (NSV):** It includes all cases not classified as segmental, including localized, generalized, and acrofacial.
3. **Vitiligo vulgaris**: In this type, multiple scattered lesions are distributed in a more or less symmetrical pattern. It is the most common presentation of Generalized Vitiligo (GV)
4. **Acrofacial vitiligo:** It affects the distal end of fingers and facial orifices in a circumferential pattern. It is a subtype of GV.
5. **Mixed vitiligo:** It is a combination of acrofacial and vulgaris, or segmental and acrofacial types.
6. **Vitiligo universalis:** It is a complete or nearly complete depigmentation of the whole body. It is the most severe form of NSV.
7. **Focal vitiligo:** It is characterized by the presence of one or few macules in one area but not distributed in a segmental pattern. It is considered a precursor form of GV.
8. **Mucosal vitiligo:** It is a term reserved for depigmentation of mucous membrane alone.

Clinical features of baraṣ (vitiligo)

Vitiligo is characterized by the appearance of patchy discoloration evident in the form of typical chalky-white or milky macules. The macules are round and/ or oval in shape, often with scalloped margins.[24] The size of the macules may vary from a few millimetres to several centimetres, with the lesions affecting the skin and/ or mucous membranes. By and large, the lesions are asymptomatic although itching/ burning may precede or accompany the onset of the lesions in a few patients.[25] Vitiligo is a slow and progressive disease and may have remissions and exacerbations correlating with triggering events.[26] Occasionally, the lesions of vitiligo may begin to form around a pigmented nevus (Sutton's Nevus/ Leukoderma Acquisitum Centrifugum) and then go on to affect distant regions.[27]

Associated diseases

Amongst autoimmune diseases, the strongest association is with thyroid disease, including hypothyroidism and hyperthyroidism. Systemic disorders like, diabetes mellitus, pernicious anaemia, Addison's disease, lymphoma, leukaemia, human immunodeficiency virus (HIV) infection, and Sjogren's syndrome are a few of the diseases associated with vitiligo.[28, 29] Autoimmunity and immune responses are of paramount significance in vitiligo.[30]

Cutaneous associations

Cutaneous associations of vitiligo are important as they commonly provide circumstantial indication to its possible aetiopathogenesis. Halo nevus, lichen planus, alopecia areata, leukotrichia, and premature greying of hair are frequently reported associations.[31] Of these, leukotrichia (poliosis) is found in up to 45%, premature greying of hair (canities) in 37%, followed by halo nevus in 35% and alopecia areata in up to 10% of cases.[22] Rarely, other skin disorders like nevus depigmentosus, dermatitis herpetiformis, giant congenital melanocytic nevus with neurotization, chronic urticaria, polymorphic light eruption and malignant melanoma have also been recorded in association with vitiligo.[32] Moreover, psoriasis vulgaris confined to vitiligo patches and occurring contemporaneously in the same patient has recently been described. Stress is associated with vitiligo in many patients.[33]

Differential diagnosis

Differential diagnosis of Baraṣ (Vitiligo) includes several dermatoses like, nevus depigmentosus, pityriasis alba, pityriasis versicolor, post- inflammatory hypopig mentation, tuberous sclerosis, idiopathic guttate hypomelanosis, Waardenburg syndrome, systemic sclerosis, borderline tuberculoid leprosy[34], chemical leukoderma, and melanoma-associated leukoderma.[35]

Diagnosis

The diagnosis of vitiligo is based essentially on clinical examination, because the lesions have a typical appearance. However, if the lesions are not distributed in the pattern of classical vitiligo, confusion with other hypomelanotic disorders can arise. Inspection with the aid of a Wood's light can then be helpful. The presence of a family history of vitiligo, the Koebner phenomenon, leukotrichia or associated autoimmune disorders such as thyroid disease can help to support a clinical diagnosis of vitiligo.[36]

Management of baraṣ (vitiligo) in conventional medicine

Current treatments for vitiligo are largely unsatisfactory, as the aetiopathogenesis of vitiligo remains poorly understood. First-line treatments consist of topical treatments (corticosteroids and calcineurin inhibitors). Once daily application of potent topical corticosteroid preparations (e.g., 0.1% betamethasone valerate and 0.05% clobetasol propionate) is recommended, but should preferably be applied in a discontinuous scheme (e.g., 15 days per month for 6 months) to avoid local side-effects (skin atrophy, telangiectasia, hypertrichosis, acneiform eruptions and striae). The use of topical calcineurin inhibitors (tacrolimus or pimecrolimus) mainly for the face and neck is an alternative to topical steroids. Twice daily applications are recommended, initially for 6 months.[37]

Second-line treatments consist of phototherapy (NB-UVB and psoralen and UVA [PUVA]) and systemic steroid treatment. Treatment with phototherapy is effective in some cases. NB-UVB (311 nm) phototherapy is at least equally effective as PUVA, with fewer side-effects because of intake of psoralens.[38] Targeted phototherapies can be used for localised vitiligo, e.g., Excimer Lamps or Lasers (peak at 308 nm). No consensus exists as to the optimum duration of phototherapy. Irradiation will most often be stopped, if no repigmentation occurs within the first 3 months of treatment, even though repigmentation sometimes starts later on. Oral Mini-Pulse (OMP) of moderate doses of betamethasone or dexamethasone (2.5mg/day) for 3-6 months can be considered in fast spreading vitiligo to stop progression.[39]

Third-line treatments consist of surgical grafting techniques and depigmenting treatments. Surgical methods are planned as a therapeutic option in patients with segmental vitiligo and those with non-segmental vitiligo with stable disease for at least 1 year after recognized non-response of medical interventions and absence of Koebner's phenomenon. Only a few patients are therefore suitable for these interventions. The surgical techniques that are mentioned in the European guidelines consist of tissue grafts (full-thickness punch, split-thickness, and suction-blister grafts) and cellular grafts (cultured melanocytes and non-cultured epidermal cellular grafts). The three tissue grafting methods seem to have much the same success rates of repigmentation. Additionally, cellular grafting techniques were, in general, equally effective, although the percentages of repigmentation were slightly inferior to the tissue grafts.[40] However, important advantages of cellular grafting are the possibility of treating large areas and better cosmetic results than with tissue grafts.[41] Furthermore, adverse events appear to be less frequently related with cellular grafts than with punch grafting, followed by split-thickness grafting.[42] Depigmenting treatment of residual areas of pigmentation should only be considered in widespread (>50% body surface area), obstinate, and disfiguring vitiligo, or highly visible recalcitrant facial or hand vitiligo. Skin-bleaching methods reported are monobenzone ethyl ester or 4-methoxyphenol.[43]

Management of *baraṣ* (vitiligo) in unani medicine

According to Unani system of medicine, there are four primary methods of treatment. These are Ilāj bi'l Ghidhā (Dietotherapy), Iāj bi'l Tadbīr (Regimen Therapy), Ilāj bi'l Dawā (Pharmacotherapy), and Ilāj bi'l Yad (Surgery). Baraṣ (Vitiligo) is a chronic disease and, hereafter, all the Unani physicians are of the view that its treatment should be started with Tanqiya (Removal of harmful material from the body) with Munḍij and Mushil (MM Therapy). The goal of Munḍij and Mushil Therapy is to correct the metabolic errors such as humoral imbalance in the body. This therapy is very exclusive which is employed to patients with persistent, chronic, systemic diseases. There are different types of Munḍij and Mushil therapies which are prescribed after clinical examination of patients and determining the dominating Humour (Khilṭ) as causative factor. Mostly Munḍij-e-Balgham Advia are given in the management of Baraṣ (Vitiligo).[44] The management of Baraṣ (Vitiligo) includes to maintain and balance the deranged Balgham (Phlegm), Ta'dīl-i Mizāj and use of appropriate ointment locally.[45] For the treatment of Baraṣ (Vitiligo), various single and compound drugs are used like, Atrilāl (Ammi majus)[46], Babchi (Psoralia corylifolia)[47], Waj (Acorus calamus), Gandhak Amlasar (Sulphur), Geru (Silicate of alumina & oxide of iron)[48], Habb-i Baraṣ, Habb-i Hindi[49], Safūf Baraṣ[50, 51], etc.

CONCLUSION

Vitiligo affects millions of people, regardless of their ethnic background. Advances in medical and surgical treatments have been made, but there is no cure for vitiligo. It is psychologically disturbing especially in the dark skin. The treatment of vitiligo depends upon the duration of vitiligo and whether it is localized or generalized. If more than two-thirds of the body is affected by vitiligo, then it is better to bleach the whole body. The patients most likely to respond are those of recent onset, and who have lesions on the face. Long standing vitiligo with white hair is most unlikely to be cured. Lips and finger tips have a poor response to treatment because of the absence of hair follicles.

Adverse effects of conventional treatment are more common, which have led to search of new alternatives. A better option for the management of vitiligo may be Unani Therapy. The advantage of Unani therapy compared with conventional therapy is that it is more effective in vitiligo and does not produce major adverse effects as evidenced through various clinical studies. Moreover, it also improves the patients' quality of life.

Until further advances are made, there should be a holistic, multi-disciplinary approach to the management of vitiligo, which includes information about the disease, cosmetic camouflage, as well as referral to psychotherapy and appropriate alternative therapies, which are promising for patients afflicted with this traditionally stigmatizing and challenging condition, like Unani therapy.

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The Concept of *niqris* (gout) and its management in unani system of medicine: A review

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Abstract
Niqris (gout) is a type of Waja' al-Mafasil (arthritis) characterised by recurrent attacks of acute pain and swelling primarily affecting one joint, usually the metatarsal joint of the big toe and small joints of the hand and feet. Gout is one of the oldest known diseases and is referred to as *niqris* in the Unani system of medicine. According to Galen (Jalinoos) and Rhaze (Zakariya Rhazi, 860-923 A.D.) Arthritis (Wajaul Mafasil), Sciatica (Irq-un-Nisa), and Gout (*Niqris*) fit in the same group and their different names denote the different areas of affliction. According to Unani theory, pathological changes in the joints are caused primarily by humoral temperament derangement and the accumulation of Morbid material (Mawad-e-Fasida) in the joint spaces. According to renowned Unani Physician Ibn-Hubal, *Niqris* primarily affect those people who have an excess of Humors (Akhlat) and their bodies are unable to excrete them, causing these humours to accumulate inside the body and around the joints and other tissues. These humours cause an inflammatory response, resulting in an acute flare with pain, swelling, warmth, and redness in affected joints. The goal of this study was to determine the Unani concept described in Unani classical literatures regarding various causes, symptoms, and management of this common arthritic disorder by Renowned Unani Physicians with the goal of spreading knowledge for preventive measures, disease relief, and management of gout by Regimenal therapy and Unani compound formulations, which are not only easily available but also have no side effects on the human body.

Keywords: *Niqris*, gout, arthritis, regimenal therapy, unani system of medicine

Introduction
Niqris is an Arabic term that is equivalent to gout. [1] It is the specific name for pain and inflammation, which usually occurs in the joints of the feet, ankles, toes and especially in the big toe joint [2, 3, 4]. The big toe joint is referred to as "Ankorus" by Ibn Hubal, [2, 5] while the pain and swelling associated with it are referred to as "*Niqris*" or Naqras and the site is called naqroos [6].

Niqris is one of the oldest and most prevalent types of inflammatory arthritis. As early as 2640 BC, the Egyptians called it Podagra (foot pain), at present understood as uric acid arthropathy [7]. A scientist named Die Vielerhadouin gave it the name "gout" in the [13] th century, which is derived from the Latin word "gutta" means "fall of matter" [8, 9].

Hippocrates (Buqrat, 460-377 B.C.), the father of medicine, referred to *niqris* as "the disease of kings" because of its association with a rich diet and wealthy men who overindulged in food and drink [7, 10].

Avicenna (Ibn Sina, c. 980- 1037 A.D.) stated that "*Niqris*resembles with other types of arthritis (Waja-ul-Mafasil), and it sometimes originates from the toes, particularly the great toe, sometimes from the heel, sometimes from the plantar side of the foot or from the borders of the foot, and it affects the entire body so severely that viscera also get affected." [2, 5, 11].

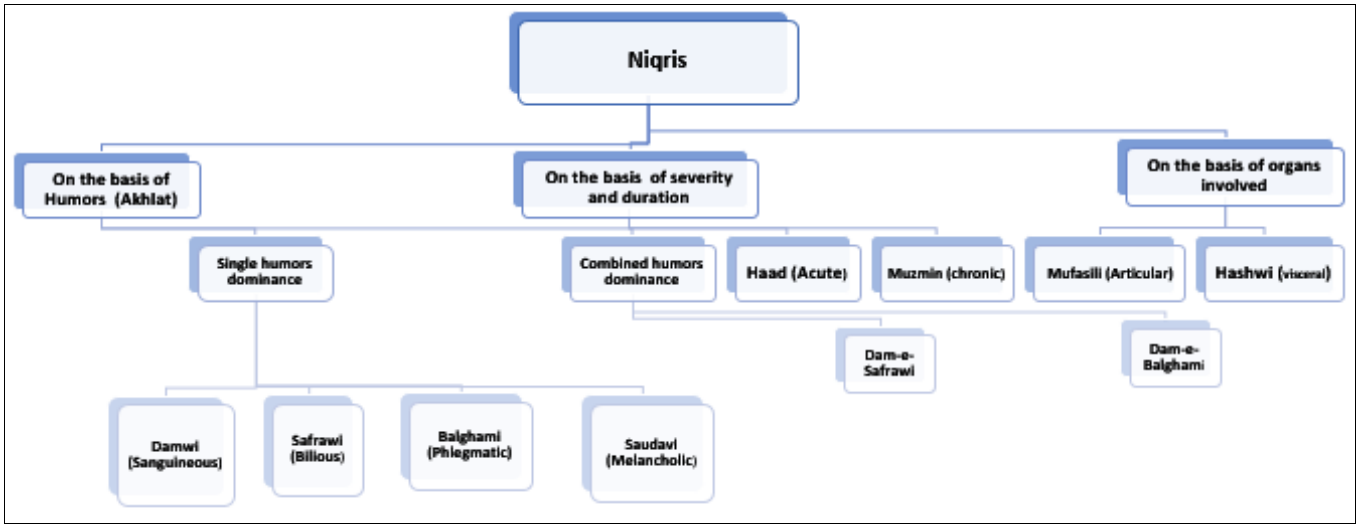
Razi claims that the discomfort begins in one joint and spreads to other joints, even in other feet and also to the bladder, rectum and knees [3, 4]. Information about the referral of pain to the wrist joint and fingers of the hands has been added by Azam Khan [5]. According to Jurjani, it might also refer to the lumber region [12]. According to Jalinus, every joint pain is the same but calls by different names depending on which joints they affect, such as gout, rheumatoid arthritis, osteoarthritis, etc. Perhaps Hippocrates (460-370 BC) recognised the *Niqris* in the fifth century BC and described it as an un-walkable disease [8]. He proposed different names for gout depending on the location, like podagral for gout in the legs, Cheiragra for gout in the elbow, Gonagra for gout in the knee, and Omagra for gout in

the shoulder. The first person to mention it under inherited disorders was Hippocrates [13].

According to Hakeem Kabeeruddin, gout (the toxic substance that causes gout/maddah-e-niqras) is basically a by-product of liver metabolism, much like urinary calculi. *Niqris* is one of the diseases associated with liver and tissue metabolism (hazm-e-kabidi or hazm-e-chaharum) [14, 15].

Classification of *Niqris*

Keeping in view the descriptions given by Unani Scholars, *Niqris*can be classified as follows: [5, 6, 14, 16].



Etiology: The majority of Unani scholars attribute the basic cause of *Niqris* to the following factors:

- Sual' mizaj sazij (Simple imbalance of temperament) [6, 16, 17],
- Sual'mizaj Maddi (Temperament imbalance caused by a change in matter): It is the most important etiological factor. It is a temperament disorder in which the body's homeostasis is disturbed due to a change in the specific ratio of Kmmiyat and Kayfiyat (quantitative and qualitative changes) of akhlat (maddah) locally or generally [6, 16, 18].
- Weakness of joints, which results in the accumulation of causative matter (maddah-e-Niqras) in the joint and thus leads to the development of Niqras [6, 18, 19],
- Excessive eating, excessive drinking, excessive intercourse, especially just after meals, sedentary lifestyle, heredity, luxurious living, and lack of exercise are the major risk factors for the development of Niqras [3, 6, 16, 18],
- Some physicians have attributed the Reeh (flatulent matter) and lead poisoning as causative factors of *Niqris* [6, 16, 17],

Etiopathogenesis

According to Hippocrates, *Niqris* is an ailment of joints caused due to excess of one of the four humours which, under certain conditions, flows or accumulates in joints and causes pain and inflammation [20]. According to Qamri, the disease occurs due to dissemination of morbid matters (mawad fasida), which is expelled by A'aza-i-raisa (vital organs) and accumulates in the peripheries due to the weakness of a particular part. Because of disturbed Quwwat-e-Hazimah (Digestive Power) and liver dysfunction, the madda is formed [19]. According to Baghdadi, the humour that causes this disease can be hot or cold, but it is usually caused by murakab madda (two or more matters along with). The accumulation of matter in the joints is caused by humour imbalances such as sanguine, phlegm, bile or black bile [5]. The painful condition and swelling are caused by the accumulation of Kaymus (chime) in the weak joints which causes stretching of the nerves and ligaments [2, 3, 4, 18]. Galen (Jalinus) has specified that the Rawasib Ramliya (tophi) fill the foot joint first. Baghdadi and Qamri believe that the joint turns red, accompanied by intense pain and inflammation. Sheikh has classified it into two types: Sada (simple) and Maddi (due to matters). Simple is unusual, and the patient feels slight heaviness, fatigue, and no change in the colour of the joint while in Maddi type the symptoms vary with the type of Madda (matter) that accumulates in the joints [3, 4, 12]. When it caused by Damwi Madda (blood), the joint will be hot, red with stiffening of joint. When the Madda is Safrawi (yellow bile), the affected area will be very hot and red, with intense pain and pricking sensation, but swelling will be minimal. This type is extremely hazardous [5]. Due to the excess accumulation of phlegm on the joint, the colour of the joint would be similar to skin, with less pain and no pricking sensation. When Madda is Saudawi, it is black or green in colour, with minimal inflammation and mild pain. According to Azam Khan, if the Madda is thick, pain will occur along with inflammation, and its duration will be longer. Sometimes the episodes of pain subside on their own without treatment, in this case, this Madda can divert to internal organs, leading to serious complications like asthma, paralysis and even death. Some Unani scholars have stated in their classical works that orchitis can occur in gout patients [12]. It is more common in men, but it can also occur in women after menopause. Females who are menstruating are not much affected by this disease [3, 4, 12]. According to Hippocrates, women are not involved until menopause, and men until puberty. Young and elderly people, as well as males who have had their testicles removed, are also prevented from the disease [3, 4, 5, 21]. It is especially severe in people with a family history of the disease [2, 3, 4, 5, 12]. According to temperament cold tempered persons are most prone to this disease [3, 4]. It usually happens during the Rabi and Kharif seasons [3, 4, 12, 18]. It worsens during the Kharif season, especially among those who consume an excessive

amount of fruits. Trauma, horseback riding, excessive coitus, overeating, changes in dietary habits, sedentary lifestyle, less physical activity, alcohol, stress, chronic dyspepsia, liver disease, and cessation of excessive purgation are all included as predisposing risk factors of the disease [3, 4, 5, 12, 18, 21]. That is why it is also known as Da al-Maluk (rich person's disease), as it primarily affects the wealthy person.

Prognosis

According to Razi, when *Niqris* is occur due to viscid Madda (matter) has a poor prognosis; if it persists for a long duration, it may lead to tahajjur of joints. In contrast, a thin Madda (matter) has a better prognosis. When both types of thick and thin matter are involved, it takes longer to cure, but not more than [40] days. Galen says that if the humours are raw and the urine is thick, the prognosis will be better. When it is hereditary, appears at an early age, is associated with kidney disease, and has frequent occurrences, it is said to have a poor prognosis [2]. Gout is uncommon in the elderly, but if it does occur, the prognosis is poor. If it occurs on the right side, the prognosis will be worse than on the left side [19].

General principles of treatment (Usool-e-Ilaj)

Most Unani scholars describe the general line of treatment (Usool-e-Ilaj) for gout as follows:

1. Modification of So'e Mizaj (unbalanced temperament) through appropriate measures and drug use with caution [11, 18].
2. The noxious matter and causative humours should be expelled from the body using diaphoretics (Moarriqat), purgatives (Mushilaat), and emetics (Muqiyat). Purgation (Ishal) is valuable in safravi madda, emesis (Qay) is valuable in balghami madda, and venesection (fasd) is beneficial in damvi madda [2, 3, 5, 11, 16, 17, 18, 19].
3. Some of the Unani scholars suggest the use of Diuretics (Mudirat) in treatment of *Niqris* [16].
4. Use of anti-inflammatory (Mohallil-e-auram) drugs both in systemic and local forms [3, 7, 18].
5. Munzij Mushil therapy according to the humour involved [19].

Rhazi stated that management of gout can be achieved if these ten procedures are followed: [8, 22].

1. Abstinence from a restricted diet.
2. Compliance with fluid and dietary regimens regarding the emphasis on certain food types and drinks.
3. Administration of laxatives.
4. Stimulation of emesis
5. Bloodletting.
6. Application of water to the feet.
7. Treatment with salves and poultices.
8. Steam baths.
9. Taking preventive measures to avoid recurrence of gouty attacks.
10. Prompt management of incipient gout using counter-acting drugs and analgesics

Preventive measures

Avicenna (Ibn Sina, 980-1037) wrote in his famous book "Canon of Medicine" that gouty patients should avoid eating meat. Rhazes (Al-Rhazi, 860-923), also suggests "avoiding excessive consumption of alcohol, sweetened foods, and meat, and using diuretics continuously to suspend the development of gout [6, 16, 19]. The main risk factors associated with an increased risk of developing gout are:

Risk factors [6, 16, 19].

- Excessive eating (ghaleez ghiza) e.g. meat
- Drinking alcohol
- Lack of exercise
- Passing a high profile-life
- Aaraz-e-nafsani e.g. anxiety, tension
- Low physical activity
- Indigestion,
- Sleeping on empty stomach
- Excessive sexual intercourse, especially on a full stomach
- Excessive sugar intake

Mode of Treatment

In their classical literature, Unani scholars have given certain principles for the treatment of *Niqris* (gout). The treatment is determined by whether the humour is acute or chronic.

Regimenal therapy

Before initiating therapy, we should inquire about things like lack of exercise, an empty stomach, Hammam, age, habit, and temperament of the patient [2, 19]. Venesection is to be done on Warid Basaliq (basilic vein) of the same side. [2, 3, 4, 5, 18]. Ibn Zohr suggested venesection on the Warid Qaifal (cephalic vein) of opposite side. If the gout is acute, a cold sponge is useful; if it is chronic, the feet should be kept in hot and then cold water. [5, 12, 19], Dry baths and hot waterfall water both are beneficial [3, 4].

Pharmacotherapy

First, determine the underlying cause, and then expel the morbid matter from the body using various methods such as purgatives, diuretics, diaphoretics etc [2]. In excess of Safra, physicians should not rush into treatment because the matter can spread to vital organs and cause death [5]. In this condition, emetics should be given first. Sikanjabin, Ab jao (barley water), Ab Muli (raphanus juice) are used for this purpose [12]. Mundij-i-Safra is used first, then after nuzj purgation should be done by Zulal Alubukhara, Zulal Tamarhindi, Sibr, Saqmonia etc. Habb-i-Suranjan should be given [2, 5]. According to Ibn Sina, purgation of phlegm should be given along with black bile, because if it is given alone, then it will give temporary relief and will take Madda back to the organs and pain will recur. Unani scholars have avoided purgation without Nuzj as it may be harmful. Ghaliz Madda may accumulate in joints and the duration of the disease will increase [12].

Anti-inflammatory drugs like Bura Armani along with mako is applied locally. Sirka (vinegar) has been advised locally by many Unani scholars along with Kafoor (camphor) and isabgol (Isubgula mucilage) [3, 5, 12, 21]. Cold and astringent medicines should be avoided because they cause Madda to solidify and accumulate in the joint, which increases the severity of the pain [3, 4]. Mubarid (cold) and mulattif (demulcent) pastes, such as Barg-i-Karnab (Lactuca sativa) with egg yolk and vinegar or rose oil, should be used locally [5]. According to Razi Maal-Asal (honey water) with Tukhm Karafs (Apium graveolens) is the best treatment for gout [21].

Unani pharmacopoeial formulation used in management of *Niqris*(Gout) [16, 19, 23, 24, 25].

1. Majoon-e-suranjan
2. Habb-e-suranjan
3. Safoof-e-suranjan
4. Habb-e-suranjan kabeer Habb
5. Habb-e-*Niqris*
6. Habb-e-sibr
7. Majoon-e-choob chini
8. Roghan-e-kalkalanj
9. Roghan-e-badam shereen
10. Roghan-e-waja-ul-mafasil
11. Roghan-e-afyoon

Conclusion

According to most Unani scholars, the body fluid associated with *Niqris* is primarily mucus (balgam) and may be either raw mucus (balgham kham) or mixed with serous fluid (mirrah). Other body fluids are less likely to cause the disease. Therefore, when the body's propulsive power (Quwwat-e-Dafiyah) attempts to expel this substance, some of it remains in the body, accumulating in various anatomical sites (joints, kidneys, etc.) and presenting with various clinical characteristics. At the same time, the blood and urine level of this substance are also raised.

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