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# EVALUATING THE THERAPEUTIC POTENTIAL OF *Cuscuta reflexa* AND *Saussurea lappa* IN THE MANAGEMENT OF MELASMA: A SINGLE BLIND RANDOMIZED CLINICAL TRIAL

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## ABSTRACT

**To scientifically validate the drugs traditionally used by Arab and Greek physicians, a single blind, randomized, standard-controlled clinical trial was conducted on 36 melasma patients aged 15-50 years, with treatment duration of 60 days. The study aimed to evaluate the efficacy of a test drug formulation comprising of a decoction of *Cuscuta reflexa* and a paste of *Sausserea lappa* (mixed with honey), compared to the recommended allopathic treatment (standard control). The test group received a decoction of *C. reflexa* (5 g orally, once a day) along with topical application of *S. lappa* paste on the affected area for 15 min once a day. The control group was orally administered with tranxemic acid tablets (250 mg, twice daily) and topical azelaic acid (10%) on the affected area. The test group exhibited significant improvement in subjective parameters with significant decrease in the severity of hyper-pigmentation. Both the groups showed significant improvement in objective parameters including melasma area and severity index (MASI) scores, by the $60^{th}$ day of treatment ($p \leq 0.001$). The test drugs demonstrated noticeable therapeutic effects on both subjective and objective parameters, without any adverse effect. No significant difference was observed between test and standard control treatment.**

**Keywords:** *Cuscuta reflexa*, decoction, hyperpigmentation, melasma, *Saussurea lappa*

## NTRODUCTION

Melasma is a significant dermatological concern with considerable cosmetic and psychological impact (Ogbechie-Godec and Elbuluk, 2017; Jo *et al.*, 2024). Although widely recognized as a common condition with no major physical consequences, it can profoundly affect an individual's quality of life and is often associated with social stigma (Shah and Narang, 2023). Clinically, melasma is characterized by brown spots or macules on exposed areas of the body, most commonly the face (Doolan and Gupta, 2021). Histological studies have shown that melasma lesions contain an increased number of mast cells and vascular endothelial growth factors (Phansuk *et al.*, 2022). Descriptions of this disease are found in various Unani classical texts, where it is referred to as *Kalaf*, a humoral disease disorder caused by disturbances in the quality and quantity of black bile, which is related to melanin (Kalam *et al.*, 2019). According to Avicenna in his renowned book '*The Cannon of Medicine* (*Al-Qanun fil Tibb*)', the disorder results from the accumulation of dead blood cells under the skin due to the trauma to local blood vessels (Al-Rais *et al.*, 2010). Other contributing factors mentioned include morbid matters, impurities, cold melancholic blood, and excess melanin (Baghdadi, 2005).

The prevalence figures about melasma in India and other South Asian countries remain inconsistent due to regional variations and differences in study methodologies (Varghese, 2019). The reported prevalence of melasma ranges from 1.5 to 33.3%, with a higher prevalence of 50-70% during pregnancy (Manasa, 2018). Melasma is more common in the individuals with darker skin tones (Fitzpatrick's skin type IV-V), particularly Asians and Hispanics. Females are frequently affected than males, and the most commonly affected age group is 30-55 years, although cases may rarely occur before puberty and after menopause (Abdalla, 2021).

Melasma is an acquired pigmentation disease of skin and its etiopathogenesis is complex, multifaceted and involves both environmental and genetic factors (Sonthalia and Sarkar, 2015; Espósito *et al*., 2022). Among the many genes involved in melanogenesis, MC1R (melanocortin 1 receptor) is considered the main gene, which is located on melanocytes (Liu *et al*., 2023). Melanocytes are epidermal cells that store and produce melanin, a dark coloured pigment which darkens skin. The exact molecular pathogenesis of melasma is yet unclear or less elucidated. Sun exposure/radiation (ultra-violet, visible and infrared light), hormonal changes during pregnancy and prolonged use of oral contraceptive pills (OCP) are well recognised triggers of melasma (Ogbechie-Godec and Elbuluk, 2017; Liu *et al*., 2023). Luteinizing hormone (LH), produced by anterior pituitary gland, stimulates ovulation and progesterone production in females and drives testosterone production in males. Elevated LH levels and reduced serum estradiol (a form of estrogen) also plays a role in pathogenesis (Gopichandani *et al*., 2015). Other factors like certain medications, skin irritation or inflammation due to harsh products or heat, health issues like hypothyroidism (underactive thyroid disease), etc., besides genetic inheritance reportedly influence the pigment cells and disease (Liu *et al*., 2023; Chen *et al*., 2024). Less common causes include nutritional deficiencies, and rarely, HIV infection (Sidharth, 2015).

The preventive measures involving consistent and strict sun protection and controlling avoidable triggering factors govern the success of any treatment strategy. Modern treatment options include topical therapies (hydroquinone, azelaic acid, kojic acid, corticosteroids, niacinamide, etc.), procedural therapies (micro-needling, laser, chemical peels, derma abrasion) and oral drugs (tranexamic acid, glutathione, etc.) (Ogbechie-Godec and Elbuluk, 2017; Bala *et al*., 2018). While effective, these treatments are often associated with high relapse rates and adverse effects. Unani physicians believe that melasma can be treated by evacuating black bile through systemic drugs, combined with topical therapies like detergents, astringents, rubefacient, and anti-inflammatory agents (Al Rais *et al*., 2010). Although several herbal formulations are used, many lack scientific validation or clinical evidence. Botanicals as alternative treatment for melasma are being explored in terms of safety and efficacy (Kalam *et al*., 2019; Popaniya *et al*., 2024). Examples include amongst nine sesquiterpene lactones from *Saussurea lappa* root extracts, only *α*-cyclocostunolide, showed notable inhibition of the melanin production, particularly the extracellular melanin content, suggesting its possible usefulness in the therapy of skin disorders (Choodej *et al*., 2019). In view of this, the present study was designed to evaluate the safety and therapeutic potential of *Cuscuta reflexa* and *Sausserea lappa* in the management of melasma.

## MATERIALS AND METHODS

### *Trial design*

The present randomized, single-blind, standard-controlled clinical trial was conducted at the Regional Research Institute of Unani Medicine (RRIUM), Srinagar, J&K (India) in compliance with the guidelines of the Declaration of Helsinki, World Medical Association (2013). Forty-two (42) patients with *Kalaf* (melasma) were primarily screened for the study, amongst which two patients did not meet the set inclusion criteria so were excluded. The participating subjects were informed of the study objectives and methods, the confidentiality of their information, potential side-effects of

research, and their rights to withdraw from the study at any time. The trial protocol was approved by the Institutional Ethics Committee, RRIUM, Srinagar vide No. RRIUM/KU/2020-21/Tech./PB-378. The trial was registered in the Clinical Trials Registry of India (CTRI) vide No. CTRI/2021/03/032083 dated 17 March, 2021. The recruitment of patients was done from the OPD/IPD of RRIUM Hospital during the study duration of 12 months starting in March 2021.

***Inclusion-exclusion criteria and experimental details***

Clinically diagnosed melasma patients of 15 to 50 years age of both sex were included in the study. Patients with a history of cardiovascular, endocrine, renal, liver disorder, skin sensitivity, pregnancy, lactation and those on oral contraceptives and anti-coagulants were excluded.

The selected patients were provided verbal and written information about the nature of study, the drugs to be administered, the protocol and duration. After their satisfaction, written informed consent was obtained from each participant before including them in the study (Nijhawan *et al.*, 2013). During selection procedure a detailed history and full body examination details were recorded in the case report form (CRF). The patients were evaluated for safety parameters (liver function tests, kidney function tests, erythrocyte sedimentation rate, blood sugar fasting, prothrombin time, and complete blood count), before starting the treatment and all biochemical tests were repeated after $60^{th}$ day i.e. at the end of trial. The selected patients were divided into control and test groups using an online randomization chart (Singh, 2014). Since the duration of study should be sufficient enough to allow accurate assessment of efficacy, and it generally varies from 8 to 16 weeks (Pandya *et al*., 2007), so for this study 60 day's treatment protocol was adopted. Follow-up visits were scheduled at $15^{th}$, $30^{th}$, $45^{th}$, and $60^{th}$ days. On every visit, the patients were inquired about the improvement or worsening of their symptoms and were subjected to clinical examination. No concomitant treatment was allowed during the protocol period. The patients taking any other medicine for melasma treatment were advised to stop the same one week before the commencement of the trial process.

Using G*POWER software (version 3.0.10), the least number of patients required in each group with 80% power, 85% effect size and 5% level of significance was worked out to be 18 per group. In present study, primarily the patients were randomly distributed into two equal groups but later two patients from each group discontinued the treatment so were dropped out from the study. Thus ultimate number of patients in each group was eighteen (18) who completed the trial.

***Drug selection, preparation and prescription***

All the drugs used were purchased from local market. The herbal specimens were identified by the Department of Taxonomy, University of Kashmir, Srinagar (India) vide No. 4280-KASH-Herbarium. For the test group, the decoction of *Cuscuta reflexa* (*Aftimoon*) was prepared by taking 5 g (dry weight) of drug in a container and then 30 mL boiling water poured over it. The container was covered until the decoction cooled down, after which it was strained and orally taken in the morning after breakfast (Khan, 1983). The paste was prepared by grinding *Saussurea lappa* (*Qust*) into a fine powder and mixing it with a sufficient quantity of honey to form a paste. Honey exhibits antiseptic and resolvent properties, besides acting as a binding agent for making a paste (Khalid *et al*., 2023). This paste was applied locally on the affected area at bedtime for 15 min and washed off with lukewarm water. In control group, patients were given tranxemic acid 250 mg tablet orally twice a day after breakfast and dinner, and azelaic acid 10% cream was applied on the affected area once a day at bedtime (Bala *et al.*, 2018).

***Drug efficacy assessment***

The efficacy of test drug and control drug was determined by assessing the subjective and objective parameters. The subjective parameters included assessing the brown and black hyper-pigmentation areas while objective parameters included assessing the melasma area and severity index (MASI score) and taking the photographs of lesions. For the assessment of subjective parameters, an arbitrary 0-4 grading scale was used to assess the severity of hyperpigmentation in patients before and after treatment (Khan, 1983), wherein 0 depicted as no hyperpigmentation lesion; 1 as slight; 2

as mild; 3 as moderate, and 4 as severe hyperpigmentation. For objective parameters, MASI score, devised on the pattern of Psoriasis Area and Severity Index (PASI) score (How *et al.,* 2020) and adopted by Kimbrough-Green *et al.* (1994) in the clinical studies of melasma, was followed. The MASI score comprised of the area, darkness and homogeneity score determination, providing all the necessary details of the lesions for objective assessment of the disease outcome (Trelles *et al.*, 2010). Before treatment, each sign and symptom was recorded in CRF as per grades and scores. Any worsening or improvement was recorded during each follow-up visit until the end of treatment.

***Statistical analysis***

The data collected from the respondents using the pre-designed schedule were compiled and statistically analysed using SPSS version 25.0 and R Studio version 4.0.3 software. Continuous variables (MASI scores) were expressed as mean ± standard deviation (SD) while categorical variables or attributes were expressed in terms of frequencies and corresponding percentages. The inter-group analysis (between test and control groups) for subjective and objective parameters was conducted by using Mann-Whitney U test. For intra-group analysis (to compare pre- and post-treatment data within each group) McNemar-Bowker test/Wilcoxon signed-rank test were followed. A p-value $< 0.05$ was considered statistically significant.

## RESULTS AND DISCUSSION

***Effect on subjective parameters***

The comparison of hyperpigmentation severity before and after treatment within and between test and control groups is given in Table 1.

***Comparison within groups***: The study revealed that in test group before treatment 4 (22.22%) patients had grade 4 (severe) hyperpigmentation and 12 (66.67%) had grade 3 (moderate) hyperpigmentation while only 2 (11.11%) patients had grade 2 (mild) hyperpigmentation with none falling in 1 or 0 grade hyperpigmentation (Table 1). After 60 days of treatment, hyperpigmentation was absent in 6 (33.33%) patients while 5 (27.78%) patients each had grade I (slight) and grade 2 (mild) pigmentation. The grade 3 (moderate) pigmentation was observed in 2 (11.11%) and grade 4 (severe) in none. The McNemar-Bowker test for intra-group analysis revealed a significant reduction ($p \leq 0.001$) in disease severity after treatments in test group. The treatment effectively eliminated hyperpigmentation in 33.33% patients and reduced the severity from grade 4 to grade 0 among the test group patients, with mean score reducing from 3.11 ($\pm$ 0.58) to 1.17 ($\pm$ 1.04).

**Table 1: Severity of hyperpigmentation in test and control group melasma patients in response to 60 days of treatment**

| Hyperpigmentation | Before treatment ($0^{th}$ day) | | After treatment ($60^{th}$ day) | |
|---|---|---|---|---|
| | Test group | Control group | Test group | Control group |
| Absent | 0 (0.00%) | 0 (0.00%) | 6 (33.33%) | 1 (5.55%) |
| Slight | 0 (0.00%) | 0 (0.00%) | 5 (27.78%) | 11 (61.11%) |
| Mild | 2 (11.11%) | 6 (33.33%) | 5 (27.78%) | 3 (16.67%) |
| Moderate | 12 (66.67%) | 10 (55.56%) | 2 (11.11%) | 2 (11.11%) |
| Severe | 4 (22.22%) | 2 (11.11%) | 0 (0.00%) | 1 (5.56%) |
| Total (n) | 18 (100%) | 18 (100%) | 18 (100%) | 18 (100%) |
| Mean score ± SD | 3.11 ± 0.58 | 2.78 ± 0.65 | 1.17 ± 1.04 | 1.50 ± 0.99 |
| Inter-group p- value* | 0.114 (ns) | | 0.375 (ns) | |
| Intra-group p-value** | $\leq 0.001$ | | $\leq 0.001$ | |

*Inter-group analysis (between test and control groups) by using Mann-Whitney U test;

**Intra-group analysis (for pre- and post-treatment data within each group) by using McNemar-Bowker test

ns = Non-significant; SD = Standard deviation

An improvement in hyper-pigmentation was observed in standard control group. Prior to the treatment, 2 (11.11%), 10 (55.56%), and 6 (33.33%) patients had severe, moderate, and mild hyper-pigmentation, respectively; while no patient was falling in slight or no hyperpigmentation category (Table 1). However, after the completion of treatment course of 60 days, only 1 (5.56%), 2 (11.11%) and 3 (16.67%), 11 (61.11%) and 1 (5.55%) patients showed severe, moderate, mild, slight and no hyper-pigmentation, respectively. The McNemar-Bowker test for intra-group analysis revealed a significant difference (p-value $\leq$ 0.001) in hyperpigmentation before and after treatments in control group. The treatment effectively eliminated hyper-pigmentation in 5.55% patients and reduced the disease severity from 11.11 to 5.55% among the control group of patients, with mean score deceasing from 2.78 (± 0.65) to 1.50 (± 0.99).

***Comparison between the groups:*** The data revealed that hyper-pigmented lesions were eliminated in 6 (33.33%) patients in test group in comparison to 1 (5.55%) patient in control group on 60$^{th}$ day of treatment (Table 1). It was reduced to slight pigmentation in 5 (27.78%) patients in test group and 11 (61.11%) patients in control group, to mild pigmentation in 5 (27.27%) patients in test and 3 (16.67%) patients in control group, and to moderate pigmentation in 2 (11.11%) patients in each group. No patient exhibited severe hyperpigmentation after treatment in test group, while 1 patient (5.56%) in control group had severe hyperpigmentation. However, statistical analysis using Mann-Whitney U test indicated no significant difference (p value 0.375) between the two groups, suggesting that both treatments were at par in reducing the subjective severity of hyperpigmentation.

***Effect on objective parameters***

The MASI scores recorded at periodical intervals in response to 60 days of treatment including base day (0 day) in test and control group patients is presented in Fig. 1 and Table 2.

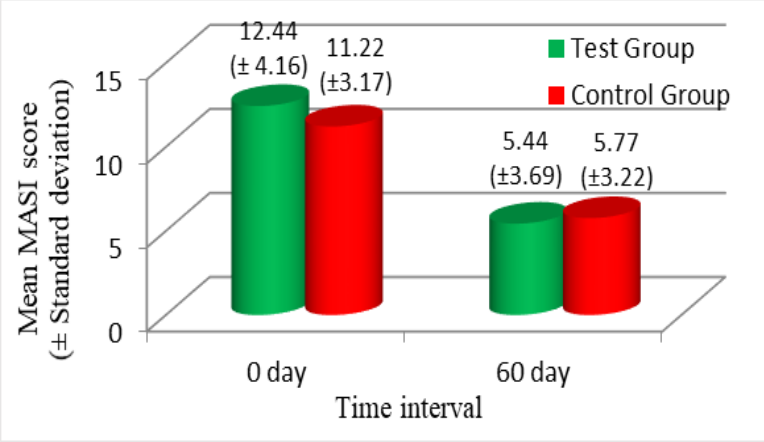


**Fig. 1: Mean MASI scores in melasma trial patients in response to 60 days of test and control drug treatment**

**Table 2: Comparison of MASI scores (mean ± SD) among test and control group melasma patients during 60 days of treatment**

| Time interval (days) | Test group | Control group | Inter-group p-value* |
|---|---|---|---|
| 0 (Baseline) | 12.44 ± 4.16 | 11.22 ± 3.71 | 0.463 |
| 15 | 11.17 ± 3.59 | 11.11 ± 3.66 | 0.923 |
| 30 | 9.50 ± 3.22 | 9.94 ± 3.13 | 0.452 |
| 45 | 7.86 ± 2.92 | 7.88 ± 2.76 | 0.710 |
| 60 | 5.44 ± 3.69 | 5.77 ± 3.22 | 0.702 |
| Intra-group p-value** | ≤ 0.001* | | ns |

* Inter-group (test vs control) analysis by using Mann-Whitney U test;
**Intra-group (pre- and post-treatment) analysis by using McNemar-Bowker test/ Wilcoxon signed-rank test; ns = non-significant.

***Comparison within groups***

The study showed a significant decreasing trend in MASI scores in both test and control groups on 30$^{th}$ day of treatment but before that i.e. upto 15$^{th}$ day of treatment the decline was non-significant in both the groups. In test group, on 30$^{th}$ day of treatment the mean MASI score declined significantly ($p \leq 0.001$) from 12.44 (± 4.16) to 9.50 (± 3.22). On 45$^{th}$ and 60$^{th}$ day after treatment, the scores showed further significant decrease to 7.86 ± 2.92 and 5.44 ± 3.69, respectively (Table 2). In control group, on the 30$^{th}$ day of treatment, the mean MASI score declined significantly (p value 0.004) from 11.22 (± 3.71) to 9.94 (± 3.13). On the 45$^{th}$ and 60$^{th}$ day of treatment, significant ($p \leq 0.001$) reductions

in mean scores were recorded to be 7.88 (± 2.76) and 5.77 (± 3.22), respectively. The comparison of test and standard drugs on the basis of MASI score showed that both could significantly manage melasma disease. The inter-group comparisons of MASI scores between test and control groups was non-significant at 30, 45 and 60$^{th}$ day of treatment with p values of 0.452, 0.710 and 0.702, respectively, indicating that both test and control drugs were equally effective in managing melasma severity. The efficacy was visually evident from pre- and post-treatment images of test-drug trial patients (Plate 1). Furthermore, all the biochemical investigations carried out before and after the treatment in patients of both groups remained within the limits of reference ranges which indicated that both test and control drugs are safe for melasma treatment.


**Plate 1**: **Appearance of melasma in test group patients at base-line [0 day] (A), and after 60 days of treatment (B)**

The improvement noticed in the test group may be attributed to the purgative of black bile (*Mushil sawdā*), concoctive (*Munḍij*), blood purifying *(Muṣaffi khūn*), and anti-inflammatory (*Muḥallil*) actions of *C. reflexa* (*Aftimoon*) given as oral decoction, and rubefacient (*Muḥammir*) and astringent (*Qābiḍ*) activities of *S. lappa (Qust)* in combination with *Jālī* (detergent) action of honey given as topical application. *Cuscuta* extract is considered an effective skin whitening agent, and it significantly reduces skin melanin synthesis in hyperpigmented areas in healthy individuals (Roohaninasab *et al*., 2022). *C. reflexa* contains various useful phytochemicals like flavonoids, alkaloids, polysaccharides cuscutin, cuscutalin, kaempferol, etc., which possess various pharmacological activities like anti-inflammatory, antioxidant, antimicrobial, anticancer, antidiabetic, and antiviral properties (Gangarde *et al*., 2024). Suppressing the release of inflammatory cytokines, alleviating the oxidative stress (a major trigger for hyperpigmentation), reducing the recruitment of inflammatory cells and regulating the proliferation and differentiation of keratinocytes or blocking melanosome transfer i.e., melanocytes to keratinocytes could be amongst the other possible underlying mechanisms of action as reported in case of *Cuscuta* extract (Liao *et al.,* 2014; Wang *et al.,* 2014) and *Saussurea* polysaccharide (Wang *et al.,* 2023; Popaniya *et al.,* 2024). Liao *et al.* (2014) have reported decrease in nitric oxide and consequent stimulation of superoxide dismutase, glutathione peroxidase, and glutathione reductase enzyme activities in liver as the mechanism of action for anti-nociceptive and anti-inflammatory effect of *C. chinensis*. Control of melanin synthesis by inhibiting the key melanin-producing enzyme 'tyrosinase' through various activities has been reported as another possible mechanism as in case of various herbs (Popaniya *et al.,* 2024) including *C. chinensis* seeds (Wang *et al.,* 2014) in the treatment of melisma. Sesquiterpene lactone '*α*-cyclocostunolide', found in *S. lappa* root extracts, is reported to act as melanin inhibitor in melanoma cells (Choodej *et al.*, 2019), so appears responsible for therapy of skin disorders. The test drug combination showed good results due to synergetic effect of both the oral and topical drugs. Further studies are required to assess the individual effects of test drugs.

**Conclusion:** The present study revealed that the test formulation i.e. *Joshanda Aftimoon* and *Zimad* of *Qust* and honey is effective in melasma (*Kalaf*) treatment with significant reduction in MASI score in test group. No adverse effects were observed in test group and the overall compliance with

test drugs was good. Treatment of melasma is often frustrating due to high relapse rates observed after discontinuing the treatment. Although, no relapse cases were observed during the study period perhaps due to relatively shorter study duration. Therefore, more detailed studies are required to address the relapse rates of test drugs.

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