

Antihirsutism activity of Fennel (fruits of *Foeniculum vulgare*) extract

A double-blind placebo controlled study

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Summary

Idiopathic hirsutism is defined as the occurrence of excessive male pattern hair growth in women who have a normal ovulatory menstrual cycle and normal levels of serum androgens. It may be a disorder of peripheral androgen metabolism.

In this study we evaluated the clinical response of idiopathic hirsutism to topical Fennel extract. Fennel, *Foeniculum vulgare*, is a plant, which has been used as an estrogenic agent. The ethanolic extract of Fennel was obtained by using a soxhlete apparatus. In a double blind study, 38 patients were treated with creams containing 1%, 2% of Fennel extract and placebo. Hair diameter was measured and rate of growth was considered.

The efficacy of treatment with the cream containing 2% Fennel is better than the cream containing 1% Fennel and these two were more potent than placebo. The mean values of hair diameter reduction was 7.8%, 18.3% and –0.5% for patients receiving the creams containing 1%, 2% and 0% (placebo) respectively.

Key words: *Foeniculum vulgare*, Fennel, hirsutism, estrogenic activity

■ Introduction

Clinical and laboratory hyperandrogenism is present in many dermatologic diseases including acne, hirsutism, androgenetic alopecia, hidradenitis suppurativa. In some, hyperandrogenism is found in routine screening of serum levels of adrenal or gonadal androgens. In idiopathic hirsutism, though hyperandrogenism is present, serum androgen levels are normal. One postulated cause is end organ hypersensitivity. 5- α -reductase, the enzyme responsible for reducing testosterone to its functionally active form, dihydrotestosterone (DHT) may be hyperactive (Fine, 1989). Therapy targeting at blocking this enzyme at the effector site, the hair, may be helpful (Ebling, 1979). To avoid known side effects of antiandrogens such as menstrual irregularities or breast tension, attempts have been made to prepare

creams which enable the active substance to be applied locally has been done (Nielson, 1982). In our literature review, we could not find any natural or herbal medicine to treat hirsutism. *Foeniculum vulgare* (Fennel), has a long history of medicinal use. It has been reputed to increase milk secretion, promote menstruation, facilitate birth and increase libido. The main constituent of the essential oil of Fennel, trans-anethol, dianethol and further oligomers with their estrogenic effect are described to be the actual pharmacologically active agents of the plant (Puelo, 1980). Fig. 1. shows the similarity of the structure of anethol and dianethol with diethylstilbestrol. This led us to investigate the effect of topical use of Fennel extract on hair growth in patients with idiopathic hirsutism.

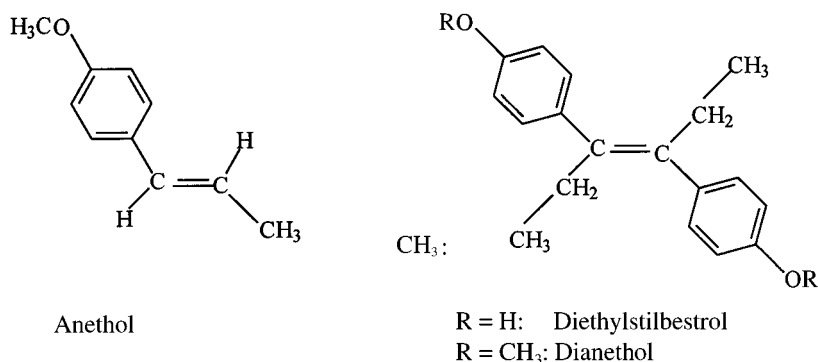


Fig. 1. Structure of anethol, dianethol and diethylstilbestrol.

Methods

Plant material

Foeniculum vulgare seeds (Fennel) were obtained from herbal medicine stores and identified by Dep. of Botany, Shiraz University. Crushed seeds were extracted with ethanol in a soxhlete apparatus for 5 hours. The solvent was removed under reduced pressure (yield-8%). The anethol content of the extract was determined by gas chromatography.

Pharmaceutical preparation

Stearic acid, cetyl alcohol, paraffin, glycerin, potassium hydroxide, methyl and propyl paraben were used in preparation of creams containing 1% and 2% Fennel extract. All of them were of pharmaceutical grade. The stability of the cream was assessed for 4 months.

Dermatotoxicity assessment

The cream containing 10% Fennel extract was prepared. Six rats were chosen and their skin was shaved in 3 places about 1 × 1 cm. The cream with a high concentration of Fennel was used topically on the shaved regions for 4 months. The rats were anaesthetized with chloroform and samples of the skin were studied for observing any evidence of toxicity or irritation.

Clinical measurements

The study protocol was approved by the Faculty of Pharmacy, Shiraz University of Medical Sciences. After obtaining a written consent, forty-five female patients aged 16–53 years (mean age 29 years) with mild to moderate forms of idiopathic hirsutism localized to the face were enrolled in the study. None had polycystic ovaries and all of them had serum androgen levels within the normal range. The degree of hirsutism was assessed by modified Ferriman-Gallwey method (limited sites scored to upper lip, chin and sides of face, determining 5 grades, zero to four for each site (Ferriman et al. 1961). In this double blind study, the patients were randomly assigned to three groups with the aid of

Table 1. Baseline characteristics of three study groups.

group no. (no. of patients)	average age	area involved			average hair diameter
		chin	cheek	upperlip	
1 (11)	29	7	2	2	67.5
2 (15)	32	10	7	4	59.9
3 (12)	27	6	3	3	55.8

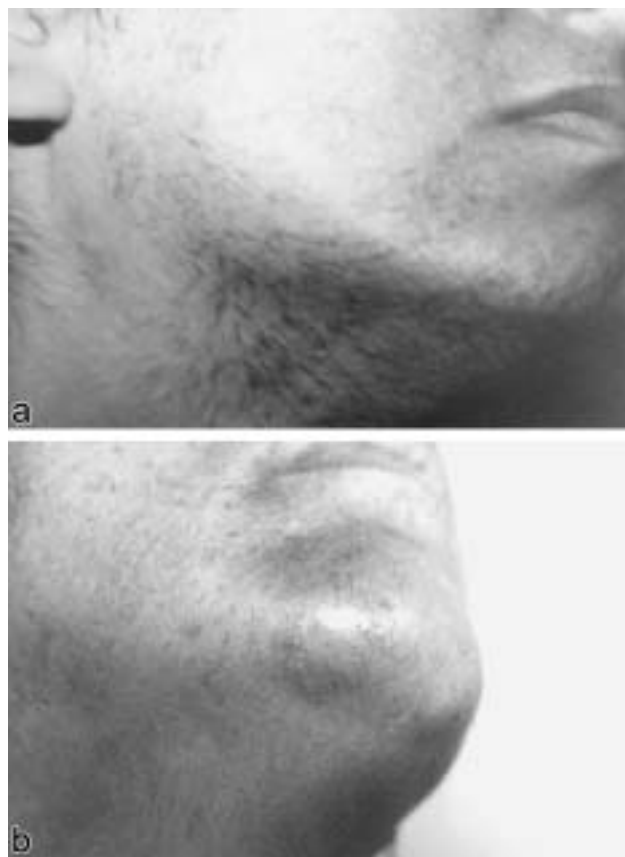


Fig. 2. A patient with facial hirsutism before (a) and after (b) treatment with Fennel.

random number table (15 patients in each group). There were no significant differences in baseline characteristics among the three treatment groups (Table 1). Group no. 1. was treated with a cream containing 1% Fennel extract, Group no. 2 was given a cream containing 2% Fennel extract and Group no. 3 received placebo, which was the vehicle of the cream without fennel extract. The duration of treatment was 12 weeks and the patients used the cream twice a day on their face. The patients were allowed to epilate and the interval between necessary epilations served as an indirect measurement of hair growth rate. Examinations were performed every 4 weeks and patient's subjective satisfaction was recorded. Density and hair growth were

noted clinically and hair diameters were measured with a micrometer with 0.1 micrometer sensitivity.

■ Results and Discussion

Of the 45 patients who entered the study, 38 patients completed the study and 7 were missed in follow-up (4 in group 1 and three in group 3). Baseline characteristics of three study groups were shown in Table 1. The first sign of clinical efficacy of treatment was reduction in hair growth (decreased frequency of epilation). The rate of hair growth was only reduced in the the two groups treated with 1% and 2% of Fennel cream com-

Table 2. Reduction of hair diameters in patients treated with 1% concentration of Fennel extract.

Patient no.	Area	Duration of therapy (weeks)	Initial diameter (µm)	final diameter (µm)	Reduction (%)	Average reduction (reduction/week) %
1	chin	12	65.3	59.1	9.5	0.8
2	chin	12	69.0	61.3	11.2	0.9
3	chin	12	72.4	71.1	4.7	0.4
4	chin	12	59.0	52.5	11.0	0.9
5	cheek	12	49.8	45.5	8.6	0.7
6	upperlip	12	72.7	65.6	10.0	0.8
7	chin	12	73.0	71.8	1.6	0.1
8	upperlip	12	52.6	46.0	12.5	1.0
9	chin	12	68.8	64.3	6.5	0.5
10	cheek	12	76.5	70.2	8.4	0.6
11	chin	12	83.1	81.6	1.8	0.1

Table 3. Reduction of hair diameters in patients treated with 2% concentration of Fennel extract.

Patient no.	Area	Duration of therapy (weeks)	Initial diameter (µm)	final diameter (µm)	Reduction (%)	Average reduction (reduction/week) %
1	chin	12	70.3	60.7	13.6	1.1
2	chin	12	67.5	53.0	21.0	1.8
3	chin	12	56.0	48.0	14.3	1.2
4	chin	12	54.4	43.1	20.8	1.7
5	chin	12	62.0	49.0	21.0	1.7
6	chin	12	64.0	57.1	11.6	0.9
7	chin	12	70.0	60.5	13.6	1.1
8	upperlip	12	48.1	32.3	32.8	2.7
9	chin	12	53.0	47.9	9.6	0.8
10	chin	12	67.4	60.0	11.0	0.9
11	chin	12	50.4	34.4	29.4	2.4
12	upperlip	12	78.5	65.3	16.8	1.4
13	cheek	12	45.0	30.2	32.9	2.7
14	upperlip	12	61.2	48.4	20.9	1.7
15	upperlip	12	51.0	48.2	5.5	0.5

Table 4. Reduction of hair diameters in patients treated with placebo.

Patient no.	Area	Duration of therapy (weeks)	Initial diameter (μm)	final diameter (μm)	Reduction (%)	Average reduction (reduction/week) %
1	chin	12	53.8	55.0	-2.2	-0.1
2	chin	12	65.6	66.0	-0.6	0.0
3	upperlip	8	69.5	69.3	0.2	0.0
4	cheek	8	44.8	46.5	-3.7	0.4
5	chin	8	47.5	48.5	-2.1	0.2
6	cheek	8	65.9	65.7	0.3	0.0
7	cheek	8	44.5	44.0	1.1	0.1
8	upperlip	8	57.8	56.3	2.6	0.2
9	upperlip	8	45.3	45.0	0.6	-0.1
10	chin	8	62.8	63.6	-1.2	-0.1
11	chin	8	65.7	64.3	2.1	0.3
12	chin	8	46.5	48.2	-3.6	-0.4

pared to group received placebo. Hair diameter from the facial area was measured in all three groups and the results for each patient are shown in Tables 2–4. These data were analysed with analysis of variance and LSD with a significant level of $\alpha = 0.01$. The mean value of reduction of hair diameter was 7.8% (SD = 3.7), 18.3% (SD = 8.3) and -0.5% (SD = 2.1) for patients who received the creams containing 1%, 2% and 0% (placebo) respectively. The P-value between three groups were 0.000524 (between the patients who received 2% and 1% of Fennel extract), 8.05×10^{-5} (between the patients who received 1% Fennel extract and placebo) and 4.96×10^{-7} (between the patients who received 2% Fennel extract and placebo). These results show that the best clinical efficacy was achieved with the cream containing 2% Fennel (Fig. 2). During the treatment period no adverse effects were observed. The mechanism of action is not clear, but it can be due to the presence of anethol, di-anethol and its polymers in the Fennel extract, showing variable estrogenic activity. In a recent study, it was found that estrogens are able to inhibit the synthesis of DHT in dermal papillae by directly inhibiting 5- α -reductase or by increasing conversion of testosterone to weaker androgens and diminishing the amount of testosterone available for conversion to DHT (Niyama et al. 2001). In conclusion, the Fennel extract is safe with no adverse effect in topical application and can be re-introduced into modern medical usage and as presented here in the treatment of hirsutism. Although it apparently caused hair diameter reduction and good patient satisfaction, further larger randomized trials and a standardization of the Fennel extract are warrant.

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