Chapter 2

Evaluation of *Glycyrrhiza glabra* Cream as Treatment for Melasma

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1. Introduction

Melasma is a common cosmetic problem in our community [1], with social and psychological burden. It is a disorder of pigmentary system characterized by irregular brown or grayish-brown, acquired hypermelanosis of sun-exposed areas especially the face [2]. Many preparations were used for treatment of melasma, but none of them was ideal [3].

Researchers recently are more involved in performing a research that evaluated the therapeutic effects of formulation that with active substance of plant origin [4]

Recently, topical polyherbal formulations are the latest additions to the treatment approaches list of melasma, with a reducing and diverting the production of melanin [5]. The therapeutic effect of such preparation was enhanced when cosmetic emulsion contained antioxidants are used as active ingredients [6]. Natural herbs are a rich source of many antioxidatively acting compounds [7]. *Glycyrrhiza glabra* is a medicinal plant with rich natural antioxidants [8].The best natural antioxidants in extract of *Glycyrrhiza glabra* are glycyrrhizin (glycyrrhizic acid) and flavonoids [9]. The role of plant extract of *Glycyrrhiza glabra* on skin is mainly attributed to its antioxidant activity particularly to its potent antioxidants triterpene, saponins and flavonoids [10]. G. glabra extract are with therapeutic effects in skin whitening [11], skin depigmenting [12], skin lightening [3], antiaging [14], anti-erythemic [14], emollient [15], anti-acne [16] and photoprotection effects [17,18]. A 2.5% G. glabra extract cream was formulated and it was with

sound chemical and physical stability [19]. In this study, 2.5% of G. glabra extract was evaluated as treatment of melasma in female.

2. Materials and methods

2.1. Study design

Double blind placebo controlled study. The study population stratified to active or placebo treatment randomly. The female with even code number receiving cream with active ingredient while female with odd code number receiving placebo. The cream distributed by a pharmacist, while the clinical evaluation was performed by a dermatologist clinician.

2.2. Study population

Hundred female volunteers were enrolled in this study between the ages of 20 and 45 years. They were recruited from Dermatology Clinic in Samarra Teaching Hospital and daily dermatology clinics. Prior to the tests, the volunteers were examined for any serious skin disease or damage especially on cheeks and forearms. Before the study, every volunteer was provided with a volunteer protocol. This protocol stating the terms and conditions of the testing were to be signed by every volunteer individually. Blood samples were collected from the 100 volunteer females suffering from melasma.They were diagnosed by consultant dermatologists. Wood's lamp (340-400) nm was used to identify the types of melasma whether epidermal, dermal or mixed (dermoepidermal). Of the total 76%were married and 24% were single. Serum of the patients and controls were investigated for levels of TSH, estrogen, progesterone, prolactin, ALT (SGPT), AST (SGOT), total protein, blood urea and S. albumin before and after treatment.

The history as well as personal information about patients was obtained by questionnaire. Volunteers were not informed about the contents of formulations. All the skin tests have been done at 25°C. Erythema of the skin are determined on the first day before application of any cream and then on days 7, 14, 21 and 28 after treatment. Fifty female from patients group received the treatment for 28 days, 7 patients were lost to follow up. The above parameters for forty three patients were determined after treatment. As well as fifty female suffering from melasma took the placebo, the same above parameters were measured before and after treatment.

None of the patients or control subjects was on any oral and/or local medication. The pregnant and lactating females or patients on any hormonal therapy (contraceptive pills) were excluded from the study. Patients with other systemic diseases like diabetes, hypertension, or on drugs for any underlying disease were also excluded.

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2.3. Formulation

Water in oil (W/O) active cream (2.5% G. glabra) and base were prepared as described previously [19].

3. Results

3.1. Age and marital status

A 100 female suffering from melasma, 93 completed the study while 7 patients were lost to follow up. The distribution of these two groups is shown in Table (1). They were divided into 3 age groups. The highest percentages (50%) and (56%) were found in the age group of (30-39) years for active cream and control patient groups respectively. The lowest percentage of incidence for active treatment females was (12%) in the age group of (40-50) years, and for control, the lowest percentage was (4%) in the age group of (40-50) years. The highest incidence of melasma was found in married women than in singles of both groups, Table (1).

	Formulation			**Placebo**		
Age group	Married (%)	Single (%)	Total (%)	Married (%)	Single (%)	Total (%)
(20-30)	13 (26%)	6 (12%)	19 (38%)	16 (32%)	4 (8%)	20 (40%)
(30-40)	22 (44%)	3 (6%)	25 (50%)	20 (40%)	8 (16%)	28 (56%)
(40-50)	6 (12%)	0 (0%)	6 (12%)	2 (4%)	0 (0%)	2 (4%)
Total	41 (82%)	9 (18%)	50 (100%)	38 (76%)	12 (24%)	50 (100%)

Table 1. Distribution of melasma percentage in females according to age and marital status.

3.2. Clinical response

Comparison between formulation treated group and placebo treated group indicated a significant differences for overall response to treatment. The improvement in active treatment group was 93% (40/43), while the corresponding value in placebo treated group was 4% (2/50), (P=0.001). Table 2. The effect of the formulated cream was demonstrated from the 1st week of treatment course (6.9%), with subsequent increase in improvement rate for week 2 (20.9%), week 3 (30.2%) and week 4 (34.8%)(P=0.007).

Variable		Number improved [%]				P value
		Formulation [43 Patient]		Placebo [50 subject]		
		Weekly improved	Cumulative improvement	Weekly improved	**Cumulative improvement**	
Treatment period	Week 1	3 [6.9]	3 [6.9]	0 [0]	0 [0]	0.18
	Week 2	9 [20.9]	12 [27.9]	1 [2]	1 [2]	0.009
	Week 3	13 [30.2]	25 [58.13]	1 [2]	2 [4]	0.005
	Week 4	15 [34.8]	40 [93.00]	0 [0]	2 [4]	0.001
P value		0.007		0.58		
Total response [%]		40 [93]		2 [4]		0.001
No response [%]		3 [6.9]		48 [96]		

Table 2. Clinical results of studied and control females with melasma after treatment with the product.

Comparison between the active treated cream and placebo on week interval indicated anon significant improvement for the first week of the treatment course (P=0.18). However, there was a significant difference in the improvement rate between the two treatment groups for week 2 (P=0.009), week 3 (P=0.005) and week 4 (P=0.001), Table 2.

4. Discussion

This clinical trial indicated that 2.5% G. glabra cream was effective as treatment for melasma in a 28 days course with minimal side effects. However, this finding needs to be strengthening in a large scale clinical trial. Licorice is an extract with an important depigmenting property, obtained from *Glycyrrhiza glabra.* Known as "alcacus", it contains many compounds, of which saponins and flavonoids have the greatest antiphlogistic action [20]. In mouse cell culture, it was observed that Licorice has glabridine, the main component of the hydrophobic fraction of the extract, with the ability to inhibit tyrosinase without affecting DNA synthesis. The *in vivo* results were compatible with those *in vitro,* and immunohistochemical analysis showed a reduction of DOPA-positive melanocytes [21]. Moreover, Licorice has anti-inflammatory action by inhibiting some enzymes of the arachidonic acid cascade, especially cyclooxigenase, released after exposure to UV rays [22]. Due to these properties, glabridine is an important depigmenting component of the extract.

Nonetheless, Licorice has other components with depigmenting effects, such as liquiritin, which disperses melanin. In addition, Licorice has other active ingredient which exert antioxidant activity and thus Licorice cosmetic properties are attributed to its wide spectrum of antioxidant activity [23].Ultraviolet radiation in the skin leads to the formation of peroxides that induce the development of free radicals [24]. Certain licorice constituents possess

significant antioxidant properties. Glycyrrhizin and glabridin inhibit the generation of reactive oxygen species (ROS) by neutrophils at the site of inflammation [6].

Traditionally, the use of depigmenting topical substances is without a doubt the best therapeutic option for the clinical treatment of melasma. Hydroquinone, although having some disadvantages, is the most used therapeutic alternative. [25,26] Nonetheless, many other substances, mostly of plant origin, have become more popular in dermatologic treatment [27]. In this study, the use of 2.5% *G. glabra* extract cream shows a reduction in melasma depending on digital evaluation and size of the lesion.

This study strengthens the clinical benefits of the *G. glabra* extract substances in the literature due to their melanin-dependent action (inhibiting tyrosinase, depleting or preventing the migration of melanosomes) and/or free radical-dependent action (melanogenic inhibition by preventing radical action on the melanocytes). The active group showed a reduction in the absolute number of lesions, according to the results obtained by digital photographic imaging, with significant statistical differences between the active and placebo group.

The adverse effects observed in both groups (Active and placebo) were well tolerated, spontaneously regressing with the use of the products. We observed, however, that these effects were less noticed in women using our formulation as only one lady developed allergic contact dermatitis. However, the side effect in the present study was less than that reported in subjects using hydroquinone (2%) [28]. Such data suggest the higher safety of *G. glabra* extract at 2.5% concentration product used by our patients as compared with hydroquinone, whose degree of tolerance has already been questioned in the literature [26,29].

The superiority of this greater depigmenting tendency could be better assessed in a prospective clinical study with a higher number of volunteers. Thus this study indicates that, depending on the concentrations used, plant extracts can be as efficient as hydroquinone in the treatment of melasma, without the side effect of hydroquinone. This confirms the viability of future competitive clinical studies to accurately elucidate a possible clinical superiority and ratify a tendency of higher tolerability of this new depigmenting alternative. In addition, combination of G. glabra extract with sun screen in a single formulated is recommended.

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