The effect of the traditional medicine product "Milk-Cuscuta" on skin hyperpigmentation in patients with Melasma

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Abstract

Background: There is relatively little information pertaining to the effects of Cuscuta extract on the hyperpigmentation of the skin.

Objective: The purpose of this study is to scrutinize the effect of the Persian medicine "Milk-Cuscuta" on hyperpigmentation of the skin in patients with melasma.

Materials and Methods: In this clinical trial, 70 patients with melasma (4 men and 66 women with the age range of 18 to 65 years) were studied. The patients received the dried extract (4.8 g) with 200 gr milk daily. The treatment continued for one month and then the patients were followed-up for two months. The efficacy of the treatment was determined through the Dermacatch apparatus, Melasma Area Severity Index (MASI) score, Investigator's Global Assessment (IGA) and the patients' questionnaires; all were performed at baseline, one month and three months after the treatment.

Results: The mean of the MASI score in one month after the treatment was 5.1 ± 3.2 and in three months after the treatment was 4.6 ± 3.2. A significant difference was observed between the groups (P ≤ 0.001). At the end of the treatment, the melanin content was significantly lower in one month (529 ± 43.1) and three months (515 ± 46.1) after the treatment against the pretreatment period (555 ± 49.6; P ≤ 0.001).

Conclusions: The findings demonstrate that the consumption of the Cuscuta extract with milk can reduce the synthesis of melatonin and consequently results in the elimination of melasma.

Key words: Cuscuta, hyperpigmentation, melasma, traditional medicine

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Background

Melasma (also known as chloasma faciei) as a symmetrical skin disorder leads to the brown skin hyperpigmentation, especially in sunlight exposure areas (1, 2). The uttermost affected areas are typically found in the cheeks, forehead, and upper lip (3, 4). Melasma most occurs in the tropical regions and in all races, particularly among the Latin and Asian races (5). There are multiple factors including exposure to ultraviolet (UV) light, gestation (6, 7), genetic aptitude (8), endocrine dysfunction or hormone treatments (9, 10), and consumption of oral contraceptive tablets (11) that contribute to melasma.

Several studies reveal that melasma treatment has not been yet known as resistant to therapy (12, 13). The current treatments of melasma run the gamut from the use of broad spectrum anti-UVA and UVB opaque sunscreen such as zinc oxide, consumption of a bleaching gel, hydroquinone creams and low concentration steroids, arbutin, azelaic acid, AHA and retinoid (3, 4, 14, 15). Also, various lasers and tranexamic acid-containing oral medications are efficacious and a safe therapeutic modality for the treatment of melasma (16).

Cuscuta reflexa Roxb (Cuscuta ceae), which is known as “amarvela” or “akashbel” in the vernacular terminology, is a parasitic plant with slender yellow stems. It spreads in tropical and temperate regions and is commonly found in various regions of Bangladesh, Iran, India, China and some other countries. It grows on different host plants, mostly the thorny herbs (17, 18). The Cuscuta species has a wide range of biological activities, so its extract containing a number of α-glucosidase inhibitory compounds (18), flavanone-reflexin (19), tetrahydrofuran derivatives and coumarin (20) has been used for the treatment of various diseases (13, 20).

The current review of the literature indicates that the present study might be the first controlled clinical trial that has examined the efficacy of Cuscuta in the treatment of a hyperpigmentary disorder in humans. To this end, the effect of “Milk-Cuscuta” was surveyed on hyperpigmentation of skin in patients with melasma.

Objectives

This study aims to survey the treatment effects of a proposed Iranian traditional medicine “Milk-Cuscuta” on hyperpigmentation of the skin in patients with melasma.

Materials and Methods

1. Study population and sample size

A clinical trial was performed on 70 patients (4 males and 66 females) at the Dermatology and Stem Cell Research Center in the Tehran University of Medical Sciences, Tehran, Iran. The patients completed the questionnaires of the permanent Inventory of Individual Information (personal, physical and mental characteristics) and were treated after the initial diagnosis. Formal informed consent was obtained from all the patients prior to their enrolment. The study period was three months. The age range of female and male patients was between 18 to 65 years. The diagnosis of epidermal and normal melasma and a minimum 6-month duration of the disease were considered as the inclusion criteria.

Also, the exclusion criteria were as follows: (a) receiving oral contraceptives at the time of the study, (b) hemorrhoids, (c) hormonal disorders, (d) sunburn in the last three months, (e) laser therapy in the last three months, (f) pulmonary problems, (g) intolerance to the desired drug, (h) use of anti-staining drugs in the last three months, (i) pregnancy, and (j) clinical lactation. The evaluations were performed by the same investigators at baseline before treatment, one month after the treatment and at the end of the three months study.

At the beginning of the study, patients’ medical histories were recorded with a particular focus on the onset time of the melasma symptoms, history of pregnancy, the use of contraceptive pills, sun exposure, drug history, previous treatments for melasma, family history of melasma and other influencing or exacerbating factors. All patients were provided with a standard broad-spectrum sunscreen with the sun protection factor (SPF) ≥50. They were instructed to apply it to their entire face and to repeat the application every 3 hours during the day throughout the study period. With the approval of the Ethics Committee of Shahid Beheshti University of Medical Sciences, this study protocol was registered in the Iranian Registry of Clinical Trials (IRCT 2016030826967N1).

2. Plant material and extraction

The dried Cuscuta chinensis Lam. (Cuscuta ceae) aerial parts were purchased from the local herbal markets and authenticated by the expert botanists at the Traditional Medicine and Material Medica Research Center (TMRC) of the Shahid Beheshti University of Medical Sciences, Tehran, Iran. The Cuscuta chinensis aerial parts (77 kg) were extracted with water (90 °C, 15 min). The filtered extract was then dried by the spray dying method (Soha Jissa factory, Salmanshahr, Iran). The dried extract (4.8 g) was packed in the containers to be used in the clinical trial.

3. The quality control evaluation

The quality control analyses of the plant material were implemented according to the Unani Pharmacopoeia of India (21). The total phenolic contents of the aerial parts and the extract of the dried Cuscuta chinensis were also determined spectrophotometrically by using the Folin-Ciocalteu reagent (22). The thin layer chromatographic evaluation of the extract was performed and the relative retention factors (Rfs) were compared to those reported in the reference (21). The extract was checked for microbial contamination according to the WHO quality control methods for the medicinal plant materials (23).

4. Clinical assessment

First, all the eligible patients were interviewed and informed about the research objectives. Clinical evaluations and evaluation of the Melasma Area Severity Index (MASI) scores were performed by the same investigators at baseline, one month, and three months after the treatment. The MASI score was then calculated based on the Kimbrough–Green equation (24).

The criteria for clinical improvement of the patients were delineated by the physicians. The patient's consent, the measurement of the contents of melanin and hemoglobin on the melasma affected skin, which determines the degree of hyperpigmentation and erythema of the skin, were carried out by the Dermacatch (25). The mean of the MASI scores were calculated by the same investigators for all patients. To gauge the patients' viewpoints and attitudes towards the efficacy of the treatment, they were requested to select an item on the list that best described the effect of Cuscuta on their melasma lesions (the list being the same as the investigator's assessment list). The Investigator's Global Assessment (IGA) was performed in accordance with Lee's scoring system (26) . The categories included :1) no effect (i.e. no visible changes of pigmentation), 2) mild (visible decrease of pigmentation but still some visible border), 3) moderate (marked decrease of visible pigmentation, but still some visible border), and 4) excellent (complete loss of visible abnormal pigmentation).

5. Statistical analysis

All the analyses were carried out using SPSS version 20. The p-value ≤ 0.05 was considered to indicate the statistical significance. For the comparison of both the MASI scores and the Dermacatch measurements in each drug group and since the data were found to be normally distributed, an independent t-test was used. The normality was assessed by the Kolmogorov–Smirnov test and the grades in objective assessment were compared using the Mann –Whitney test.

Results

1. Baseline patient characteristics and demographic data

After evaluating 90 patients, 20 patients were omitted in two stages of the study because of issues like bloating, nausea, personal issues and/or non-adherence to the treatment. The flow diagram of the contributors in the trial based on the CONSORT guidelines is shown in Figure 1. The mean age of the patients was 41.5± 8.6, ranging from 18 to 65 years. The percent of participating females and males were 94.3% and 5.7%, respectively (Table 1).

2. The quality control assessment

The results of the quality control evaluation of Cuscuta chinensis displayed that the assessed parameters including total Ash (8.20%), acid insoluble ash (6.35%), alcohol soluble extractive (13.16%), water soluble extractive (16.00%), total phenol (pyrogallol equivalent per 100g plant material, 462.16±18.20 mg), total phenol (pyrogallol equivalent per 100g plant material, 462.16±18.20 mg), and total phenol (pyrogallol equivalent per 100g plant material, 5.36±0.18 g) were in acceptable limits (Table 2). The Rfs from the thin layer chromatography of the plant (according to the Pharmacopoeia of India) were similar to those of the references. Also, the microbial quality control of the extract did not signify any contamination of oral pathogens and could therefore be used by the patients in the present study (Table 3).

3. Clinical evaluation

The IGA scores and patients' viewpoints on efficacy at the end of the study are specified in Table 4. The mean of the MASI scores before treatment and one month after the treatment were 7.5 ± 3.99 and 5.1± 3.2, respectively (Figure 2). There was a significant difference between two groups (p=0.001). At the end of the treatment period (i.e. after three months of treatment), the mean of the MASI scores was 4.6 ± 3.2 in the Cuscuta receiving group; the difference was meaningfully remarkable in comparison with before-treatment group (p< 0.0001). The mean of the MASI scores were not considerably different after three month of treatment compared with those elicited after one months of treatment (p= 0.6), which confirmed the stability of the treatment.

With the use of the Dermacatch, the mean differences in the melanin content of the lesions and the surrounding normal areas were calculated before treatment, after one month's treatment, and after two months follow-up (Figure 3). Statistically significant differences were found between the groups that received Cuscuta before treatment (556 ± 49.6) compared to the one-month group (529.2 ± 43.2) with a p≤ 0.002 (Figure 3). The mean melanin content was 515.2 ± 46.11 at the termination of the study (after three months of treatment); so the meaningful difference was observed in comparison with the before treatment period (p≤ 0•0001).

The effect of Cuscuta was studied in the treating cyclophosphamide-induced alopecia in mice, which resulted in hair growth of the mice and proliferation of active hair follicles (28).

Table 1. Baseline patient and demographic characteristics

Variables	
Age (mean ± SD)	41.5± 8.637
Gender *n* (%) Male Female	 4 (5.7%) 66 (94.3%)
Duration of melasma (month), mean ± SD	50.34 ± 27.78

Table 2. The quality control assessment of the plant material and the extract.

Assay	Results	Acceptable limit [2]
Total Ash	8.20%	Not more than 10%
Acid insoluble ash	6.35%	Not more than 9%
Alcohol soluble extractive	13.16%	Not less than 9%
Water soluble extractive	16.00%	Not less than 16%
Total phenol (pyrogallol equivalent Per 100g plant material)	462.16±18.20 mg	-
*Total phenol (pyrogallol equivalent per 100g extract)	5.36±0.18 g	-

Table 3. The microbial quality control of Cuscuta chinensis spray dried extract.

	Staphylococcus aureus	Pseudomonas aeruginosa	Salmonella	Escherichia coli	Total aerobic bacterial count (CFU/g	Total fungi count (CFU/g)	enterobacteria (bile tolerant) per g/ml of material
C. chinensis extract	-	-	-	-	-	-	≤1

Table 4. The hyperpigmentation decrease grading in the Cuscuta receiving group assessed by the investigators and patients

Hypopigmentation grading	Investigator's Global Assessment	Patient's viewpoint
No effect	2 (3%)	1 (1.5%)
Mild	24 (34%)	17 (25%)
Moderate	43 (61.5%)	38 (54%)
Excellent	1 (1.5%)	14 (19.5%)

Figure 1.The flow diagram of the contributors in the trial based on the CONSORT guidelines

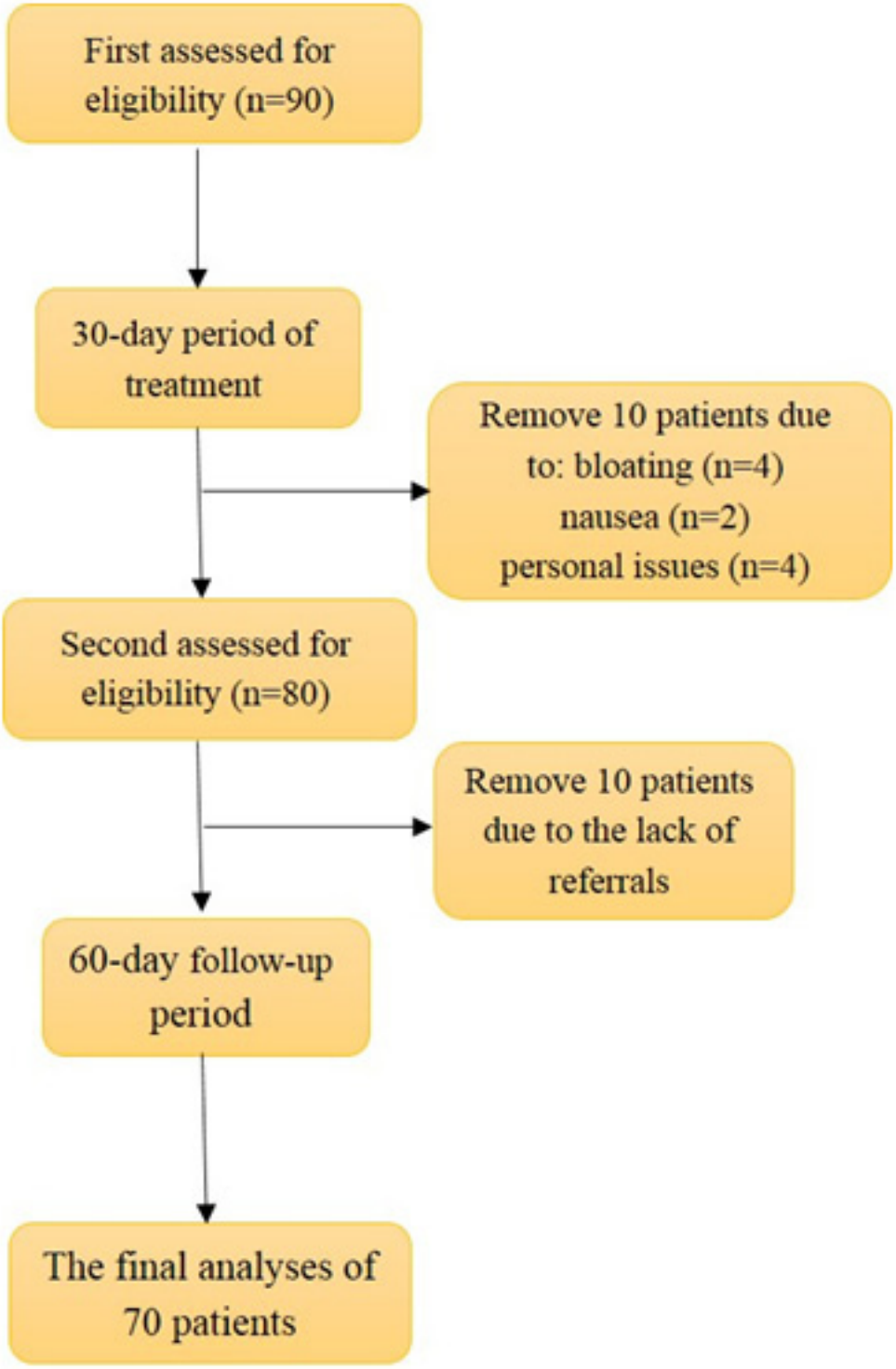


Figure 2: The MASI score before treatment, after one month's treatment, and after three months' follow-up.

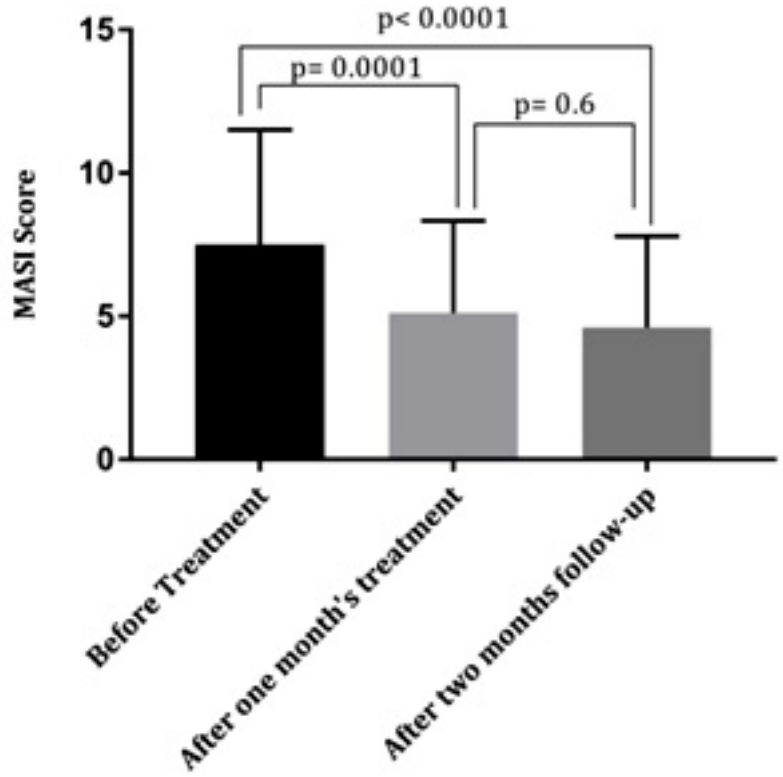
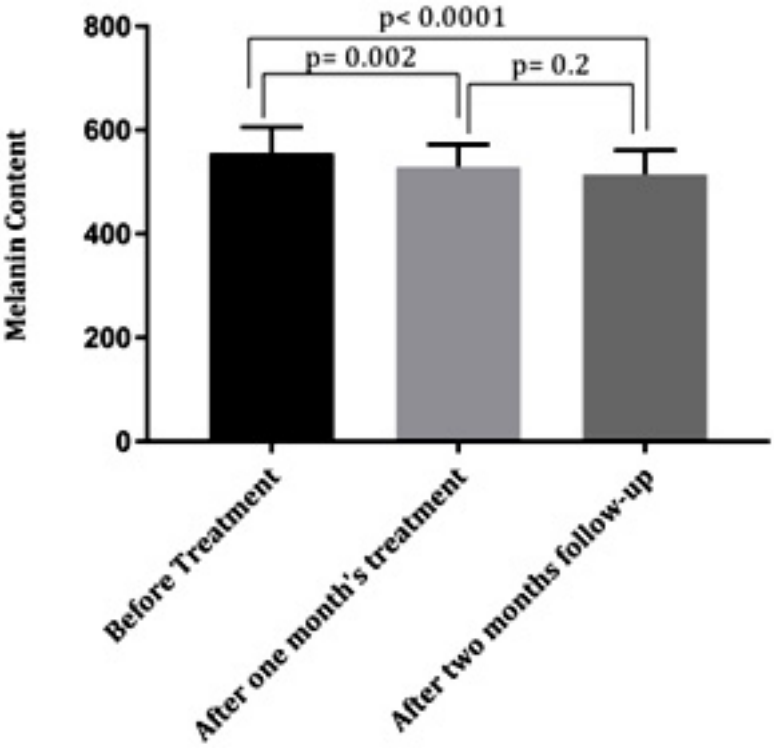


Figure 3: The melanin content of skin using Dermacatch before treatment, after one month's treatment, and after three months' follow-up.



Discussion

The present study reveals that the consumption of Cuscuta extract with milk seemed to ameliorate and decrease the hyperpigmentation in the patients with melasma. Furthermore, the reduction of melasma after two months from consumption of Cuscuta extract showed that the Cuscuta extract shrinks the melanin synthesis. The study is in accordance with the previously published works as well.

Yeon Jung and colleagues have reported that the aqueous fraction from Semen Cuscutae (AFSC) wards off the p38 microphthalmia-associated transcription factor (MAPK), phosphorylation with suppressed cAMP levels and subsequently down-regulates the microphthalmia-associated transcription factor (MITF) and tyrosinase-related protein (TRP) expression. Therefore, their findings revealed that they caused a marked reduction of melanin synthesis and tyrosinase activity in the α-MSH-stimulated B16F10 cells (27).

The effect of Cuscuta was studied in the treating cyclophosphamide-induced alopecia in mice, which resulted in hair growth of the mice and proliferation of active hair follicles (28).

Another study reported that the ethanol extract of Cuscuta reflexa Roxb has some potential antihistaminic properties (29). It has been also stated that the consumption of whey, together with field dodder, can target the quintessential pathophysiological facets of the atopic dermatitis by reducing inflammation, aiding immunomodulation, improving the skin lesions and modifying the skin barrier function. This amalgam can also be used as a complementary treatment for the atopic dermatitis with minimum ramifications for reducing the intensity and frequency of attacks (30).

Moreover, the milk protein proffered some advantages in controlling the atopic dermatitis. The milk protein stimulated the osteoblast proliferation and differentiation and is able to reduce the risk of the osteoporosis and osteopenia developments due to the inflammatory nature of the diseases and the long-term consumption of corticosteroids (31-33).

In addition, the treatment of melasma is severe, prolonged and symptomatic (34). It has long been identified that Cuscuta reflexa comprises a number of compounds like flavonoids, kaempferol, quercitin, coumarins and flavonoid glycosides (19). Also, since quercetin is one of the derivatives of Cuscuta, it can block the intermediate materials involved in the allergies and can act as an inhibitor of the mast cell secretion which is a factor of paramount importance in the pathogenesis of atopic dermatitis attacks (35). The Cuscuta aqueous extract can be effective in the prevention and the treatment of various cancers, especially papilloma and skin cancers (36). Other studies also have found that the consumption of some kinds of food as well as the soda-extracting herbal medicines such as Curainia Sophia, fumitory, Polypodium vulgare, Aftimon and eating terminalia Chebula can reduce melasma (37). It would not go amiss to state the fact that in some studies, the anti-melanogenic effects of Cuscuta have been investigated in vitro on mouse melanoma; so, it can be construed that by suppressing cAmp, they decreased the activity of tyrosine and the synthesis of melanin (27).

The findings of the current research reveals that the treatment with Cuscuta met the requisite primary upshot of diminishing the melanin content of the lesions after 1 and 2 months follow-up. The consumption of Cuscuta extract with milk can reduce the synthesis of melanin and ameliorate the elimination of melasma.

It is hoped that the clinical trials such as the present one will be conducted in the near future to pave the way to determine more cogently and accurately the depigmentation efficacy of Cuscuta in comparison with other known skin depigmentation compounds in humans.

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