Randomized Clinical Trial of Unani Formulations in Chloasma/ Melasma

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Abstract

Hyperpigmentation is defined as predominance of black-bile (ghalba e sauda) in skin or in blood, in the Unani system of medicine. The various hyperpigmentation conditions are kalaf, namash, barash, also known by the names of jhaeen, nuktay, lehsun, etc. The hyperpigmentation itself is not a disease but a manifestation that creates a condition of concern and stress for the patient. Melasma is a common acquired symmetric hypermelanosis which is characterized by the presence of light brown-to- dark brown-to –black macules and patches mostly on the sun exposed areas of skin of the face. There are multiple etiologic factors associated with melasma (pregnancy, inflammatory, racial, endocrinal, photo toxicity, photosesnsitivity of drugs and food) but one of the primary causes of its exacerbation is exposure to sunlight. The purpose of this study is to ascertain and assess the efficacy and safety of treatment with Unani formulations in participants with moderate to severe melasma. The study design is Randomized, Single blind Controlled Clinical trial. The control group received oral plus topical treatment with Unani formulations coded as MN and XM, respectively.

Key Words: Melasma/Chloasma, Hyper pigmentation, Inflammatory, Unani formulations.

Introduction

Melasma also known as *chloasma,* appears as a blotchy, brownish pigmentation on the face that develops slowly. The pigmentation is due to overproduction of melanin by the pigment cells, melanocytes (Pandya *et al*., 2007). In the Unani System of Medicine, the hyperpigmentation or melasma is defined as the *ghalba sauda* i.e. imbalance (predominance) of the humor called black bile or *sauda* in the blood and or skin (Azhar, 2002; Cochran and Cox, 1992; Ruxton and Colegrave, 2006). The objective of this study is to conduct a clinical trial to assess the safety and efficacy of Unani formulations as a combination therapy comprising MN (oral) and XM (topical) in the treatment of chloasma/ melasma and also to assess ADR/side effect/toxicity of Unani Dermatological drugs used in this clinical study.

Causes of Chloasma/Melasma

Pregnancy – the pigment often fades a few months after delivery (Bhutani,

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2009).Hormonal contraceptives, including oral contraceptive pills and injected progesterone, genetic predisposition, sun exposure (Khanna, 2009). Scented or deodorant soaps, toiletries and cosmetics – a phototoxic reaction, unknown factors, when it arises in apparently healthy, normal, non-pregnant women (Pandya *et al*., 2007).

Female sex hormones estrogen and progesterone stimulate melanocytes to produce more melanin when the skin is exposed to sunlight. Several hormones influence melanogenesis and the most important being melanocyte stimulating hormone secreted by the pituitary gland (Khanna, 2009).

Clinical features

Melasma affects the forehead, cheeks and upper lips resulting in macules (freckle-like spots) and larger patches. Occasionally it spreads to involve the sides of the neck, and a similar condition may affect the shoulders and upper arms. Melasma is divided into epidermal (skin surface), dermal (deeper) and mixed types.

Centro facial: affecting forehead, cheeks, nose, chin and skin above upper lip. Mandibular type: ramus mandibularis is involved. Cheek type (Malar type): affecting cheek and nose closely. The other symptom of melasma pigmentation is that it darkens on sun exposure (Khanna, 2009).

The eyelids and central part of the upper lip however, are never involved (Pasricha & Ramji, 2006).

Histological difference

Melanin is increased in the epidermis, in the dermis, or (most commonly) in both locations in melasma patients (Khanna, 2009)

Epidermal: Epidermal melanin is found in Keratinocytes in basal and suprabasal area. Sometimes melanocytes do not increase in number. But are larger, more dendritic and more active.

Dermal: Dermal melanin is found in superficial and mid dermis within macrophagus which often congregate around small, dilated vessels. Inflammation sparse or absent.

Methods

Selection criteria (Inclusion Criteria)

1. Individuals with moderate to severe melasma.

2. All patients with hyper pigmentation of skin.

3. Age: 15 – 60 years, both gender (male & female)

Exclusion criteria: Diabetes mellitus, Hepatic or Renal damage, Tuberculosis, Cancer, Drug & Alcohol abused and Pregnancy.

Study Design: Randomised single blind study

Forty two individuals were randomly selected and then underwent a combination therapy of Unani formulations for oral and local use for the treatment of melasma.

The combination therapy for Group A, comprised of the formulations, coded MN (*Majoon*) for oral use, 10gms twice a day and XM (Powder) for local application as paste in rose water, twice a day for 30 minutes before washing off with water. While Group B (placebo group) received placebo of *Majoon* MP, orally 10 gms twice a day and XP Powder as paste in water, twice a day for local application.

Randomisation was done using Random Number Generator, so as to remove bias in patient allotment in each group.

The diagnosis and type of melasma was determined by Wood's Lamp examination (Ruxton and Colegrave, 2006).

Complete haemogram (Hb%, TLC, DLC & ESR), Liver Function Test (Total, direct and indirect bilirubin, SGOT, SGPT and Serum Alkaline Phosphatase) and Kidney Function Test (Blood urea and serum creatinine) were performed initially and two more samples were taken at every 45 days to check and assess the toxicity and ADR.

Hyper pigmented spots were evaluated at every 4 weeks interval for a period of 12 weeks.

Outcome measures included physicians' global assessment a MASI Scoring, subjective evaluation of melasma patch (Pandya *et al*., 2007).

The MASI (Melasma Area and Severity Index) is an index devised to more accurately quantify the severity of melasma and changes during therapy. The MASI is calculated based on the area (A) of involvement, the darkness (D) of melasma, and the homogeneity (H) of the hyperpigmentation. The forehead (F), right malar (RM), left malar (LM) and chin (C) correspond to 30%, 30%, 30% and

10% of the total face, respectively, giving a total facial surface area of 100%.

The area of involvement (A) in each of these areas is given a numerical value of 0 to 6:

0 – *indicates no involvement*; 1, *0% - 9%*; 2, *10% - 29%*; 3, *30%- 49%*; 4, *50%- 69%*; 5, *70%- 89%*; and 6, *90%- 100%.*

The severity of melasma is also determined by measuring two additional variables: darkness (D) and homogeneity (H), rated on a scale from 1 to 4:

0 – *indicates absent*; 1 *slight*; 2 *mild*; 3 *marked*; and 4 *maximum*.

The MASI score is calculated by adding the sum of the severity ratings for darkness and homogeneity, multiplied by the value of the area of involvement, for each of four facial areas. The values for each side are then totalled. The maximum score for each side is 24 and minimum is 0. The readings were taken at baseline, weeks 4, 8 and 12.

Observations

It was observed that the incidence of this disease is highest in the age group of 21- 30 years (50%) and least common in the age group of 51- 60 years, (3%). In our study the ratio of females (64%) is higher than the males (36%) (Table 1, Fig 1 & 2).

Table 1: Sex and age-wise distribution in the cases of melasma/chloasma

AGE GROUP	MALE	FEMALE	TOTAL	%
15 - 20 yrs	4	7	11	26%
21- 30	8	13	21	50%
31- 40	1	5	6	14%
41- 50	1	2	3	7%
51- 60	1	--	1	3%
Total	15	27	42	100%

The incidence of melasma was found to be more common in the middle income group, 81% and in the low income group the incidence was 19% (Fig. 3).

This condition was found to be quite common among the students (41%) and housewives (24%) (Fig. 4).

57% participants took mixed diet i.e. vegetables and animal products. 38% participants took purely vegetarian diet and those who were purely non-vegetarians were only 5% (Fig. 5).

Fig. 1 Age wise distribution

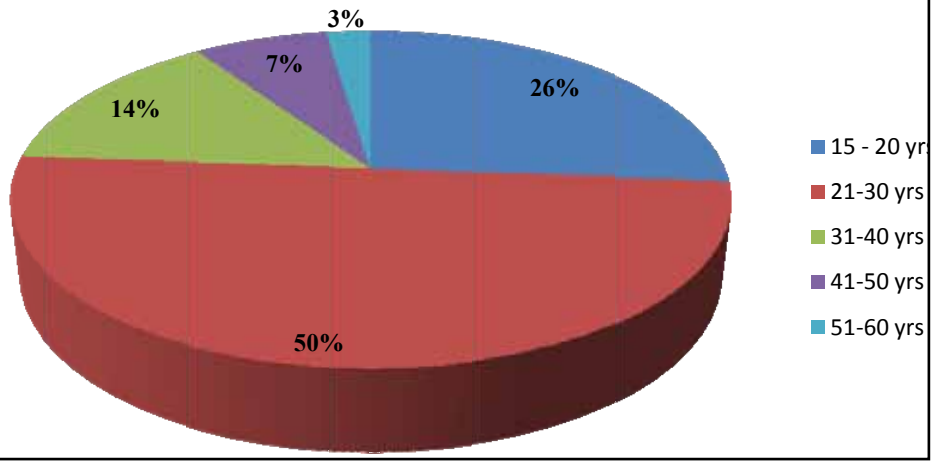


Fig. 2 Sex wise distribution

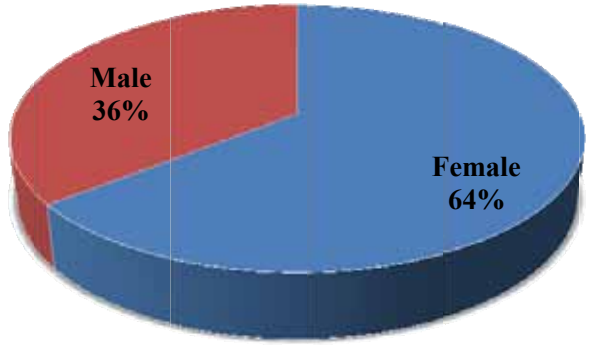
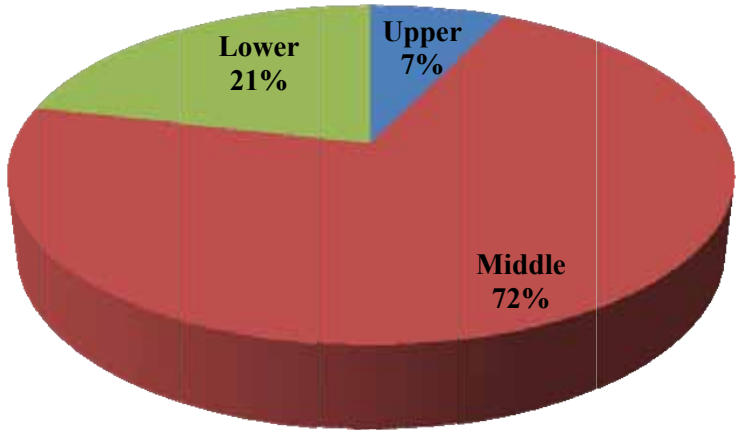


Fig. 3 Socio- economic status



It was found that the common type of melasma is the epidermal melasma (57%), followed by the dermal type (31%) and then mixed type of the melasma (12%) in the 42 participants (Fig. 6).

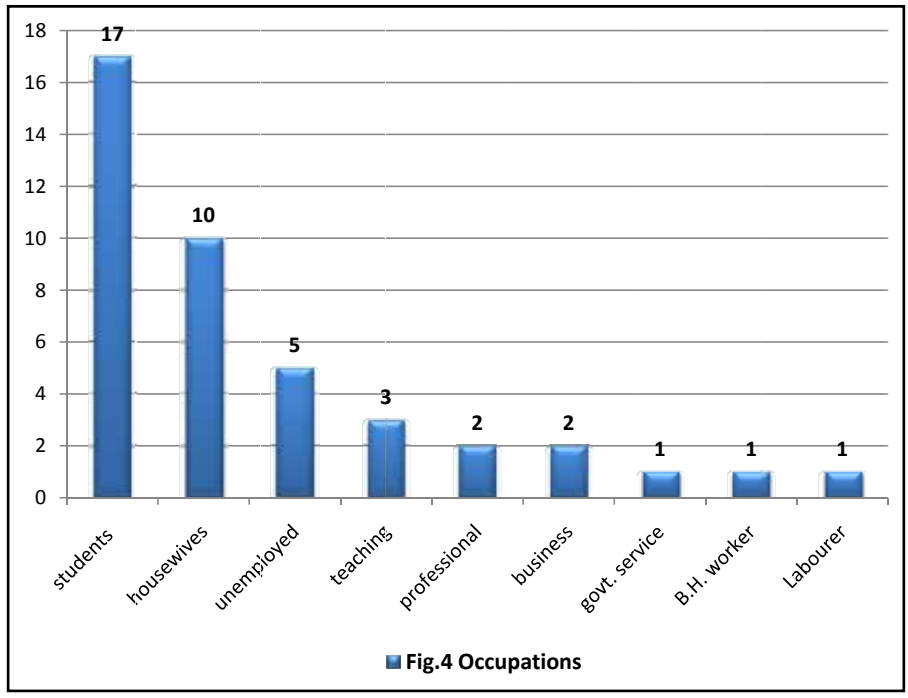


Fig. 5 Dietary habit

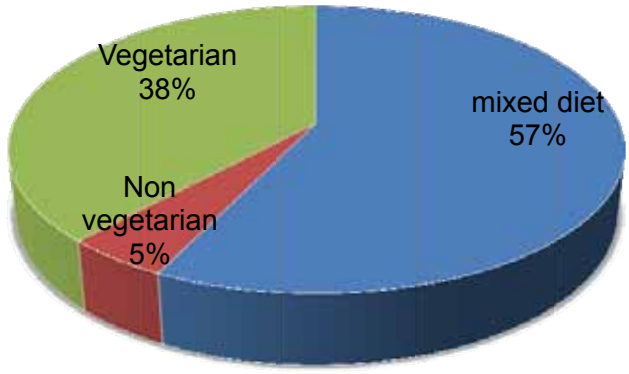
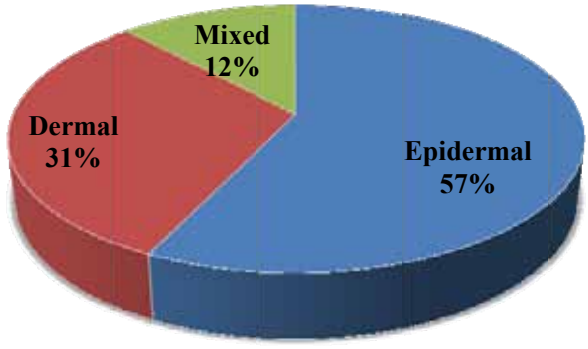
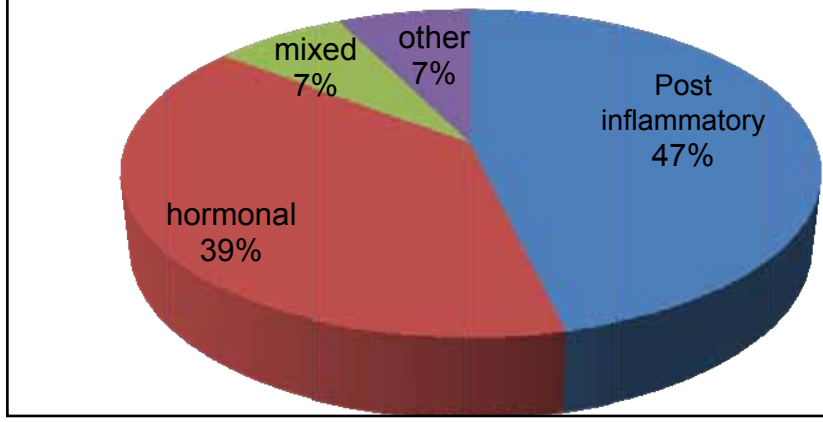


Fig . 6 Type of Melasma in all the patients



The melasma due to inflammation seems to be most common cause of epidermal (12), dermal (5) and mixed (3) type of melasma in 20 participants. The melasma due to hormonal influence were seen in 16 participants (epidermal in 12, dermal in 3 and mixed in 1 participant). Mixed causes i.e. both inflammatory and hormonal were seen in a single participant affected with mixed melasma and 2 participants of dermal melasma. The other causes of melasma were seen in 3 participants with dermal melasma- (Fig 7& 8).

Fig. 7 Cause of hyperpigmentation



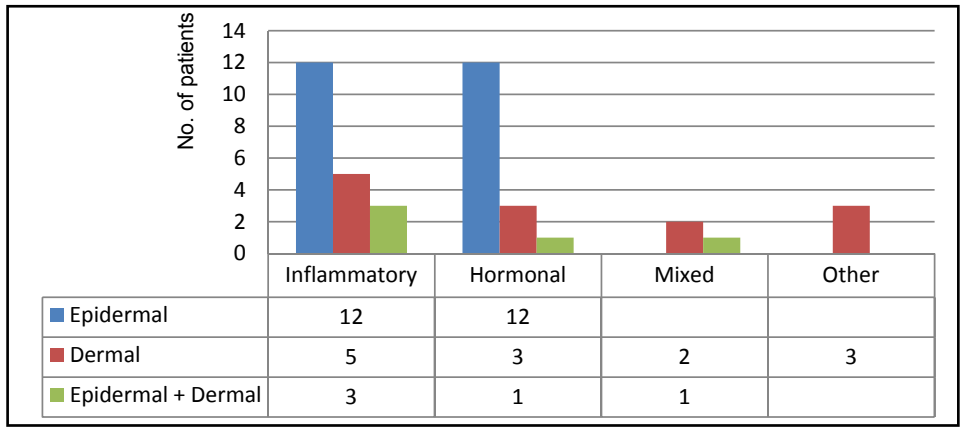


Fig. 8: Type of hyperpigmentation according to cause

The investigations like complete haemogram with ESR, Liver F.T. and Renal F.T. were performed in every patient of each group and was found to be within normal limits (Table 5).

Results

The group that received combination therapy demonstrated significant improvement in the subjective evaluation of melasma. The response of the combination therapy was found excellent (19%) in four patients, good (38%) in eight patients, and satisfactory (33.5%) in seven patients, slow (9.5%) in two patients and there was not a single patient who showed no response (Table.2 & Fig. 9).

Table 2: Showing the response of treatment in the Group A and B

Improvement	Total improvement		Partial improvement		Failure	Total Therapeutic Response
Response	Excellent (80-100%)	Good (70%)	Satisfactory (30%)	Slow (15%)	No Response (0%)	
Group A (Intervention)	19%	38%	33.5%	9.5%	0%	100%
No. of patients	4	8	7	2	-	21
Group B (Placebo)	0	0	9.5%	28.6%	61.9%	100%
No. of patients	0	0	2	6	13	21

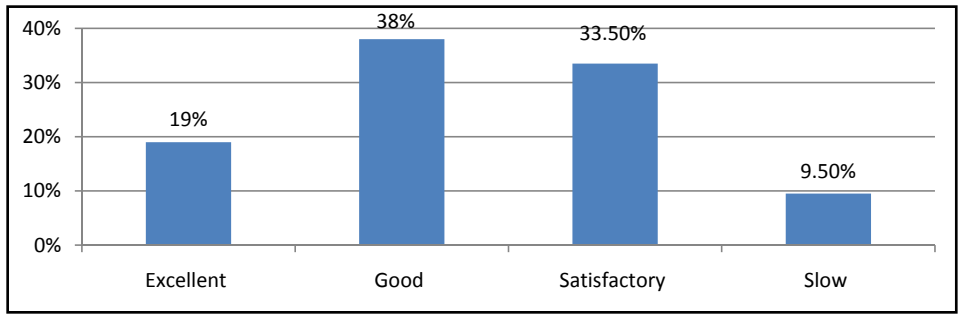


Fig. 9: Showing response in Group A

The patients of placebo group showed no response in 61.9% cases. Satisfactory response was seen in only 9.5 % cases and slow response was seen in 28.6% cases (Table 2, Fig. 10).

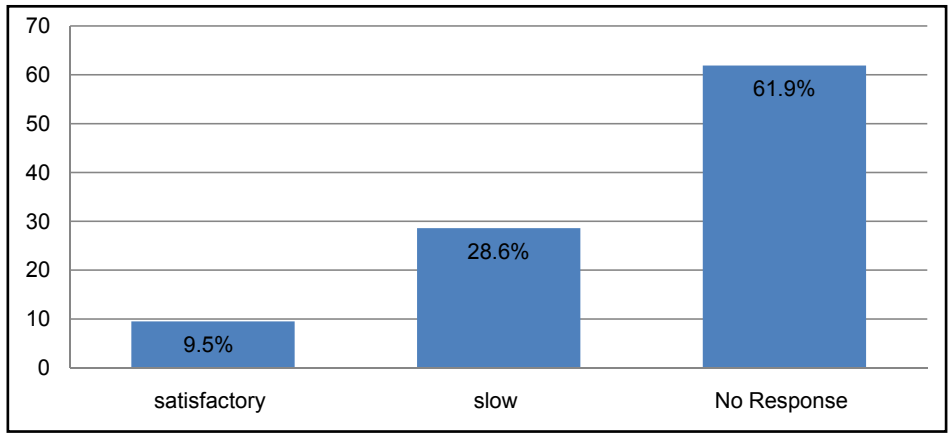


Fig. 10: Graphical representation of response in group B (Placebo)

In Intervention Group (A) the Total improvement of about 57 % was seen in 12 patients and Partial improvement of 43% was seen in 9 patients out of 21 patients at 12 weeks. Failure to treatment was not seen. In the Group B (placebo), only Partial improvement of about 38.1% was seen in about 8 patients out of the 21 patients. Failure rate of about 61.9% in the 13 patients was noted in this group at 12 weeks (Table 3).

Table 3: Showing Total improvement Vs. Partial improvement Vs. Failure in patients of Group A and B.

Group	Total improvement	Partial improvement	Failure
A (Intervention)	57%	43%	0%
No. of patients	12	9	-
B (Placebo)	0%	38.1%	61.9 %
No. of patients	-	8	13

Epidermal melasma showed response in a total of 53% subjects with 4 cases getting 70% relieve and 3 cases getting more than 80 % cured. Dermal melasma showed response in 33% cases. Mixed type of melasma showed response in 14 % cases of group A (Table 4 & Fig.11).

Table 4: Relation of response with type of melasma in Group A

Type	15% Slow	30% Partially relieved	Up to 70% Relieved	80—100% Cured	Total (n= 21)
Epidermal	1	2	4	3	11 (53%)
Dermal	1	3	3	1	7 (33%)
Mixed	0	2	1	0	3 (14%)

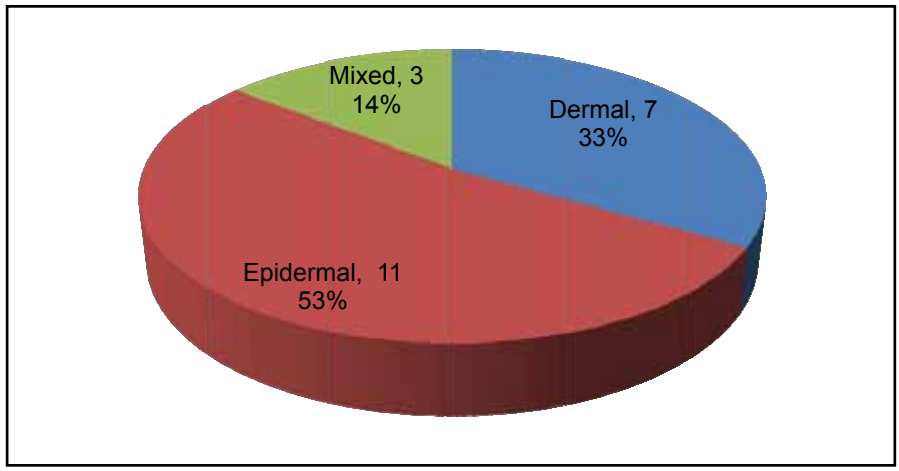


Fig. 11: Type of Melasma in Group A

The mean MASI score of Group A (Drug) at Baseline was 8.34 which decreased considerably to 3.22 at 12th week but in the Group B (Placebo) the mean MASI score at baseline was 6.07 which only came down to 5.26 at the 12th week (Fig 12).

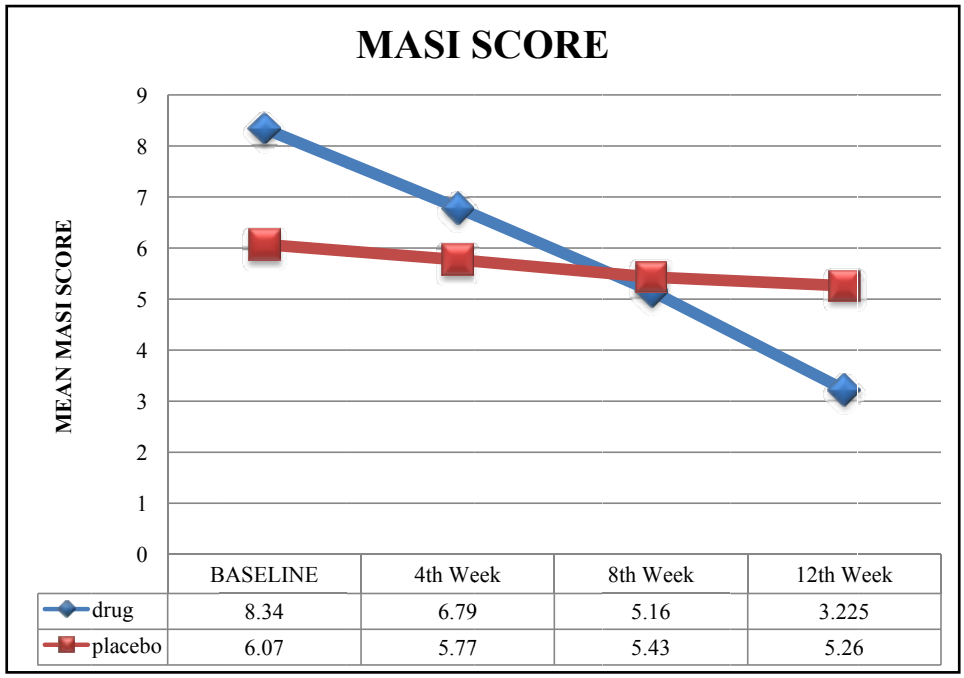


Fig. 12: Mean MASI score at baseline, 4th week, 8th and 12th week in Group A and Group B

Discussion

The response of combination therapy of *Majoon* MN and powder XM was found excellent in 19% cases, good in 38% cases, satisfactory in 33.5% cases and slow in 9.5% cases. The total therapeutic response achieved was 100%.

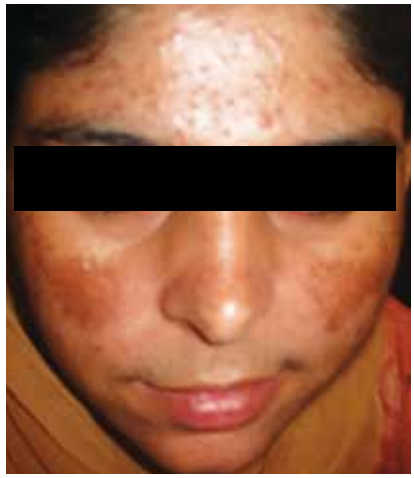
It has been clearly observed that this combination therapy showed good and excellent results in cases of epidermal type of melasma related with inflammatory causes. A partial improvement of 38.1% and no response of 61.9% was seen in group B that received Placebo.

It may be assumed that in melasma due to inflammatory causes, the accumulated melanin in exposed part of the skin get easily dissolved or disintegrated. It is to be further seen that whether the melanocytes decrease in number or in size.

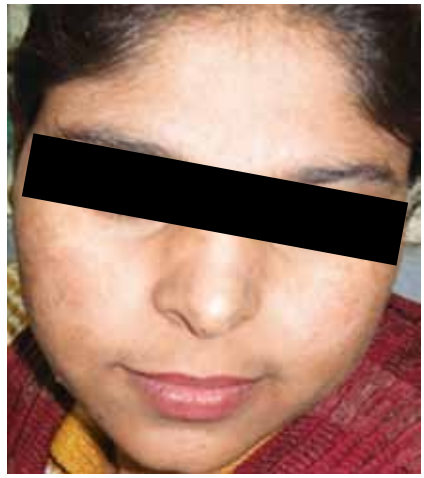
No side effect was seen in any case of melasma.

Table 5: ESR, LFT, RFT etc. Tests in patients

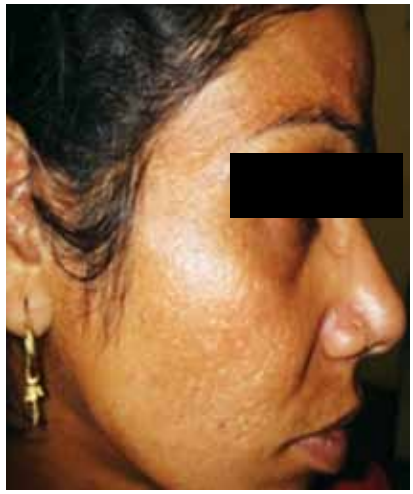
GROUP	TEST I	TEST II	TEST III
Group "A" (Intervention)	Within normal limits	WNL	WNL
Group "B" (Placebo)	Within normal limits	WNL	WNL

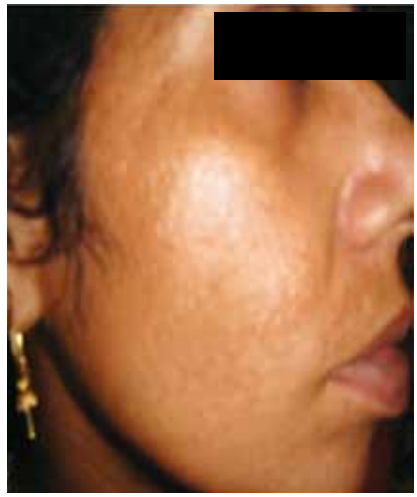


Before Treatment



After Treatment





Before Treatment

After Treatment

Fig. 13: Photographs of Patients

Conclusion

This Unani Herbal formulation, a combination therapy of majoon (MN) for oral use and powder (XM) for topical application has showed significant efficacy in melasma cases showing a positive trend, and thus provides vital information for follow-up future research.

Acknowledgement

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