Original Article

The effect of fennel (*Foeniculum vulgare*) gel 3% in decreasing hair thickness in idiopathic mild to moderate hirsutism, A randomized placebo controlled clinical trial

Ozra Akha (MD) [1]
Khadijeh Rabiei (MD) [*2]
Zahra Kashi (MD) [1]
Adele Bahar (MD) [1]
Elham Zaeif-Khorasani (MD) [1]
Mehrnoush Kosaryan (MD) [3]
Majid Saeedi (PhD) [4]
Mohammad Ali Ebrahimzadeh (PhD) [5]
Omid Emadian (MD) [6]

1- Diabetes research Center, Mazandaran University of Medical Sciences, Sari, Iran.
2- Traditional and Complementary Medicine Research Center, Mazandaran University of Medical Sciences, Sari, Iran.
3- Thalassemia Research Center, Mazandaran University of Medical Sciences, Sari, Iran.
4- Department of Pharmaceutics, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran.
5- Department of Medicinal Chemistry, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran.
6- Department of Pathology, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran.

*** Correspondence:**
Khadijeh Rabiei, Traditional and Complementary Medicine Research Center, Mazandaran University of Medical Sciences, Sari, Iran.

E-mail: mprabie@yahoo.com
Tel: 0098 151 3244893
Fax: 0098 151 3244893

Received: 29 April 2013
Revised: 5 Sep 2013
Accepted: 2 Oct 2013

Abstract

Background: Hirsutism is a common symptom presenting to primary care endocrinologists, gynecologists, and dermatologists. Management is usually a long and troublesome process. This study was designed to evaluate the effect of fennel topical gel on mild to moderate idiopathic hirsutism.

Methods: The randomized, double-blind, placebo-controlled clinical trial was carried out from 2009 to 2011, in Sari, Iran. Forty four women with mild to moderate idiopathic hirsutism were randomly divided to case and control groups, each group included 22 cases. The case group received fennel gel 3% and the control group received placebo. The effect of fennel gel 3% was defined as reduction of thickness of facial hair in micrometer by microscope in comparison with placebo. Measurements were performed at zero time and 24 weeks after treatment. This study was registered in the Iranian Registry of Clinical Trial (www.irct.ir) with registration number 138901213672N1.

Results: The mean age of patients was 26.9±6.7 and 25.6±4.3 years in case and control groups, respectively. Hair thickness was similar between the two groups before intervention. The hair thickness reduced from 97.9±31.5 to 75.6±26.7 micron in patients receiving fennel gel after 24 weeks ($P<0.001$). Four patients complained of itching (3 in case group) and 4 patients complained of irritation and itching (3 in case group). However, this difference was not statistically significant.

Conclusion: The study indicated that fennel gel 3% is effective in decreasing hair thickness in women with idiopathic mild to moderate hirsutism.

Keywords: Idiopathic Hirsutism, Gel, *Foeniculum vulgare* (fennel), Hair thickness.

Citation:
Akha O, Rabiei KH, Kashi Z, et al. The effect of Fennel (*Foeniculum vulgare*) gel 3% in decreasing hair thickness in idiopathic mild to moderate hirsultism, a randomized placebo controlled clinical trial. Caspian J Intern Med 2014; 5(1): 26-29.

Caspian J Intern Med 2014; 5(1): 26-29

Idiopathic hirsutism is defined as the growth of androgen-sensitive hair in areas where these are naturally absent (1-3). Usually no reason is found for this complaint (idiopathic) and that is why there is no definite treatment for it (4). Therefore, depending on the severity of this problem, frequent use of various depilation methods (temporarily/permanent) is required. Hormonal therapies such as anti-androgenic agents, also have transient effects and notable cost and side effects (5). Fennel (*Foeniculum vulgare*) is edible, cheap and a native plant of Iran, used as spice or herbal remedies without important side effects (6-8). The most popular part of the plant is its seed; however, leaves and stalk are being used as pickles, too. The amount of the chemical compounds of fennel essence is quite different, based on plant variety and its origin (9-10).

The essential oil of fruits contains, d-α pinene, camaphene, d-α phellanderin, dipentene, trans-anethole, d-fenchone, estragolefoeniculin, anisaldehyde and several alkaline compounds which cause its peculiar smell. The main chemical compounds of fennel include: trans-anethol, di-anethol with their estrogenic effect (11-13). It is also used to induce sputum and urine production and also increases lactation. Fennel is also used as antimicrobial agent- for example, in treating gum inflammation (14- 16). It has been said that fennel was used to treat anorexia, colic, amenorrhoea, dysmenorrhea, diarrhea, nausea, cold and coughs (17-18). Fennel fruit possesses a kind of estrogenic effect and causes weight gain (14, 19). Fennel probably has antispasmodic effects via acetylcholine and histamine molecules (15). As traditional temporarily depilation techniques were hard to be matched between patients, fennel extract was compared to placebo in the women suffering from mild to moderate idiopathic hirsutism.

Methods

This randomized, double-blind, placebo-controlled clinical trial was carried out from 2009 to 2011. Patients with mild to moderate idiopathic hirsutism limited to face (upper lip, check and chin) and aged 15- 45 years old were entered in the study. Randomization was according to sequential entering into two matched blocks for 15-30 and 31-45 years of age. In each block, there were 26 places randomly assigned for drug or placebo. Each new patient had to occupy the next available place. A pharmacy technician who was responsible for dispersion of bottles was aware. No other member of team was aware of type of the dispersed bottle. Modified Ferriman- Gallwey scoring system was used for case selection (1). The primary outcome was the changes in hair thickness. The effect was evaluated by comparing hair thickness before and after intervening blindly by a pathologist with a microscope (Nikon made in Germany with accuracy of 0.1 micrometer). The possible side effects of treatment including redness, itching and burning sensation were the secondary outcome.

Fennel gel 3% and placebo were prepared and used freshly in similar-coded containers. This project was approved by the Ethics Committee of and the registration (IRCT: 138901213672N1) was allocated to this project by Iranian Registration of Clinical Trial. Exclusion criteria were; increased serum androgen level, irregular menstrual cycle, severe hirsutism, history of using spironolactone, cyproterone acetate, cyproterone compound, corticosteroids, medroxy progesterone acetate, contraceptive pills. Also, pregnant and lactating women, as well as patients who used Laser therapy for hair depilation during the previous 6 months were excluded. Sample size was calculated for the study power of 80%, probability of 95% and the predicted difference of 20% in reducing hair thickness between groups. A written consent form was signed by the participants. Duration of follow up was 24 weeks. In a running period of 48 hours, fennel gel was applied to a small area of the forearm skin for detection of any side effects. The following chemicals were used as received from the suppliers. Methyl and propyl paraben, PEG 200, PEG 300, PEG 400, isopropyl alcohol, glycerin, ethanol, triethanolamine (Merck, Germany), and Carbopol 934P (BF. Goodrich, USA).

Plant material and extraction: The fennel seeds were purchased from herbal medicine market and were identified. These seeds were powdered so that all the material could passed through a mesh size no larger than 0.5 mm. The powdered seeds were macerated in ethanol 80%, and the step was repeated twice, following by filtration through filter paper. The filtrate was dried by evaporation under reduced pressure.

Preparation of the formulations: Several solvents (PEG 200, 300, 400; ethanol, propylene glycol, glycerin) were used as cosolvent with water in the solubility of extract in several systems was evaluated. The extract was dissolved in preserved solvent system (methyl paraben 0.18% and propyl paraben 0.02%) before adding of polymer and stirred with a double bladed mixer (Ika-werk, Germany) 500 rpm for 30 min. Carbopol was dispersed in this solution overnight. The system was homogenized and neutralized by triethanolamine.

The formulations were kept in 4, 25, and 40 ^{o}C for physical stability evaluation during two weeks. Final formulations for clinical trial were controlled microbiologically based on USP XXIV (USP 24) (20). The same formulation without any extract was used as placebo.

Statistical analysis: Statistical analysis was performed using SPSS 15. Hair thickness changes in groups were compared by paired t-test. Hair thickness difference between groups was compared by student t-test.

Fisher's exact test was used to compare the side effects between the groups (17). In all cases, $P<0.05$ was considered as statistically significant.

Results

Twenty two women randomly were assigned in case and control groups. The mean age of the patients in the case group was 26.9±6.7 and in the control group was 25.6±4.3 years. The basic characteristics of these two groups are presented in table 1. Hair thickness difference was not significant before intervention in both groups. A reduction of 22.3 microns (22.7%, 95%CI: 5.5-39.9) was noticed in patients using fennel gel by paired t-test (p<0.01) (table 2). Four patients (3 in intervention group) complained of itching and 4 patients (3 in intervention group) complained of irritation and itching. This difference was not significant. Two patients in the control group abandoned the study.

Table 1: Demography of women with mild to moderate idiopathic hirsutism, received either fennel gel 3% or placebo, Iran, 2009-2011

Characteristics	Case (N=22)	Control (N=20)	P value
Age, year ($(\overline{X} \pm S.D)$	26.9±6.7	25.6±4.3	P<0.3
History of hirsutism, year $(\overline{X} \pm S.D)$	4.5±4.2	5.2±2.9	P<0.5
Degree of hirsutism:	**No (%)**	**No (%)**	
Mild	2 (9)	8 (40)	NS
Moderate	20 (9)	12 (60)	
Family history of hirsutism:			
negative	9 (41)	4 (21)	NS
positive	13 (59)	16 (80)	
Usual hair removal method:			
hair removal cream	2 (9)	1 (5)	P<0.000
shaving	2 (9)	1 (5)	
epilating	18 (82)	18 (90)	
Area involved:			
chin	19 (86)	16 (80)	NS
chin+ upper lip	2 (9)	2 (10)	
chin+ cheeks	1 (4.5)	2 (10)	

NS: Non significant

Table 2: Hair thickness, before and after using fennel gel and placebo, Iran, 2009-2011

Hair thickness	Case (N=22) (Mean±SD)	Control (N=20) (Mean±SD)	P value
before (Micron)	97.9±31.5	92.1±29.5	NS
After (Micron)	75.6±26.7	97.0±29.6	P<0.01
P value	P<0.000	NS	

Discussion

The study indicated that fennel gel 3% was effective in treating idiopathic hirsutism and did not have notable side effects. This result was similar to the study of Javidnia et al in 2003. They studied 38 women, 16-56 years old with mild to moderate idiopathic hirsutism, in three random groups (two case groups and one control group). They were treated with fennel cream 2%, 1% and placebo. Hair thickness and growth speed were measured. The mean reduction of hair thickness was reported as 7.8%, 18.3% and 0.5% for the patients using 1% and 2% creams and placebo, respectively. The best clinical response belonged to the group using 2% cream. The effectiveness level was 18.3±8.3 for patients who received the cream containing fennel extract 2% in their study (21). This figure is similar to the result of the present study. Therefore, 2% gel is effective like 3% gel plus the fact that the drug is cheap and does not have any notable side effects. The mechanism of action is not clear. It may be due to anti-androgenic effect of trans-anethole and di-anethole.

Recent studies have indicated that estrogens harness the making of dihydrotestosterone (DHT) in the papilla cells of skin by controlling 5-alfa reductase enzyme or increasing the conversion of testosterone to weaker androgens and decreasing the testosterone available for conversion to DHT (22). More randomized clinical trials need to be done. A standardization of the fennel extract is also necessary to introduce it as a modern medical drug in the treatment of hirsutism. Limitations of the study were: 1. Cases with severe hirsutism were not included; 2. If the follow-up period had been longer, the effect could have been better. Another study, with more patients, longer follow- up (for 1 to 2 years), and severe hirsutism is recommended

Acknowledgments

We sincerely thank the patients who trusted us to perform the study, the Deputy for Research of Mazandaran University of Medical Sciences for approving and funding the research. This study is a part thesis in General Medicine by Dr. Elham Zaeif- Khorasani.

Funding: Costs were provided by the Deputy for Research, Mazandaran University of Medical Sciences (Grant Number: 88-146).
Conflict of interest: No conflict of interest.

References

1. Ferriman D, Gallwey JD. Clinical assessment of body hair growth in women J clin Endocrinal Metab 1961; 21: 1440-7.
2. Azziz R, Carmina E, Sawaya ME. Idiopathic hirsutism. Endocr Rev 2000; 21: 347-62.
3. Glickman, SP, Rosenfeid, RL. Androgen metabolism by isolated hairs from women with Idiopathic hirsutism is usually normal. J Invest Dermatol 1984; 82: 62-6.
4. Kokaly W, Mckenna TJ. Relapse of hirsutism following long-term successful treatment with oestrogen-progestogen combination. Clin Endocrinal 2000; 52: 379-382.
5. Martin KA, Chang RJ, Ehrmann DA, et al. Evaluation and treatment of hirsutism in premenopausal women: an endocrine society clinical practice guideline. J Clin Endocrinal Metab 2008; 93: 1105-20.
6. He W, Huang B. A review of chemistry and bioactivities of medicinal spice: *Foeniculum vulgare*. J Med Plants Res 2011; 5: 3595-600.
7. Zargari A. Medicinal Plants. Vol.2. 5th ed. Tehran: Tehran University publication 1991.
8. Grieve M. A modern herbal. 1st ed. New York: Dover Publishers 1979; 824-8.
9. Trease GE, Evans WC. Pharmacognosy. 11th ed. London: Bailliere Tindall 1978; 414-7.
10. The British Pharmaceutical CODEX. 1 1th ed. London: The Pharmaceutical Press 1979; 352.
11. Stahl E, Dumont E, Jork H. Analyse chromatographique et microscopique des drogues. Paris: Technique et Documentation 1975; 148-9.
12. Leung AY, Foster S. Encyclopedia of common natural ingredients used in food, drugs and cosmetics. 2nd, 1996; New York: John Wiley& Sons, Inc.
13. Stahl E. Essential oil from fennel plants-studies on the composition. Deutsche Apotheker Zeitung 1982; 122: 2324-26.
14. Laweless J. The encyclopedia of essential oils, Dorest: Element Books Ltd 1992; 96-7.
15. Forster H B, Niklas H, Lutz S. Antispasmodic effects of some medicinalplants. Planta Med 1980; 40: 309-19.
16. Paris R P, Moyse H. Preciesde Matiere Medical. Paris: Masson and cieed 1967; 2: 473-5.
17. Karnick CR. Pharmacopoeial standards of Herbal plants. Delhi: Sri Satguru publications 1994; 1: 139-141.
18. Tu G. pharmacopreia of the people's Republic of china (English Edition). Beijing: Guangdong science and Technology press 1992; 70.
19. Tanker M, Tanker N. Farmakognozai. Istanbul: Ozisik Matbass 1973; 89-91.
20. Saeedi M, Morteza-Semnani K, Ghoreishi MR. The treatment of atopic dermatitis with licorice gel. J Dermatol Treat 2003; 14: 153-7.
21. Javidnia K, Dastgheib L, Mohammadisamani S, Nasiri A. Antihisutism activity of fennel (fruits of Foeniculum vulgare) extract. A double-blind placebo controlled study. Phytomedicine 2003; 10: 455-8.
22. Niiyama S, Happle R, Hoffmann R. Influence of estrogens on the androgen metabolism in different subunits of human hair follicles. Eur J Dermatology 2001; 11: 195-8.