Therapeutic Evaluation of a Topical Unani Formulation, Tila-i Muhāsā in Buthūr Labaniyya (Acne Vulgaris): A Randomized, Controlled Clinical Study

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ABSTRACT
Introduction: Buthūr Labaniyya (Acne vulgaris) is a multifactorial disorder of the pilosebaceous units characterized by non-inflammatory and inflammatory clinical lesions. Several Unani medications have been used for centuries to treat acne.

Objectives: Evaluation of safety and efficacy of Tila-i Muhāsā in patients with acne vulgaris

Materials and Methods: This clinical study was conducted in patients with acne vulgaris. Patients applied Tila-i Muhāsā or 5% Benzoyl Peroxide (BPO) once daily for 6 weeks. Assessment of efficacy was carried out by Global Acne Grading System (GAGS) and Patient Global Assessment (PGA) scores. In addition, overall severity of acne was evaluated on a 5-point Cook’s acne grading scale using photographic standards. Assessment of safety was performed through adverse drug reactions, local dermal tolerability, vital signs, and routine laboratory investigations.

Results: A total of 60 patients (30 in each group) completed 6 weeks of treatment. The mean percentage reduction in GAGS score at 6 weeks from baseline in Unani group (66.97%) and BPO group (59.09%) was statistically significant (P<0.0001). After 6 weeks of therapy, the mean percentage reduction in PGA score compared to baseline in Unani group (57.44%) and BPO group (50.23%) was statistically significant (P<0.0001). No serious adverse events were reported in both groups; however, mild adverse events occurred more frequently in BPO group (30%) compared to Unani group (10%).

Conclusion: Tila-i Muhāsā was found to be effective and safe in the treatment of acne vulgaris. However, further clinical studies with larger sample size and longer duration of therapy need to be conducted.

Keywords Acne vulgaris, Buthūr Labaniyya, Unani, Tila-i Muhāsā, Benzoyl peroxide

INTRODUCTION
Acne vulgaris (acne simplex or common acne) is a multifactorial disorder of the pilosebaceous units characterized by non-inflammatory and inflammatory clinical lesions. The non-inflammatory lesions are comedones, which may be either closed (whiteheads) or open (blackheads). The inflammatory lesions include papules, pustules, and nodules (Papadakis et al., 2019; Griffiths et al., 2018). These are sites of maximum density of sebaceous follicles (Patterson and Hosler, 2016). The primary site of acne is the face (99%) and to a lesser degree the upper back (60%), and chest (15%) (Griffiths et al., 2016). Post-inflammatory hyperpigmentation and scarring are common complications of acne, which may contribute to significant physical and psychosocial impact. Acne scarring can be minimized by early effective treatment (Griffiths et al., 2016; Patterson and Hosler, 2016; Goodman, 2001). Acne affects approximately 633 million people globally, making it the 10th most prevalent disease worldwide as per the Global Burden of Disease 2015 (Vos et al., 2016). It is most common between the ages of 12 and 20 years, and affects over 90% of adolescents. It often begins around 10-13 years of age, lasts 5-10 years and usually resolves by age 20-25 (Ralston et al., 2018). The relationship between diet and acne remains a subject of controversy. However, various studies have shown that some dietary factors, including high glycaemic index (GI) foods, skimmed milk, nuts, chocolates, oily foods, whey protein supplements for body building, vitamin B12 supplementation, etc. may potentially trigger the development of acne (Bologna et al., 2018; Griffiths et al., 2016).

Acne begins with the overproduction of sebum, often secondary to an increase in androgen levels (Zeind and Carvalho, 2018). The pathogenesis of acne is multifactorial, but four principal pathogenetic events identified are: (1) hyperkeratinization with occlusion of pilosebaceous duct due to retention of keratinous material in the follicle, (2) increased sebum production by sebaceous glands, (3) hypercolonization of pilosebaceous ducts by the gram-positive anaerobic diphtheroid Propionibacterium acnes (P. acnes), and (4) inflammation & release of inflammatory mediators to the skin (Papadakis et al., 2019; Ralston et al., 2018; Patterson and Hosler, 2016; Griffiths et al., 2016; Goldsmith et al., 2012; Williams et al., 2012). These various processes are interrelated and under hormonal and immune influence (Patterson and Hosler, 2016; Goldsmith et al., 2012).

Androgens stimulate sebaceous glands to produce more...
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sebum. The infundibulum of the sebaceous follicle is plugged due to hyperkeratinisation (retention hyperkeratosis), and this follicular plugging prevents drainage of sebum, leading to accumulation of keratin, sebum, and bacteria (acne bacillus) in the follicle. These impacted follicles are termed ‘microcomedones’. Components of sebum, triglycerides and lipoperoxides may play a role in acne pathogenesis. There is overgrowth of *P. acnes*, normal flora of the pilosebaceous unit, which produce lipase, and this bacterial lipase converts triglycerides to free fatty acids and produce proinflammatory mediators (IL-1, TNF-α) that lead to an inflammatory response. These free fatty acids promote further bacterial clumping and colonization of *P. acnes*, incite inflammation, and may be comedogenic. Lipoperoxides also produce proinflammatory cytokines. *P. acnes* stimulate the release of hydrolases from neutrophils, which may damage the follicular wall. In addition, continued production of sebum and keratin, leads to rupture of the follicular wall, releasing the contents of the follicle (fatty acids, sebum, keratin, bacteria) into the dermis and initiating an inflammatory response. There is irritation by accumulated fatty acids, and foreign-body reaction to extra-follicular sebum. This inflammation in the dermis is responsible for the papules, pustules, and nodules. Intense inflammation leads to scars (Papadakis et al, 2019; Ralston et al, 2018; Griffiths et al, 2016; Patterson and Hosler, 2016; Wolff et al, 2013; Goldsmith et al, 2012; Sehgal, 2011).

Acne vulgaris is associated with significant psychological disability such as reduced self-esteem, anxiety, depression, and suicidal ideation (Barnes et al, 2012; Goodman, 2006). It is estimated that 30-50% of adolescents experience psychiatric disturbances due to acne (Goldsmith et al, 2012). The consequences can be devastating, leading to embarrassment, school avoidance, and life-long effects on ability to form friendships, attract partners, and acquire and keep employment. Even, mild acne can adversely affect the patients’ quality of life (Ralston et al, 2018).

Acne treatment can reduce its severity and minimize scarring, but there is no known cure for acne. Therefore, the safe and most effective treatment for acne is needed. The goals of the treatment are to relieve discomfort, improve skin appearance, prevent scarring, and restore emotional well-being and self-esteem (Ralston et al, 2018; Zeind and Carvalho, 2018).

In Unani system of medicine *Buthūr Labaniyya* (acne vulgaris) is defined as an appearance of white papules on the face and nose accompanied by discharge of viscous fluids from them. These are mostly due to the inflammation of sweat glands in young people (Anonymous, 2012). According to Ibn Sīnā, acne lesions are small white eruptions on the nose and cheeks, which resemble a drop of condensed milk. Hence, in Unani system of medicine, acne vulgaris is termed as *Buthūr Labaniyya*, meaning eruptions of milk (Sinā, 2010).

Renowned Unani physicians Zakariyya Rāzī, Ibn Sīnā, Ibn Hubal Baghdādī, Dā’ūd Antākī and Ḥakīm Akbar Arzānī have mentioned in their books, *Buthūr Labaniyya* (acne vulgaris) is a dermatological disorder of adolescents that present as whitish eruptions over the face caused by *Mādda Sadādiyya* (purulent matter) or preponderance of *Ghulāz Mādda Balghamiyya* (thick phlegmatic matter), which enters the skin pores and is not resolved in the skin due to its viscosity (Rāzī, 1994; Sinā, 2010; Baghdādī, YNM; Anjākī, 2010; Arzānī, 2001).

In Unani System of Medicine, several polyherbal medications with *Jālī* (Detergent), *Muhalīl* (Resolvent) and *Mujaffīf* (Desiccative) properties have been used for centuries to treat *Buthūr Labaniyya* (Acne vulgaris). *Ṭila-i Muhāsā*, a topical polyherbal Unani formulation containing *Beikh-i Sosan* (*Iris ensata*), *Post-i Siras* (*Albizia lebbeck*), and *Barg-i Neem* (*Azadirachta indica*) is used in acne vulgaris, but there is no documentary clinical evidence on its efficacy and safety (Sinā, 2010; Arzānī, YNM; Kabīrūddin, 1977). Therefore, a randomized controlled clinical study was conducted to evaluate the efficacy and safety of *Ṭila-i Muhāsā* versus 5% Benzoyl Peroxide (BPO) in patients with acne vulgaris on modern scientific parameters.

### METHODS AND MATERIALS

This prospective, single-blind (assessor blinded), randomized, active-controlled, parallel-group clinical study was conducted in patients with acne vulgaris at Central Research Institute of Unani Medicine (CRIUM), Hyderabad (now upgraded to NRIUMSD). *Ṭila-i Muhāsā* was selected for the study from *Al-Qaraḥāda* (a Pharmacopoeia of Unani Medicine). It is a topical polyherbal Unani formulation, containing three herbs, *Iris ensata*, *Albizia lebbeck*, and *Azadirachta indica* (Table 1). All the ingredients in equal weight were powdered in a pulveriser and passed through a sieve of mesh number 80 to prepare a fine powder. Thus, the test drug *Ṭila-i Muhāsā* in powder form was prepared and supplied in air tight containers by the Institute’s GMP-certified Pharmacy. The study protocol was approved by the Institutional Ethics Committee (38-18/2015-16/CRIUM/Hyd/IEC/03/M) and registered in Clinical Trial Registry of India (CTRI/2017/12/010974). Written informed consent was obtained from all the participants before participating in the study. Patients younger than 18 years signed the assent for the study and their parents or legal guardians signed the informed consent form. Patients reached the age of consent during the study were re-consented at the next study visit.

**Table 1. Composition of Ṭila-i Muhāsā**

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Plant Drug</th>
<th>Botanical Name</th>
<th>Part Used</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Beikh-i Sosan</td>
<td><em>Iris ensata</em> Thumb.</td>
<td>Root</td>
<td>100 g</td>
</tr>
<tr>
<td>2.</td>
<td>Post-i Siras</td>
<td><em>Albizia lebbeck</em> Linn. Wild.</td>
<td>Stem Bark</td>
<td>100 g</td>
</tr>
<tr>
<td>3.</td>
<td>Barg-i Neem</td>
<td><em>Azadirachta indica</em> A. Juss.</td>
<td>Leaves</td>
<td>100 g</td>
</tr>
</tbody>
</table>

Patients clinically diagnosed as acne vulgaris attending the outpatient department (OPD) of CRIUM, Hyderabad, between August, 2018 and April, 2019 were screened for the study. Of the 113 patients screened during this period, 73 acne patients aged between 14 and 40 years were enrolled into this study. Patients below 12 and above 40 years of age, patients with other variants of acne (acne rosacea/ acne fulminans/ acne necrotica), pregnant and lactating women, mentally retarded persons, patients on corticosteroid or anticonvulsant therapy or taking oral contraceptives, patients with renal, hepatic, or severe cardiac comorbidities and patients unable to attend treatment schedule regularly were excluded from the study. Patients who had used any topical and systemic treatments in previous 4 weeks were also excluded.

Each acne patient was subjected to a detailed medical history taking and a complete dermatological examination. The patients who met inclusion criteria were randomly allocated to test group (n=37) and control group (n=36) through block randomization method with block size of 4, using sequentially numbered, sealed, opaque envelopes containing computer-generated block
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randomization codes supplied by the Institute’s Statistics Unit. Of the 73 patients randomized, 30 patients in each group completed 6 weeks of treatment. Seven patients in test group and six patients in control group were lost to follow-up.

**Unani treatment group (test group):** Patients were given a topical Unani formulation, Ṭila-i Muhāsā in fine powder form and advised to make its homogenous paste with lukewarm water, and apply on the acne-affected skin of the prewashed & dried face at night and then wash the face with lukewarm water in the morning.

**Benzoyl peroxide group (active control group):** Patients were given a conventional allopathic drug, 5% Benzoyl Peroxide (BPO) cream and advised to use the medication in the same manner as paste in test group.

The duration of treatment was 6 weeks and patients were followed up at 2, 4, and 6 weeks of treatment. Treatment compliance was evaluated by examining the quantity of drug left at each follow-up visit, and <75% treatment compliance was considered for withdrawal of patients from the study. Concomitant use of any topical or systemic anti-acne medications was not allowed during the study.

![CONSORT Flow Diagram of Study](image)

**Fig. 1.** CONSORT Flow Diagram of Study
Global Acne Grading System (GAGS) (Doshi et al, 1997; Adityan et al, 2009) and Patient Global Assessment (PGA) scores were used to assess clinical severity of acne and efficacy of treatment. PGA of acne severity was scored using 0-100mm horizontal Visual Analogue Scale (PGA-VAS), and patients were asked to place a vertical mark on the scale corresponding to their disease severity level at each clinical visit, and the distance in millimetres from zero to the patient's mark was measured and recorded. In addition, overall severity of acne was evaluated on a 5-point (0-8 grades) Cook's acne grading scale using photographic standards (Cook et al, 1979). Facial photographs of patients were taken by using digital zoom camera (Sony IMX398 Exmor RS Sensor, 16 MP f/1.7) with fixed distance and the same place at baseline and after 6 weeks of treatment. Assessment of safety was performed through adverse drug reactions, local dermal tolerability, vital signs at each follow-up visit, and routine laboratory investigations, including haemogram (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. Any local or systemic adverse effects were recorded at each clinical follow-up visit for both groups.

Statistical Analysis
Statistical analysis of data was performed on per-protocol (PP) basis, using the statistical software IBM SPSS Statistics 23.0 (Mac OS). Categorical variables were expressed as number (%), whereas continuous data were presented as mean ± standard deviation (SD). Chi-Square test was used to compare the categorical variables between the test and control groups. Continuous data were compared between the groups using independent samples t test. Paired t test was used to compare continuous data before and after treatment in each group, and P-value <0.05 was considered statistically significant. The primary outcome was a reduction in GAGS score from baseline to 6 week.

RESULTS
A total of 113 patients were screened, of them, 73 patients who met the eligibility criteria were enrolled in the study, and they were randomized with 37 patients receiving Unani treatment and 36 patients receiving 5% Benzoyl Peroxide (BPO). Of 73 patients randomized, 60 patients (30 in each group) completed 6 weeks of treatment; seven patients from Unani group and six patients from BPO group were dropped out of the study due to loss to follow-up. Data were analysed by per-protocol (PP) analysis, and 13 non-completers were excluded from the analysis (Fig. 1).

Clinico-demographic Profile
The mean age ± SD of patients in Unani treatment group was 22.47±6.08 years, 10 were male and 20 were female with male to female ratio 1:2. The mean age ± SD of patients in BPO Group was 21.13±5.12 years, 11 were male and 19 were female with male to female ratio 1:1.7. The mean disease chronicity ± SD in Unani treatment group was 3.0±0.7 months, and the mean disease chronicity ± SD in BPO Group was 2.97±2.66 months. There were no significant differences (P > 0.05) in the baseline demographic and clinical characteristics of acne patients between Unani treatment group and BPO group (Table 2).

### Table 2. Clinico-demographic Profile of Acne Patients in Unani and BPO Groups (PP Population)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Unani Group (n=30)</th>
<th>BPO Group (n=30)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, Years (Mean±SD)</td>
<td>22.47±6.08</td>
<td>21.13±5.12</td>
<td>0.458</td>
</tr>
<tr>
<td>Age Distribution, years, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14-20</td>
<td>19 (63.3)</td>
<td>14 (46.7)</td>
<td></td>
</tr>
<tr>
<td>20-30</td>
<td>10 (33.3)</td>
<td>14 (46.7)</td>
<td>0.458</td>
</tr>
<tr>
<td>30-40</td>
<td>1 (3.4)</td>
<td>2 (6.6)</td>
<td></td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>10 (33.3)</td>
<td>11 (36.7)</td>
<td>0.500</td>
</tr>
<tr>
<td>Female</td>
<td>20 (66.7)</td>
<td>19 (63.3)</td>
<td></td>
</tr>
<tr>
<td>Age of Onset, Years (Mean±SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14-20</td>
<td>17.47±3.53</td>
<td>17.13±3.25</td>
<td>0.494</td>
</tr>
<tr>
<td>Disease Chronicity, months (Mean±SD)</td>
<td>5.4±4.2</td>
<td>5.37±4.66</td>
<td>0.739</td>
</tr>
</tbody>
</table>

PP = Per Protocol; SD = Standard Deviation

GAGS (Global Acne Grading System) Score
In Unani treatment group, the mean GAGS score was significantly reduced from 28.97±8.24 at baseline to 9.57±5.39 after 6 weeks of treatment (P<0.0001). In BPO group, the mean GAGS score was significantly reduced from 31.70±10.47 at baseline to 12.97±5.13 after 6 weeks of treatment (P<0.0001) (Table 3).

### Table 3. GAGS Score in Unani Treatment Group vs BPO Group

<table>
<thead>
<tr>
<th>Visit</th>
<th>Mean±SD</th>
<th>P-Value</th>
<th>Mean±SD</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>28.97±8.24</td>
<td></td>
<td>31.70±10.47</td>
<td></td>
</tr>
<tr>
<td>After 2 weeks</td>
<td>23.50±7.03</td>
<td>0.0076</td>
<td>25.93±9.65</td>
<td>0.0304</td>
</tr>
<tr>
<td>After 4 weeks</td>
<td>16.06±5.18</td>
<td>&lt;0.0001</td>
<td>18.67±6.14</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>After 6 weeks</td>
<td>9.57±5.39</td>
<td>&lt;0.0001</td>
<td>12.97±5.13</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

SD = Standard Deviation; *P = p-value of comparison from baseline visit (Paired t test)

Percentage Reduction in GAGS Score
The percentage reduction in the mean GAGS score after 6 weeks of treatment from baseline in the Unani treatment group was 66.97%, and in BPO group was 59.09% (Table 4).

### Table 4. Percentage Reduction in Mean GAGS Score in Unani Group vs BPO Group

<table>
<thead>
<tr>
<th>Visit</th>
<th>Percentage Reduction in GAGS Score (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>66.97</td>
</tr>
<tr>
<td>After 2 weeks</td>
<td>18.88</td>
</tr>
<tr>
<td>After 4 weeks</td>
<td>44.56</td>
</tr>
<tr>
<td>After 6 weeks</td>
<td>69.09</td>
</tr>
</tbody>
</table>
In Unani treatment group, the mean PGA score was significantly reduced from 72.83±9.79 at baseline to 31.0±13.48 after 6 weeks of treatment (P <0.0001). In BPO group, the mean PGA score was significantly reduced from 74.0±11.02 at baseline to 36.83±10.87 after 6 weeks of treatment (P <0.0001) (Table 5).

Table 5. PGA Score in Unani Treatment Group vs BPO Group

<table>
<thead>
<tr>
<th>Visit</th>
<th>PGA Score Mean±SD</th>
<th>P-value</th>
<th>PGA Score Mean±SD</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>72.83±9.79</td>
<td></td>
<td>74.0±11.02</td>
<td></td>
</tr>
<tr>
<td>After 2 weeks</td>
<td>61.5±9.21</td>
<td>0.0001</td>
<td>64.0±10.7</td>
<td>0.0007</td>
</tr>
<tr>
<td>After 4 weeks</td>
<td>44.83±8.79</td>
<td>&lt;0.0001</td>
<td>50.67±11.12</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>After 6 weeks</td>
<td>31.0±13.48</td>
<td>&lt;0.0001</td>
<td>36.83±10.87</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

The percentage reduction in the mean PGA score after 6 weeks of treatment from baseline in the Unani treatment group was 57.44%, and in BPO group was 50.23% (Table 6).

Table 6. Percentage Reduction in Mean PGA Score in Unani Group vs BPO Group

<table>
<thead>
<tr>
<th>Visit</th>
<th>Percentage Reduction in Mean PGA Score(%)</th>
<th>Unani Group (n=30)</th>
<th>BPO Group (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0.00</td>
<td>74.0</td>
<td></td>
</tr>
<tr>
<td>After 2 weeks</td>
<td>15.56</td>
<td>13.51</td>
<td></td>
</tr>
<tr>
<td>After 4 weeks</td>
<td>38.45</td>
<td>31.53</td>
<td></td>
</tr>
<tr>
<td>After 6 weeks</td>
<td>57.44</td>
<td>50.23</td>
<td></td>
</tr>
</tbody>
</table>

The overall severity of acne measured by Cook’s acne grading scale was significantly reduced after treatment in both groups. In Unani treatment group, acne severity grades on Cook’s scale at baseline were 2, 4, 6 and in 1 (3.3%), 4 (13.3%), and 25 (83.4%) patients respectively, and after treatment, Cook’s severity grades were 0, 2, and 4 in 8 (26.7%), 18 (60%) and 4 (13.3%) patients respectively. In BPO group, acne severity grades on Cook’s scale at baseline were 2, 4, 6 and in 1 (3.3%), 4 (13.4%), 24 (80%), and 1 (3.3%) patients respectively, and after treatment, Cook’s severity grades were 0, 2, and 4 in 13.3%, 24 (80%) and 2 (6.7%) patients respectively (Table 7).

Table 7. Cook’s Acne Severity Score

<table>
<thead>
<tr>
<th>Grade</th>
<th>Unani Group (n=30), n (%)</th>
<th>BPO Group (n=30), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>After treatment</td>
</tr>
<tr>
<td>0</td>
<td>---</td>
<td>8 (26.7)</td>
</tr>
<tr>
<td>2</td>
<td>1 (3.3)</td>
<td>18 (60.0)</td>
</tr>
<tr>
<td>4</td>
<td>4 (13.3)</td>
<td>4 (13.3)</td>
</tr>
<tr>
<td>6</td>
<td>25 (83.4)</td>
<td>---</td>
</tr>
<tr>
<td>8</td>
<td>---</td>
<td>1 (3.3)</td>
</tr>
</tbody>
</table>

Safety Evaluation

Clinical adverse effects, including dry skin, itching and burning at the site of application were reported in 3 (10%) patients in Unani treatment group and 9 (30%) patients in BPO group. Hyperpigmentation was observed in some patients, but it was considered to be post-inflammatory and was not associated with treatment. These adverse effects were minimal and self-limited, and no serious adverse events (SAEs) were reported in both treatment groups. Moreover, values of all haematological and biochemical safety parameters measured at baseline and after 6 weeks of treatment were within the normal range.

DISCUSSION

Acne vulgaris is a multifactorial disorder, in which the pilosebaceous units of the skin become plugged and distended, presenting as comedones, papules, pustules, or nodules (Zeind and Carvalho, 2018). Despite various scientific studies, complete pathogenesis of acne remains unclear, and a single, primary cause has not been identified. The development of acne involves the combination of four factors, including hyperkeratinization, excess sebum production, overgrowth of Propionibacterium acnes, and inflammation (Bolognia et al, 2018; Williams et al, 2012). Propionibacterium acnes (now renamed Cutibacterium acnes), a gram-positive anaerobic bacterium is a member of the normal human skin microbiota essential for the maintenance of a healthy skin. It is predominant in pilosebaceous follicles, and it plays a critical role in the development of inflammatory lesions in acne (Ingham, 1999).

Anti-acne therapies exhibit one or more of the four mechanisms: normalizing follicular keratinization, decreasing sebum production, suppressing P. acnes, and reducing inflammation (Zeind and Carvalho, 2018). Oxidative stress-initiated inflammation and its maintenance within the pilosebaceous unit are important initial steps for the subsequent pathogenic processes of acne development. The favourable environment created by the oxidation of sebum for P. acnes to grow is also an important contributing factor for these steps. This mechanism suggests the oxidative stress as a therapeutic target in the treatment of acne vulgaris (Grange et al, 2009).

Long-term use of oral antibiotics is associated with the development of bacterial resistance and disruption of the gut microbiota. So, the use of antibiotics for acne is discouraged in clinical practice. Topical therapies are the most appropriate first-line treatment for comedonal acne. Benzoyl peroxide is an effective topical agent for the treatment of acne, which works through three mechanisms: antimicrobial, anti-inflammatory, and keratolytic effects (Zeind and Carvalho, 2018).

Ṭila-i Muhāsā, a topical polyherbal Unani formulation containing Beikhi-i Sosan (Iris ensata), Post-i Siras (Albizia lebbeck), and Barg-i Neem (Azadirachta indica) has been used as an effective topical treatment for acne vulgaris. This clinical study was conducted to evaluate the efficacy and safety of Ṭila-i Muhāsā in the treatment of acne vulgaris. In this study, Ṭila-i Muhāsā was compared with 5% Benzoyl Peroxide (BPO) in patients with acne vulgaris. Ṭila-i Muhāsā was effective in acne vulgaris, as it showed a statistically significant reduction in GAGS and PGA scores from baseline to 6 weeks of treatment (P<0.0001).

The GAGS score was significantly reduced after 6 weeks of treatment in BPO group also (P<0.0001), and no statistically significant difference was found between the efficacy of test and control drugs. Thus, both drugs were found to be equally effective in reducing acne severity.
effective in the treatment of acne vulgaris. However, *Tila-i Muhāsā* showed rapid onset of efficacy, as a significant reduction in GAGS score was evident as early as week 2 and GAGS score was continued to reduce till the end of treatment. Moreover, topical application of *Tila-i Muhāsā* once daily for 6 weeks showed significant improvement in the overall severity of acne assessed by the Cook’s acne severity grading scale.

In present study, none of the patients reported any serious adverse events (SAE) in both treatment groups. However, clinical adverse effects, including dry skin, itching and burning at the site of application were observed in both groups, but frequency of these adverse effects was higher (30%) in BPO group than in Unani treatment group (10%), and this difference was statistically significant. These adverse effects were minimal and self-limited. Hyperpigmentation was observed in some patients, but it was considered to be post-inflammatory and was not associated with treatment. Moreover, pathological and biochemical safety parameters were remained within normal limits after treatment. Thus, once-daily topical application of *Tila-i Muhāsā* for up to 6 weeks did not exhibit significant adverse effects, and it was found to be safe and well tolerated during study.

The exact mechanism of action in the treatment of acne is not yet known. The antimicrobial, anti-keratinization, and anti-inflammatory and antioxidant effects have been implicated. In the present study, the analyzed results showing the efficacy of *Tila-i Muhāsā* in acne vulgaris may theoretically be attributed to Muhālī-i-Waram (anti-inflammatory), Dāfī-i-‘Ufīnat (antiseptic), Musaṣṣīf-i-Dam (blood purifier), Muḥāmmīr (Rubefacient), Jāfī (detergent), and Mujāṣṣif (desiccative) properties of its ingredients as described in the classical texts of Unani Medicine. Its Mujāṣṣif (Desiccative) property may help in reducing sebum production, and it may improve the post-inflammatory hyperpigmentation due to its Jāfī (Detergent) property (Ali, 2010; Ibn Sinā, 2010; Ghani, 2010; Anonymous, 2007; Hakīm, 2002; Anonymous, 1987).

Recent studies have indicated that inflammation and oxidative stress may play an early role in initiating the pathogenesis of acne. The activities of antioxidant defense enzymes, including superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) in leukocytes are decreased in acne patients. Thus, the drugs with antioxidant effects may be valuable in acne treatment (Basak et al., 2001). In patients with acne, the cutaneous and systemic oxidative stress is increased as indicated by observation of oxidative stress biomarkers. Administration of local and systemic antioxidants appears to be effective against acne (Bowe et al., 2012).

It has been reported that *Iris ensata* (roots) possesses a broad spectrum antibacterial activity (Ganaie et al., 2018; Wągaj and Jain, 2018) and a significant free radical scavenging activity. Its antioxidant activity may contribute the anti-inflammatory effects (Ganaie et al., 2018). The root extract of *Iris ensata* is used in cosmetic preparations for the prevention of skin roughness and ageing (Khare, 2007).

*Albizia lebbeck* (stem bark) has been reported to possess remarkable anti-inflammatory (Babu et al., 2009; Saha and Ahmed, 2009; Pramanik et al., 2005; Das et al., 2003), broad spectrum antibacterial (Ali et al., 2018; Abriham and Paulos, 2015; Tasnim et al., 2014; Salem et al., 2013; Chulet et al., 2010; Khare, 2007; Rashid et al., 2003; Ganguli and Bhatt, 1993), antioxidant & free radical scavenging (Ali et al., 2018; Abriham and Paulos, 2015; Tasnim et al., 2014; Zia-Ul-Haq et al., 2013; Suruse et al., 2013), immunomodulatory (Chaudhary et al., 2012), antiseptic, and anti-allergic activities (Khare, 2007).

*Azadirachta indica* (leaves) has been reported to possess antibacterial (Benisheikh et al., 2019; Ghonmode et al., 2013; Maragathavalli et al., 2012; Yerima et al., 2012; Aditi et al., 2011; Sarmiento et al., 2011; Mahfuzul Hoque et al., 2007; Khare, 2007), anti-inflammatory (Dinda et al., 2011; Schumacher et al., 2011; Mosaddek et al., 2008; Khare, 2007; Kaur et al., 2004; Jain and Basal, 2003; Chattopadhyay, 1998; Chattopadhyay et al., 1993), antioxidant (Patel et al., 2011; Ghimray et al., 2009; Sithisarn et al., 2005), immunomodulatory (Durrani et al., 2008; Renu et al., 2003; Sadekar et al., 1998; Ray et al., 1996; Upadhyay et al., 1992; van der Nat et al., 1987), wound healing activities (Osuwoke et al., 2013; Barua et al., 2010), and skin renewal (epidermal turnover) effect (Wadher et al., 2009; Kamlesh et al., 2009). *Propionibacterium acnes*, an anaerobic pathogen, plays an important role in the pathogenesis of acne by inducing certain inflammatory mediators. *Azadirachta indica* possesses anti-inflammatory activity and it significantly suppresses the capacity of *P. acnes*-induced ROS and pro-inflammatory cytokines (IL-8 and TNF-α), the two important inflammatory mediators in acne pathogenesis (Jain and Basal, 2003). *Azadirachta indica* leaf extract is profoundly anti-microbial and capable of inhibiting the growth of *Propionibacterium acnes* (Abya et al., 2018; Balakrishnan et al., 2011).

Thus, anti-acne effect of this combination of three ingredients in the form of *Tila-i Muhāsā* shows that it may act by targeting the different steps in the pathogenesis of acne vulgaris, including inhibition of hyperkeratinization, reduction in sebum secretion, suppression of *P. acnes*, and reduction in inflammation by inhibiting the production of reactive oxygen species (ROS) and pro-inflammatory cytokines.

In summary, findings from the present study suggest that *Tila-i Muhāsā* containing *Iris ensata, Albizia lebbeck* and *Azadirachta indica* may provide the safe and effective alternative treatment for acne vulgaris.

**CONCLUSION**

In this randomized controlled clinical trial, *Tila-i Muhāsā* was successfully evaluated for its antiacne activity. There was no statistically significant difference in the efficacy of *Tila-i Muhāsā* compared to 5% Benzoyl Peroxide (BPO) in the management of acne vulgaris; however *Tila-i Muhāsā* reported less adverse effects than BPO. In conclusion, the results of the present study suggest that *Tila-i Muhāsā*, a topical polyherbal Unani formulation containing *Beikk-i-Soxan* (*Iris ensata*), *Post-i-Siras* (*Albizia lebbeck*), and *Barg-i Neem* (*Azadirachta indica*) may be an effective, safe and well-tolerated topical medication in the treatment of acne vulgaris. These therapeutic results may probably be attributed to antioxidant, anti-inflammatory, immunomodulatory, and antimicrobial activities of the ingredients of *Tila-i Muhāsā*. However, the limitation of this study was small sample size and short duration of therapy; to overcome these limitations, additional clinical studies with larger sample size and longer duration of therapy need to be conducted in the future, which could further reinforce the scientific evidence.

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CONFLICT OF INTEREST
The authors have no conflicting financial interests.

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