JMM
pISSN: 2288-6478, eISSN: 2288-6761
https://doi.org/10.6118/jmm.2018.24.1.29
Journal of Menopausal Medicine 2018;24:29-33

Original Article

The Effect of Short-term Treatment with Fennel on Lipid Profile in Postmenopausal Women: A Randomized Controlled Trial

Maliheh Afiat[1], Elham Amini[2], Masumeh Ghazanfarpour[3], Bahareh Nouri[4], Mahsa Sadat Mousavi[5], Masoudeh Babakhanian[6], Hassan Rakhshandeh[7]

[1]Obstetrics and Gynecology, Women's Health Research Center, Department of Obstetrics and Gynecology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran, [2]Department of Midwifery, School of Nursing and Midwifery, Mashhad University of Medical Sciences, Mashhad, Iran, [3]Evidence-Based Care Research Center, Mashhad University of Medical Sciences, Mashhad, Iran, [4]Department of Medical Science, Mashhad University of Medical Sciences, Mashhad, Iran, [5]Department of Midwifery, Isfahan (Khorasgan) Branch, Islamic Azad University, Isfahan, Iran, [6]Social Determinants of Health Research Center, Semnan University of Medical Sciences, Semnan, Iran, [7]Pharmacological Research Center of Medicinal Plants, Mashhad University of Medical Sciences, Mashhad, Iran

Objectives: The present trial aimed to assess the effects of Fennel (Foeniculum vulgare Mill.) on lipid profiles.
Methods: In this double blind, randomized and placebo-controlled trial, sixty eligible postmenopausal women were randomly assigned into the fennel and placebo groups. Total blood cholesterol, cholesterol fractions, and triglycerides were tested at the baseline, and after three-month follow-up.
Results: There was no significant difference in triglyceride (*P* = 0.679), total cholesterol (P = 0.103), low-density lipoprotein cholesterol (LDL-C; *P* = 0.146) and high-density lipoprotein cholesterol (HDL-C; *P* = 0.266) levels between the two groups. In addition, in both groups, a paired *t*–test showed no significant difference in all mentioned parameters, except for HDL-C, indicating significant borderline improvement (*P* = 0.052) in the fennel group.
Conclusions: The fennel group revealed a very slight positive change in LDL-C, triglyceride and HDL-C. Further studies with longer durations, higher doses, and larger sample sizes are recommended to validate the results. **(J Menopausal Med 2018;24:29-33)**

Key Words: Foeniculum · Lipids · Postmenopause

Introduction

Menopause, with its notable hormonal profile, is related with unfavorable metabolic changes, particularly in plasma lipoprotein and cholesterol levels and a greater risk of cardiovascular disease.[1,2] Estrogen treatment, when initiated early in menopause, is also connected with a decline in likelihood of cardiovascular events.[3,4] Nevertheless, short-term estrogen use can prompt vaginal dying, while long-term usage can elevate the risk of breast cancer, stroke, and cardiovascular sickness.[5] Accordingly, a growing number of postmenopausal women prefer compounds that contain non-hormonal materials like phyto-oestrogens as a more secure alternative.[6] Phytoestrogen has been the subject of increasing attention for its bone-sparing features.[4] Fennel is a type of phytoestrogen[7] which include phenolic compounds such as flavonoids, hydroxycinnamic acids, phenolic acids, tannins and coumarins.[8] There is a paucity nevertheless, there are

Received: July 10, 2017 **Revised:** November 5, 2017 **Accepted:** November 6, 2017
Address for Correspondence: Masumeh Ghazanfarpour, Evidence-Based Care Research Center, Mashhad University of Medical Sciences, Mashhad 13944-91388, Iran
Tel: +98-91-5315-2455, Fax: +98-51-1859-7313, E-mail: Masumeh.Ghazanfarpour@yahoo.com

many animal studies that suggest the use of fennel might be effective for improving lipid profile.[9,10] The main goal of this study is to evaluate the impact of fennel on lipid profile.

Materials and Methods

This is part of a larger study that explores the effect of fennel on bones health and lipid profiles. A first part of the trials was published elsewhere.[11] It was conducted in compliance with the standards of Declaration of Helsinki and endorsed by Ethics Committee of the Mashhad University of Medical Science.

All participants of the study were enlisted in the healthcare center of Imam Reza Hospital in Mashhad, Iran. Inclusion criteria were: (1) postmenopausal status, which was defined as over 40 years of age without any vaginal bleeding for one year; (2) no regular consumption of phytoestrogen or products made of soy (which was defined as digestion more than once a week); and (3) a normal mammogram in the previous year. Exclusion criteria were: (1) use of any fluoride or bisphosphonates; (2) illness or prescriptions influencing bone metabolism; (3) current (or over past 6 months) utilization of estrogen or calcitonin; (4) a history of endometrial or breast cancer; (5) any bone fracture; and (6) regular physical exercise or sensitivity to Fennel (Foeniculum vulgare Mill.). In the following stage, participants signed an informed consent form alongside verbal assurance about voluntary nature of the study and that they could drop out of the study at will. Moreover, assurance was given to participants regarding the confidentiality of data during and after the study. At the baseline, 60 subjects were randomized to fennel or placebo group. Participants were expected to take soft capsule three times a day − (morning, noon and night). Each 100-mg fennel capsule contained a combination of 30% fennel (Standardized to 21-27 mg anethole) and sunflower oil. Active elements of each capsule were Transanthol, Methyl chavicol, fenechon and stragol.

Placebos were similar in shape and size but filled with sunflower oil. These capsules were the courtesy of Barij Essence Company. The distribution was on the basis of an arbitrary number table. That is, to ensure the concealment of allocation, a numbered, sealed and non-transparent plastic bottle was used, which contained sufficient capsules for 30 days. An employee of Barij Essence Pharmaceutical Company, who was not directly involved in the study, was in charge of allocation sequencing and packing. Also, both subjects and research group were blind to the treatment.

1. Laboratory methods

Blood samples were collected after 12-hour fast and moved in a cooled container to the laboratory. The levels of plasma total cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol (LDL-C) and high-density lipoprotein (HDL) cholesterol (HDL-C) were measured by Hitachi 902 auto-analyzer (Hitachi High Technologies Corporation, Tokyo, Japan) using analytical kits produced by Pars Azmoon Co. (Pars Azmoon, Tehran, Iran).

2. Statistical tests

Kolmogorov-Smirnov test was used to test whether samples had a normal distribution. Paired *t*-tests (within group) was used to compare between the baseline and three-month period, and Student's *t*-test was used to compare between treatment groups. Statistical tests were two-sided, and a *P*-value < 0.05 was considered statistically significant.

Results

The two groups were similar in variables such as age, history of hysterectomy, body weight, body mass index, and duration of menopause at the baseline, as shown in Table 1. Side effects were observed in 6 subjects in the fennel group and 3 subjects in the placebo group. In the fennel group, subjects complained of allergic rash (n = 1), weight gain (n = 1), hypertension (n = 1) and vaginal bleeding (n = 2). Only one patient in placebo group complained of stomachache. Table 2 showed the lipid levels at baseline and after three treatments. There was no significant difference in profiles lipids triglyceride ($P = 0.679$), total cholesterol ($P = 0.103$), LDL concentrations ($P = 0.104$) and HDL ($P = 0.266$) between groups. Also, in both group, Paired *t*-test showed no significant difference in all mentioned parameters except HDL-C that showed a significant borderline improvement ($P = 0.052$) in the fennel group.

 https://doi.org/10.6118/jmm.2018.24.1.29

Table 1. Baseline characteristics of subjects in the groups

Items	Fennel group (n = 25)	Placebo group (n = 29)	*P* value
Age (years)	56.1 ± 6.5	56.2 ± 4.7	0.933
Height (m)	1.53 ± 5.57	1.51 ± 4.71	0.206
Duration of menopause (months)	97 ± 81	86 ± 59	0.587
Body weight (kg)	68 ± 25	72.03 ± 11.5	0.206
No. of children	4.29 ± 1.9	3.7 ± 1.7	0.334
History of hysterectomy	1 (4.0%)	4 (13.8%)	0.354
Cigarette smoking	2 (8.0%)	0 (0.0%)	

The data is presented as mean ± standard deviation or n (%)

Table 2. Effect of fennel on lipid parameters in postmenopausal women

Variable	Fennel group (n = 25)	Placebo group (n = 29)	*P* value
Total cholesterol (mg/dL)			
Start point (0 week)	236.6 ± 44.7	227.83 ± 34.3	0.419
End point (12 weeks)	238.64 ± 40.1	222.83 ± 29.69	0.103
Paired *t*-test	0.761	0.291	
LDL cholesterol (mg/dL)			
Start point (0 week)	149.84 ± 35.06	133.41 ± 27.34	0.060
End point (12 weeks)	147.16 ± 36.22	133.69 ± 30.8	0.146
Paired *t*-test	0.630	0.950	
HDL cholesterol (mg/dL)			
Start point (0 week)	46.6 ± 8.87	51.45 ± 9.18	0.055
End point (12 weeks)	48.8 ± 8.97	51.55 ± 8.95	0.266
Paired *t*-test	0.052	0.926	
Triglycerides (mg/dL)			
Start point (0 week)	121.36 ± 41.71	127.48 ± 52.9	0.643
End point (12 weeks)	118 ± 38.11	122.45 ± 40.1	0.679
Paired *t*-test	0.649	0.378	

LDL: low-density lipoprotein, HDL: high-density lipoprotein

Discussion

To the best of our knowledge, this is the first study to assess the effects of fennel on lipid the profiles among the postmenopausal women. According to the results of this study, the group treated with fennel showed a very slight positive change in LDL-C and triglyceride. Moreover improved HDL concentration reached the borderline level of statistical significance (P = 0.052) after three months. However, no significant difference was found between the two groups on the lipid parameters.

As we know, there is no human study on the fennel effectiveness of on the lipid profiles. Nevertheless, considering that phytoestrogen is an active biological compound in fennel, we referred to studies evaluating the effects of phytoestrogen on the lipid profiles. The phytoestrogens are plant compounds with properties similar to the estrogen. The major types of phytoestrogens are isoflavones, lignans, flavonoids and coumestans.[12] Soy and red clover have high content of isoflavones.[4] Lignans are mainly found in flaxseed[13] and fennel is a rich source of flavonoids.[8] Hallund et al.[14] evaluated the effect of flaxseed on the lipid profiles only in a randomized, double blind, placebo-controlled clinical trial with a 6-week wash out period in post menopause. The present results demonstrated that the lipid profiles (total cholesterol, LDL-C, HDL-C and triglycerides) were not affected by both treatments. In a recently published meta-analysis, Tokede et al.[15] assessed the effect of soy products on the serum lipids. There was a significant decrease in LDL-C of −4.83 mg/dL (95% confidence interval [CI], −7.34, −2.31), total cholesterol −5.33 mg/dL (95% CI, −8.35, −2.30) and triglycerides of −4.92 mg/dL (95% CI, −7.79, −2.04) in the patients treated with soy. A significant increase was observed in serum HDL-C concentration of 1.40 mg/dL (95% CI, 0.58, 2.23) in the soy group. The LDL-lowering effect was more exhibited in hypercholesterolemic subjects.

Two animal studies investigated the effect of fennel on the lipid profiles. The first study was conducted by Helal et al.[10] on 30 rats divided into 5 groups of 6. The Group 1 rats were as control. The rats in the Group 2 experienced hyperlipidemia for 3 week that was sacrificed then. The rats in the Group 3 were made hyperlipidemia for 3 week, and maintained further 3 weeks without any treatment. The rats in the Group 4 were made hyperlipidemia and then treated by fennel for further 3 weeks. The rats in the Group 5 were

made hyperlipidemia for 6 weeks. The rats in the Group 6 was made hyperlipidemia for 3 weeks and then treated with fennel for 6 weeks. When comparing with the control group, the Groups 4 and 6 showed higher significant decrease ($P < 0.01$) in levels of liver total lipids. They concluded that the fennel might shift liver total lipid value to normal level. The possible mechanism of action of the fennel on reducing lipids could be attributed to its anti-oxidative properties and radical scavenging activity.[10] Fatiha et al.[16] performed the second research on 18 rats with the mean weight of 20 ± 2 g divided into three group of six. The Group 1 (control) received intraperitoneal normal saline and water via gavages. The Group 2 was made hyperlipidemia by Triton WR-1339. In the Group 3, the rats was made hyperlipidemia by WR-1339, and then treated with the fennel. The blood samples were collected after scarifying the rats. Then, the samples were immediately centrifuged to separate the plasma for analyzing the lipid parameters (total cholesterol, HDL-C), and LDL-C, triglycerides, apolipoproteins. The second group showed 35%, 50% and 50% decrease in the total cholesterol, triglycerides and LDL-C, respectively. They concluded that administration of methanol extract of fennel might have anti-atherosclerotic and hyperlipidemic effects.

Conclusion

There were several limitations in our study. First, the sample size was relatively small and the research units were followed-up only for three month. Seconded limitation of the current study was its failure to control the lifestyle habits, like physical activity and diet. However, the subjects were requested not to change their routine diet and physical activity over the study period. Third, we did not calculate the inter- and intra-assay coefficients.

The fennel revealed a very slight positive change in the LDL-C, triglyceride, and HDL concentrations. Further studies with longer durations, higher doses, and larger sample sizes are required to validate the results of this study.

Acknowledgement

Hereby, the authors would like to thank and appreciate the Barij Essence Pharmaceutical Company for producing the fennel soften capsule and its placebo, as well as all menopausal women who patiently participated in this trial.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

References

1. Kannel WB, Hjortland MC, McNamara PM, Gordon T. Menopause and risk of cardiovascular disease: the Framingham study. Ann Intern Med 1976; 85: 447-52.
2. Terzic MM, Dotlic J, Maricic S, Mihailovic T, Tosic-Race B. Influence of red clover-derived isoflavones on serum lipid profile in postmenopausal women. J Obstet Gynaecol Res 2009; 35: 1091-5.
3. Rossouw JE, Prentice RL, Manson JE, Wu L, Barad D, Barnabei VM, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. JAMA 2007; 297: 1465-77.
4. Atkinson C, Compston JE, Day NE, Dowsett M, Bingham SA. The effects of phytoestrogen isoflavones on bone density in women: a double-blind, randomized, placebo-controlled trial. Am J Clin Nutr 2004; 79: 326-33.
5. Kreijkamp-Kaspers S, Kok L, Grobbee DE, de Haan EH, Aleman A, Lampe JW, et al. Effect of soy protein containing isoflavones on cognitive function, bone mineral density, and plasma lipids in postmenopausal women: a randomized controlled trial. JAMA 2004; 292: 65-74.
6. Colacurci N, Zarcone R, Borrelli A, De Franciscis P, Fortunato N, Cirillo M, et al. Effects of soy isoflavones on menopausal neurovegetative symptoms. Minerva Ginecol 2004; 56: 407-12.
7. Garga C, Khan SA, Ansari SH, Suman A, Garg M. Chemical composition, therapeutic potential and perspectives of Foeniculum vulgare. Pharmacogn Rev 2009; 3: 346-52.
8. Prestwood KM, Kenny AM, Kleppinger A, Kulldorff M. Ultralow-dose micronized 17beta-estradiol and bone density and bone metabolism in older women: a randomized controlled trial. JAMA 2003; 290: 1042-8.

9. Dongare V, Kulkarni C, Kondawar M, Magdum C, Haldavnekar V, Arvindekar A. Inhibition of aldose reductase and anti-cataract action of trans-anethole isolated from Foeniculum vulgare Mill. fruits. Food Chem 2012; 132: 385-90.
10. Helal EGE, Eid FA, Wahsh AM, Ahmed E. Effect of fennel (Foeniculum vulgare) on hyperlipidemic rats. Egypt J Hospital Med 2011; 43: 212-25.
11. Ghazanfarpour M, Amini E, Khadivzadeh T, Babakhanian M, Nouri B, Rakhshandeh H, et al. The effect of short-term treatment with fennel on bone density in postmenopausal women: A rndomized controlled trial. J Menopausal Med 2017; 23: 124-30.
12. Wei P, Liu M, Chen Y, Chen DC. Systematic review of soy isoflavone supplements on osteoporosis in women. Asian Pac J Trop Med 2012; 5: 243-8.
13. Clifton-Bligh PB, Nery ML, Clifton-Bligh RJ, Visvalingam S, Fulcher GR, Byth K, et al. Red clover isoflavones enriched with formononetin lower serum LDL cholesterol-a randomized, double-blind, placebo-controlled study. Eur J Clin Nutr 2015; 69: 134-42.
14. Hallund J, Ravn-Haren G, Bügel S, Tholstrup T, Tetens I. A lignan complex isolated from flaxseed does not affect plasma lipid concentrations or antioxidant capacity in healthy postmenopausal women. J Nutr 2006; 136: 112-6.
15. Tokede OA, Onabanjo TA, Yansane A, Gaziano JM, Djoussé L. Soya products and serum lipids: a meta-analysis of randomised controlled trials. Br J Nutr 2015; 114: 831-43.
16. Fatiha O, Noreddine G, Mohamed EM, Hakima B, Mustapha D, Souliman A. Hypolipidemic and anti-atherogenic effect of methanol extract of fennel (Foeniculum vulgare) in hypercholesterolemic mice. Int J Sci Knowl 2014; 31: 42-52.