

Therapeutic Evaluation of Unani Herbal Medicine for Topical Application (Zimad of Tukhme Turb, Tukhme Karafs and Sirka) in Melasma (Kalaf) - A Single Blind Randomized Controlled Study



Medical Science

KEYWORDS : Kalaf, Melasma, Raphanus sativus, Apium graveolens

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ABSTRACT

Background: Melasma is a common diagnosis in any dermatology clinic and can reach an incidence of 0.25% to 4% of cases seen in any dermatology institution of Asia. Despite the effective therapeutic regimes currently available for Melasma in contemporary medicine, there remain many patients who fail to respond adequately or develop side effects. Considering this unconvincing scenario, Unani medicine axiomatically comes to the fore as the Kalaf (Melasma) has successfully been treated since antiquity without any significant, obnoxious effects on the body.

In view of above, a clinical study was conducted to find the efficacy of the Unani topical formulation consists of Tukhme Turb (Seeds of Raphanus sativus), Tukhme Karafs (Seeds of Apium graveolens) and Sirka (vinegar) in the management of Melasma.

Objective: Evaluation of the safety and efficacy of Zimad (Tukhme Turb, Tukhme Tarafs and Sirka) in the management of Kalaf (Melasma).

Methodology: The study was designed as Parallel group, Randomized, Single blind with standard control on 40 patients of Melasma. Test group comprised of 20 patients and were given test drug in the form of Zimad (paste) {Tukhme Turb (Seeds of Raphanus sativus), Tukhme Karafs (Seeds of Apium graveolens) and Sirka (vinegar)} once a day for a period of 45 days. Control Group was comprise of 20 patients in which standard drug, Azelaic acid 10% cream, was applied topically once a day for the same duration. Patients were kept under strict observation and assessment of the efficacy of treatment in test and control group was carried out on the basis of subjective and objective parameters.

Result: Significant improvement was observed statistically in both test and standard control drug ($p < 0.05$). In the area of Melasma strongly significant change ($p = 0.001$) was observed in test group and Suggestive significant change ($p = 0.056$) was observed in control group. In the darkness of the lesion, highly significant change ($p < 0.001$) was observed in test group and significant change ($p = 0.001$) was observed in control group. Similarly highly significant change ($p < 0.001$) and significant change ($p = 0.015$) was observed in test and control groups respectively in homogeneity of the lesion. Comparing the total MASI score statistically highly significant changes was observed in both groups as $p = 0.001$ in test group and $p = 0.007$ in control group.

Conclusion: Study revealed that test drug was equally effective to standard control drug in ameliorating the lesions of Melasma. Mild burning and peeling was experienced in some patients of both groups. Therefore, the test drug may be considered as safe and well tolerated in treatment of Melasma.

Introduction:

Skin disorders are well recognized since Greco-Arabic period. Unani physicians evidently explain the aetiology, clinical presentation, and management of various skin diseases. It is notable that, though the skin pigmentation disorders are not painful but develops cosmetic problem and social stigma.¹ Kalaf (Melasma) is a chronic skin disease characterized by blackish discoloration (hyperpigmentation) occurring superficially and rarely slightly deep to the skin of face.^{2,3,4} It is a humoral disease occurring due to alteration in the quality and quantity of khilte Sauda (black bile).⁵

In modern perspective, Kalaf is synonymous to Melasma which is a common acquired symmetric hypermelanosis characterized by irregular light-brown to grey-brown macular patches on sun exposed areas of the skin.^{6,7} This is seen mainly in women, and occurs exclusively on the sun exposed skin of the face.⁸ In Asia, it is a common diagnosis with an incidence of 0.25% to 4% of cases seen in any dermatology institution.⁹ Melasma is so common in pregnancy that it has been dubbed the "mask of pregnancy."^{10,11,12,13,14}

The goals of Melasma management include symptomatic relief, reversion of pathology and restoration of normal colour of skin.¹⁵

Topical therapy alone is often insufficient to clear Melasma. Chemical peels, microderm abrasion, lasers, and intense pulse

light are often used in combination with topical therapy.¹⁵ These procedures showing promising results but are invasive methods and associated with adverse reactions.⁸

Unani system of medicine claims local application of medicines is more beneficial in skin disorders. On the basis of principle of *Ilaj biz Zid*, (Heteropathic) various regimes are adopted including the topical application of drugs having hot temperament that possess *Jali*, (cleanser) *Muhassine laun* (color fairing agent) and *Muhammir* (rubeficient) properties.³ These drugs resolve the disease causing substances and restore the normal pigmentation of skin.¹⁵ Keeping this basic concept in view, the present Unani formulation, consists of *Tukhme Turb* (Seeds of *Raphanus sativus*), *Tukhme Karafs* (Seeds of *Apium graveolens*) and *Sirka* (Sugarcane vinegar) was selected for study from '*Aksire Azam*'.¹⁶ Although, the above mentioned formulation has been recommended and used since long but is not yet explored on modern scientific parameters, thus no data is available on its safety and efficacy.

So, it was decided to carry out a randomized single blind standard controlled clinical study to evaluate the safety and efficacy of this topical Unani formulation in the management of Melasma on scientific parameters.

Materials and Methods:

This study designed as single blind randomized standard controlled study and conducted on the patients who attended Hos-

pital of National Institute of Unani Medicine, Bangalore from March 2013 to January 2014. Total 40 patients were enrolled and randomly allocated to test group (n= 20) & control group (n= 20). Randomization was done by computer generated random numbers. During the study period, 2 patients from test and 2 from the control group were dropped out due lost to follow-up, and were further recruited to complete the total no. in each group. The study approved by the institutional ethics committee, NIUM, Bangalore, on 18th April 2012. The ethical registration number is IEC NO: NIUM/IEC/2011-12/006/Moal/06.

Clinically diagnosed patients of *Kalaf* of both genders aged between 15-50 years were included in study. The patients with any concomitant disease, skin sensitivity and pregnancy were excluded from study. Prior to the study; written informed consent were taken. The treatment protocol was fixed as 45 days for both test and control groups. Patients were advised to attend OPD fortnightly for follow up. Concomitant treatment was not allowed during the period of study in either of the groups.

Investigation:

Haemoglobin, Total leukocyte Count, Differential Leukocyte Count and ESR were carried out in all recruited patients before starting the study.

Intervention:

The test formulation consist of *Tukhme Turb* (Seeds of *Raphanus sativus*) *Tukhme Karafs* (Seeds of *Apium graveolens*) *Sirka* (*Sugarcane vinegar*). *Tukhme turb* and *Tukhme karafs* were taken in equal quantity and pulverized into fine powder after clearing unwanted material and impurities.

The test group patients were provided the powder of the above ingredients and asked to prepare the paste just before the application by mixing 1-2 gm powder with sufficient quantity of *Sirka* and apply it topically over the affected area once daily at night and rinsed with lukewarm water after 10-15 minutes for 45 days.

Azelaic acid 10% cream in similar wrappings were provided to the patients of standard controlled group for topical application and advised to apply over the affected area once daily at night and rinsed with lukewarm water after 10-15 minutes for 45 days.

Assessment the Efficacy of Treatment:

The efficacy of the test and control groups was assessed on subjective and objective parameters. Subjective parameter comprises mitigation in brown and blackish discoloration. Objective parameters comprise the Melasma area severity index and photographs of the lesions.

Melasma area severity index (MASI) developed by Kimbrough Green et al for the assessment of Melasma. The severity of the Melasma in each of the four (Forehead, Right Malar Region, Left Malar Region and Chin) was assessed based on three variables; percentage of the total area involved (A), darkness (D), and homogeneity (H).

The Formula for calculation of MASI score is Forehead 0.3 (D+H) A + Right malar 0.3 (D+H) A + Left malar 0.3 (D+H) A + Chin 0.1 (D+H) A.

The safety of the treatment was assessed clinically by erythema, itching or any other related adverse effect.

Facial photographs, bilateral and frontal, were taken using a digital camera (Sony) on the day of initiation of treatment, first follow up, second follow up and just after completion of treatment, so that hyperpigmentation could be assessed properly. Photographs were taken at a suitable distance. Attempts were made to ensure that photographs were taken in the same manner and

with the same lighting.

Descriptive and inferential statistical analysis was carried out in the study. Student's t test (two tailed, dependent) were used to find the significance of study parameters on continuous scale within each group. Fisher Exact test was used to find the significance of study parameters on categorical scale between two groups. Paired proportion test has been used to find the significance within group analysis.

Result:

In the study 40% and 35% patients belongs to 31-40 year of age and 41-50 year of age respectively. 17 out of 20 patients were female were in both test & control group. The patient distribution according to marital status revealed 18 out of 20 in test and 17 out of 20 in control group were married.

Occupationally, 12 (60%) and 13 (65%) were house wife in test and control groups respectively. There was no positive family history in 80% of test group patient and 75% of control group patients. The 50% patients of test group and 70% of control group were presented with a history of > 24 month illness. Nearly all (95%) patient irrespective of groups possess symmetrical pattern of disease. The itching was poorly associated with melasma and observed only in 15% patient in each group.

Thirty five% improvements were observed in test group and 20% in control group on subjective parameter (Brown/blackish pigmentation).

In MASI score A (area) Strongly significant change (0.001) was observed in test group and Suggestive significant change (0.056) was observed in control group, In MASI score D (darkness) highly significant change (<0.001) was observed in test group and significant change (0.001) was observed in control group, In MASI score H (Homogeneity) highly significant change (<0.001) was observed in test group and significant change (0.015) was observed in control group. In MASI score T (Total) strongly significant change (0.001) was observed in test group and strongly significant change (0.007) was observed in control group.

The 2 patients of test group and 1 patient from control group were developed mild adverse event i.e. burning sensation and erythema.

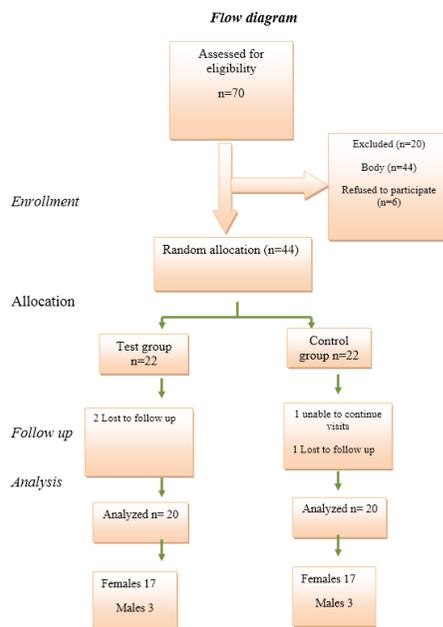


Table No. 1 Demography

	Test group	Control group
Age in years (Mean \pm SD)	37.90 \pm 7.06	37.80 \pm 8.48
Female: Male	17: 3	17: 3
Married: Unmarried	18:2	17:3
OCP Consumers: Non OCP Consumers: N.A	2:15:3	1:16:3
Pregnancy (Female) Yes: No: N.A	2:15:3	3:14:3
Duration (1-12:13-24:>24 month)	5:5:10	2:4:14
Sun Exposure(< 1Hr:1-3 Hrs:> 3 Hrs)	13:4:3	15:3:2

Mean \pm SD (Min-Max), N.A= Not Applicable,

Table No. 2 Subjective Parameter

Brown/black pigmentation	BT	AT	% change
Test group			
0	0(0%)	7(35%)	35.0%
1	9(45%)	11(55%)	10.0%
2	8(40%)	2(10%)	-30.0%
3	3(15%)	0(0%)	-15.0%
Control group			
0	0(0%)	4(20%)	20.0%
1	11(55%)	13(65%)	10.0%
2	8(40%)	2(10%)	-30.0%
3	1(5%)	1(5%)	0.0%
P value	0.729	0.718	

BT= Before treatment, AT=After treatment,

Table No. 3 Objective Parameter

MASI Score	BT	AT
MASI Score A		
Test group	0.28 \pm 0.17	0.19 \pm 0.18
Control group	0.25 \pm 0.18	0.22 \pm 0.16
P value	0.578	0.566
MASI Score D		
Test group	3.65 \pm 1.79	2.20 \pm 1.15
Control group	3.70 \pm 1.87	2.80 \pm 1.77
P value	0.931	0.211
MASI Score H		
Test group	3.55 \pm 1.57	2.15 \pm 1.42
Control group	3.10 \pm 1.33	2.75 \pm 1.37
P value	0.335	0.183
MASI Score T		
Test group	1.17 \pm 1.07	0.52 \pm 0.60
Control group	0.96 \pm 0.88	0.72 \pm 0.70
P value	0.495	0.345

P Value= Probability (p) Value

MASI A= Melasma area severity index Area

MASI D= Melasma area severity index Darkness

MASI H= Melasma area severity index Homogeneity

MASI T= Melasma area severity index Total

Discussion:**Age:**

In this study 8 patients (20%) were in age group 21-30 years, 18 patient (45%) were in the age group of 31-40 years and 14 patients (35%) belong to 41-50 years of age (Table 1). The above mentioned data indicated the preponderance of the disease in age group of 31-50 (mean age 38.5) years which implied that the disease is more prevalent in the 4th and 5th decade of life. This prevalence of disease according to the age corresponds with the findings of Kulthanan k et al.¹⁷ who suggests that mean age of Melasma is 40 years. (Table 1)

Gender:

In this study out of 40 patients 34 (85%) were female which suggest that female are more prone to developed Melasma (Table 2). The higher incidence of Melasma in females may be attributable to a hormonal influence as in pregnancy and use of oral contraceptive pills. The observation of this study is in congruence to the description of Klaus Wolff and Richard Allen Johnson.⁶ This study is also in accordance with the study of Sharquie K E, Danish S A and Sarkar R.¹⁸ As per these studies in India 10% patients of Melasma are males.

Marital status:

In this study 35(87.5%) out of 40 patient were married (Table 4). As the present study data suggests that 34 patients were female, so probably pregnancy, OCP and hormonal imbalance may be the contributing factors; since these risk factors are seen more in married women. This finding is in conformity with the description of Thomas B. Fitzpatrick, Richard Allen Johnson, Klaus Wolff, Machiel K. Polano and Dick Suurmond.⁹

Pregnancy:

In present study only 12.5% of patients give a positive history of pregnancy association with Melasma. This data is in accordance with Hexsel D et al and Moin A et al.¹⁹ However it is contrary to the description of Unani classical text where it is clearly mentioned that the excreta of menstruation cannot be eliminated during pregnancy and there being deposited beneath the skin.²⁰

Age of onset:

As far as the age of onset is concerned 32 (80%) patients were found between 21-40 years of age (Table 11). This study is in accordance with the description of Sharique KE.¹⁸

Duration:

Around 60% patients have a history of more than 24 months of duration (Table 1). This indicates chronic nature of disease as described by Zakaria Razi, Ibn Sina and Ahmad Bin Mohd Tabri.^{2,3,5} This is also in consonance with the finding mentioned by Vazquez et al.²¹

Subjective Parameter:

The patients were evaluated on subjective parameter (brown black pigmentation). 35.0% patients in test group and 20% in control group showed total relief which is suggestive of significant improvement in test and control groups as p=0.002 in test group and p=0.019 in control group. This improvement in test group may be because of *Jali*, *Muhammir* and *Muhassine Laun* activities of *Tukhme Turb*, *Tukhme Karafs* and also due to *Mulattif* and *Qateh Akhlate Ghaleeza* properties of *Sirka* present in *Zimad*. However, it is more likely that improvement in this symptom was the sequel of overall improvement in the disease process.

Objective Parameter:

In the area of Melasma strongly significant change (p=0.001) was observed in test group and Suggestive significant change (p=0.056) was observed in control group. In darkness of the lesion, highly significant change (p<0.001) was observed in test group and significant change (p=0.001) was observed in control

group. Similarly highly significant change ($p < 0.001$) and significant change ($p < 0.015$) was observed in test and control groups respectively in homogeneity of the lesion.

However, comparing the total MASI score statistically highly significant changes was observed in both groups ($p = 0.001$) in test and ($p = 0.007$) in control group. The response of test formulation and regression of hyperpigmentation may be attributed to the *Haar Mizaj* (Hot temperament) of all the ingredients present in the test formulation. By virtue of their hot temperament, they are endowed with *Jali*, (cleanser), *Muhallil* (Resolvent), *Musakhhkhin* (Calorific), *Muhassine laun* (color fairing agent), *Mulattif* (Demulcent), *Sareeun Nufuz* (Highly Permeable) and *Muhammir* (Rubefacient) properties. After topical application the drug reach deeper into the skin under the influence of *Sareeun Nufuz* effect of *Sirka*. The *Muhammir* property of *Tukhme Turb* and *Tukhme Karafs* produced excessive heat over the site of lesion which leads increased blood circulation to the affected part. This increased blood circulation, over the affected area, supports the *Muhallil*, *Mulattif* and *Jali* activities of *Tukhme Turb*, *Tukhme Karafs* and *Sirka*; hence, the disease causing substance is removed. Further, *Muhassine Laun* activity of *Tukhme Turb* makes the complexion of skin fairer while restoring the normal pigmentation of skin. This is in consonance with the pharmacological actions of drugs described in classical Unani literature.^{3,22}

Local application of these drugs with *Sirka* may be a key factor in improving the overall condition in disease process as *Sirka* possesses *Jali*,²³ *Sareeun Nufuz* (fast to penetrate),²⁴ *Qate Akhlate Ghaleez* (Lytic of Viscid Humour)^{25,26} properties that probably enhance the effects of other drugs. This is supported by statement of Hippocrate who recommended vinegar preparation for cleansing purpose. The beneficial effect of test formulation is corroborated by the use of these drugs in a variety of skin diseases by eminent Unani scholars like *Razi*, *Ibn Baitar*, *Ibn Sina*, *Azam Khan* and *Najmul Ghani*.^{2,3,16,22,23}

Conclusion:

The present study proved that *Zimad* (*Tukhme Turb*, *Tukhme Karafs* and *Sirka*) is effective in treatment of melasma. Our hypothesis, that above said *Zimad* is efficacious and safe topical treatment for *Kalaf* is proved valid. The Limitations of the study were small sample size and shorter period. A double blind long term clinical study, with larger sample size to establish treatment duration, obnoxious effects and its additional applications, are recommended. An In vitro study is also recommended to establish the possible mode of action of *Zimad*.

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