



Review article

The Effect of Fennel on Pain Relief in Primary Dysmenorrhea: A Systematic Review of Clinical Trials

Mojgan Nazari¹ , Masoumeh Rostami-Moez^{2*} , Fatemeh Ebrahimi³

¹Assistant Professor of Reproductive Health, School of Nursing and Midwifery, Guilan University of Medical Sciences, Rasht, Iran

²PhD in Health Promotion, Research Center for Health Sciences, Education Development Center, Hamadan University of Medical Sciences, Hamadan, Iran

³MSc in Community Nutrition, Rafsanjan University of Medical Sciences, Rafsanjan, Iran

Abstract

Background and aims: Fennel is often advocated for primary dysmenorrhea. Whether this herb has a real effect on pain relief is still a matter of debate in medicine. Therefore, this study was conducted to evaluate the effect of fennel on primary dysmenorrhea.

Methods: This systematic review was conducted on clinical trials (non-randomized, randomized, historical study with concurrent control) published in PubMed (MEDLINE), Web of Science, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL), ProQuest, and Persian databases (Magiran, IranMedex, SID, Irandoc) regarding the effect of fennel on pain intensity in primary dysmenorrhea from 1990 to 2019. Nine studies met all inclusion criteria. Any clinical trials on young women with primary dysmenorrhea were included in the study. Studies that used fennel plus other products investigated fennel effect on premenstrual syndrome (PMS) and bleeding; studies without a control group and nonclinical trials were excluded. In all studies, participants were young female university or high school students. All of them had moderate to severe primary dysmenorrhea.

Results: In all of the studies except for one, fennel had been more effective than placebo in pain relief ($P < 0.01$). Non-steroidal drugs had the same result as fennel for pain relief. However, in one study, the difference between non-steroidal anti-inflammatory drugs (NSAIDs) and fennel in pain relief was observed. Only one study reported increasing vaginal bleeding after fennel consumption in some cases.

Conclusion: Collectively, these studies favored fennel over NSAID, other herbal drugs, and placebo. But more investigation is needed to draw a firm conclusion.

Registration: PROSPERO - 42015023725

Keywords: Foeniculum, Herbal medicine, Traditional treatment, Dysmenorrhea

*Corresponding Author:

Masoumeh Rostami-Moez, PhD, Education Development Center, Research Center for Health Sciences, Hamadan University of Medical Sciences, Hamadan, Iran, Tel: +98 813 8380246, Mobile: 09183163764, Fax: +98 813 8380509, Email: ma.rostamimoez@gmail.com

Received: 6 Oct. 2019
Accepted: 25 Nov. 2019
ePublished: 26 Mar. 2020



Introduction

Primary dysmenorrhea is one of the most important public health problems among young females worldwide, which interfere with their social responsibility and quality of life. Primary dysmenorrhea is defined as painful menstrual cramps of the uterus without any obvious gynecological problem.¹ The elevated level of Prostaglandins E_2 and $F_2\alpha$ (PG E_2 and $F_2\alpha$) has been known as a cause of primary dysmenorrhea. Ischemia and pain were induced by increasing vasopressin, and uterine contraction was induced by PG E_2 and F_2A . Foeniculum vulgare (Fennel) is used as foodstuff and also an herbal drug in traditional medicine. It is an anti-inflammatory and anti-spasmodic substance.² In a study, Ostad et al. reported a decrease in the frequency and intensity of uterine contraction in rats

after using fennel.³ The standard treatment to relieve pain is medical therapy by oral contraceptive or non-steroidal anti-inflammatory drugs (NSAIDs) such as mefenamic acid or ibuprofen.^{4,5} The treatment with NSAID_s still has 20% to 25% failure rates.¹ Moreover, due to the side effects of medical treatment, many women are currently seeking conservative treatment. Considering the side effects of chemical therapy, it seems that some herbal drugs may be a good substitute. Fennel is known as an anti-inflammatory and estrogenic substance. It has demonstrated beneficial effects in the treatment of primary dysmenorrhea.⁶ The authors' search showed that there are several clinical trials that compare different types of fennel with other herbs, NSAIDs, and placebo for pain relief in young women. Therefore, this study aimed to review the effect of fennel

on primary dysmenorrhea since this product has fewer side effects compared to NSAID.

Materials and Methods

The authors summarized the evidence from several bibliographies and scientific databases including CENTRAL, MEDLINE via PubMed, Scopus, Web of Science, ProQuest, and Persian databases (MagIran, IranMedex, SID, Irandoc) regarding the effect of fennel on primary dysmenorrhea. We did not find any article in Grey literature from Scopus and Google Scholar for conference proceedings (www.greylit.org).

Search terms used were as follows: TITLE-ABS-KEY (fennel OR "Foeniculum Vulgare") AND TITLE-ABS-KEY (dysmenorrhea OR menstrua*) AND TITLE-ABS-KEY (trial* OR intervention* or comparative OR clinical trial* OR randomized controlled trial) AND DOCTYPE (ar OR re) and PUBYEAR from 1989 to 2019.

All articles retrieved in the search were screened by title and abstract for relevance. The full-text articles that have been potentially relevant were included in this study. Articles that fulfilled all of the inclusion criteria were included. The inclusion criteria were as follows: Any clinical trials (non-randomized, randomized, historical study with concurrent control) on young women with primary dysmenorrhea were included in this study. Studies which used any type and dose of fennel in the form of a soft capsule, extract, or essence were included. Studies with any types of control groups such as standard treatment (NSAIDs [mefenamic

acid and ibuprofen] and vitamin E), placebo, no treatment, or other herbal drugs were included. Studies that measured pain relief by any scale such as visual analogue scale (VAS), checklist, or questionnaire were included. Studies that assessed secondary dysmenorrhea were excluded.

The data extraction and quality assessment were independently carried out by two authors using a predefined data extraction form. Disagreements were solved through discussion. To assess the risk of bias, two reviewers independently evaluated the included studies using a modified CONSORT 2010 checklist. The inclusion criteria were random sequence generation, blinding procedure (single, double, triples), allocation concealment, completeness of outcome, and reporting of outcome and other sources of bias. Primary studies that used fennel plus other products investigated the effect of fennel on premenstrual syndrome (PMS) and bleeding; studies without a control group and nonclinical trials were excluded.

The qualities of the included trials were assessed by two authors. Due to the sensitivity of this part, any disagreement between the two authors was discussed. Studies that were duplicated with identical data were considered one study.

Results

Study Inclusion

Figure 1 shows the flow chart of the screening and selection process of articles. Initially, 418 publications

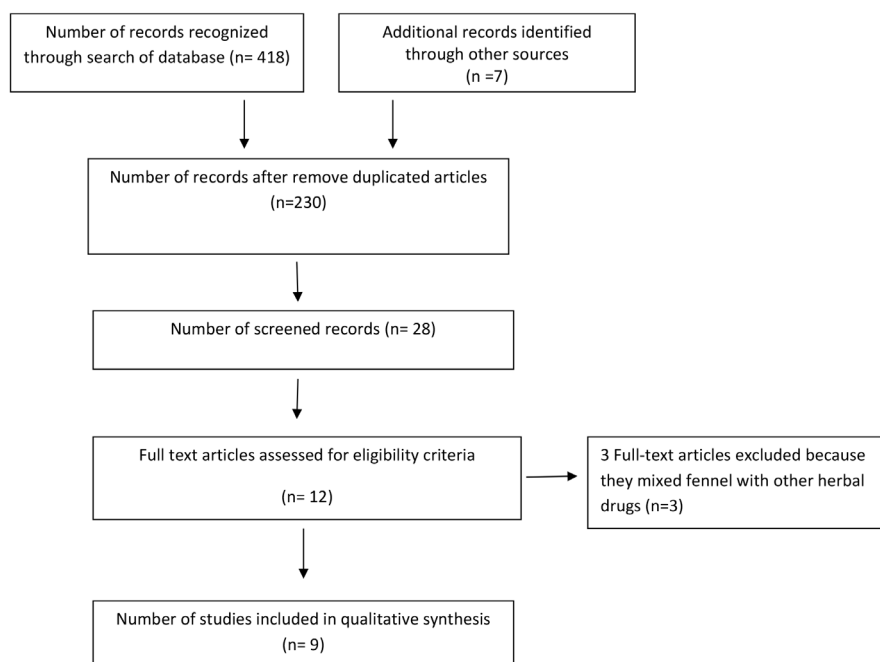


Figure 1. The Flow Chart of Study Selection.

Table 1. Controlled Trials of Fennel for Pain Relief in Primary Dysmenorrhea

First author (year),	Quality score	Sample	Design	Treatment	Control	Duration of treatment	Measurement tool	Outcome measure	Side effect of fennel	Result
Ghods, 2014	18	80 University students	RCT	30 mg * 6 daily fennel (cap), 3 days	No medication	3 months (From beginning of the menses)	Visual analogue scale, McGill pain questionnaire	Nausea intensity and weakness & pain	Not mentioned	A significant difference after 2-3 months of use was reported ($P \leq 0.001$).
Modaresnejad, 2006	10	120 high school student	RCT	30 drop of fennel extract * 4 daily	250 mg mefenamic acid * 4 daily	2 months (during the first 3 days of the menses)	Multidimensional verbal scale	Pain relief	Not mentioned	Higher decrease of pain in treatment group was observed, but there was no significant difference between 2 groups ($P > 0.05$).
Torkzahrani, 2007	12	90 university students	CT Double blinded	46 mg cap * 5 daily	Placebo cap * 5 daily	2 months (during the first 3 days of the menses)	Multidimensional verbal scale	Decrease in pain intensity & Clinical sign	No side effect	Pain relief difference was significant ($P \leq 0.001$), and no differences in clinical signs were reported.
Nazarpour, 2007	12	104 university students	CT	fennel (20-30 drop) * 6 or 3	Mefenamic acid cap 250 mg * 4 or placebo drop	2 months (from beginning of the menses)	10 point linear analog technique	pain severity & clinical sign	Not mentioned	Decrease in pain severity was not significantly different ($P > 0.05$). There were no differences in clinical sign among 3 groups ($P > 0.05$).
Moslemi, 2012	13	50 university students	RCT Double blind	46 mg fennel extract (cap) * 4	Placebo * 4 day	2 months (during the menses)	Multidimensional verbal scale	Pain relief	Not mentioned	There was significant difference in pain relief in the second cycle ($P < 0.006$). Duration of pain was lower in intervention ($P < 0.001$).
Namvarjahromi, 2003	13	70 university and high school students	CT	second cycle: mefenamic acid (250 mg * 4 daily), third cycle: fennel 25 drops * 6 daily	No medication during the first cycle	3 months (from beginning of the menses)	Multidimensional verbal scale	Pain relief	5 subject dropped out due to odor and one for increase of bleeding	Both of the drugs had significant difference with the control cycle ($P < 0.001$). Mefenamic acid had a more potent effect than fennel on the 2th and 3th days ($P < 0.05$), however, the difference on the other days was not significant.
Delaram, 2010	20	60 university students	CT	30 drop * 3 daily	Placebo, 30 drops * 3	2 month (during the first 3 days of the menses)	Visual analogue scale	Pain relief	Not mention	A significant difference was observed ($P < 0.05$).
Zeraaty, 2014	12	105 university students	RCT Double blind.	Fennel (30 drop) * 4 daily	1. Vitagnus, 40 drops morning 2. Mefenamic acid cap., 250mg * 6 daily 3. placebo, 30 drops * 6	3 month (one day before the start of the cycle until the third day)	Visual analogue scale	Pain relief	No side effect	Fennelin had similar effects as Vitagnus, mefenamic acid had less effect than both drugs ($P < 0.05$).
Motevali, 2017	13	72 university students	CT	15.5 mg fennel (3-5drop) * 3 daily	Gelophen cap 400 mg * 4 daily.	3 month (For the first 3 days of the menses)	Multidimensional verbal scale	Pain relief	No side effect	Both of the two groups reported a decrease in pain, but it was not significant ($P > 0.05$).

were identified by systematic search. Nine studies met our defined criteria and were reviewed.^{5,7-14} The quality assessment revealed a score of at least equal or higher than 12 in all of studies using the CONSORT checklist. Most of the studies had been done on female university students and only one study had been done on high school students. In addition, in one study, both high school and university students were selected.

Study Characteristics and Findings

In all of the studies except one, fennel had been more effective than placebo in pain relief ($P \leq 0.001$ for most of them, and with $P > 0.006$ for one). NSAIDs such as mefenamic acid or gelofen had the same result as fennel for pain relief. However, the difference between NSAIDs and fennel in pain relief was observed in one study. The decrease in clinical signs was implied in two studies and there were no significant differences between NSAIDs and fennel. In one study, fennel had reduced menstrual bleeding better than non-steroidal drugs on the third day of menstruation after the second cycle ($P > 0.04$), and there were no differences in nausea, headache, and other somatic signs between three groups ($P > 0.05$). Table 1 shows the summarized key data.

In one study, nausea intensity and weakness decreased during the menstrual period, and a significant difference was found after two and three months of use. Moreover, difference in the quality of well-being after one and three months was significant. The pain relief was observed after using fennel and continued considerably over time. In another study, there was no pain in 80% of the fennel group and 73% of the mefenamic acid group. In regard to the limitation of activities, 83% in the fennel group and 71% in the mefenamic acid group had no rest after treatment.

Only in one study, three cycles of menstruation were compared with each other. These cycles were compared day by day for the effect, potency, time of initiation of effect, and drug complications using a self-scoring system. Both of the drugs (fennel and mefenamic acid) effectively relieved menstrual pain as compared with no medication as the control cycles ($P < 0.001$). The mean duration of initiation of effect was 67.5 ± 46.06 minutes for mefenamic acid and 75 ± 48.9 minutes for fennel after using them; however, the difference was not statistically significant ($P > 0.57$). In another study, mefenamic acid had a more potent effect than fennel on the second and third menstrual days ($P < 0.05$); however, the difference on the other days was not significant. One study found that fennel had similar effects as Vitagnus for treatment of dysmenorrhea and mefenamic acid was less effective than both of the mentioned drugs ($P < 0.05$).

Discussion

The aim of this study was to evaluate the efficacy of

different types of fennel on primary dysmenorrhea. The quality assessment revealed a score of at least equal or higher than 12 in the majority of studies using the CONSORT checklist. For all systematic reviews, publication bias is a major concern that may lead to a false-positive result and negative studies might remain unpublished.

Different types of fennel consisting of extract, drop, and soft capsule have been compared with NSAIDs, other herbal drugs, and placebo for relieving pain. The majority of the studies reported that fennel (extract, drop, and capsule) is more effective than NSAIDs and other herbal drugs or placebo. In one study, the researchers reported that the effectiveness of fennel was not as strong as the mefenamic acid. The difference between the positive outcome and negative result from other RCT is not readily explicable, but the researcher stated that the dose of the drop may not be sufficient for pain relief.⁸

Fennel is generally used as foodstuff and spice in pickles, so it is assumed that it is free of serious adverse effects. However, it can be an unsafe substance. For example, it may be safe when used in low doses as a spice, but it may be harmful when it is taken in higher doses as a drug.

There were no reports of the side effects of fennel in some studies.^{9,13,14} The other studies did not mention any adverse effects of fennel.^{7,8,10-12} In one study, the researchers stated that one subject was reported to have increased menstrual bleeding after consuming fennel drop.⁵ It seems that more studies are needed to assess the side effects of fennel. Because of the diversity of the dose and duration of fennel administration in various studies, it is not possible to summarize the results of the studies, which is the limitation of this study.

Conclusion

In summary, we found that fennel is a promising herbal drug with pain-relieving properties, but it seems that the clinical investigation is not sufficient to draw a firm conclusion because all of the presented studies had a small sample size. Further rigorous studies are needed to establish whether fennel is the most effective herbal drug for primary dysmenorrhea.

References

1. Khodakarami B, Masoomi SZ, Faradmal J, Nazari M, Saadati M, Sharifi F, et al. The severity of dysmenorrhea and its relationship with body mass index among female adolescents in Hamadan, Iran. *J Midwifery Reproductive Health*. 2015;3(4):444-50. doi: 10.22038/jmrh.2015.4618.
2. Momenzadeh F, Ashtoghi M, Taghizadeh M, Mahlogi M, Rafiei F. Comparison of the effect of soft phenyl capsule and mefenamic acid capsule on the severity of primary dysmenorrhea. *Iranian Journal of Obstetrics & Gynecology*. 2017;20(4):44-9. [Persian].
3. Ostad SN, Soodi M, Shariffzadeh M, Khorshidi N, Marzban H. The effect of fennel essential oil on uterine contraction as a model for dysmenorrhea, pharmacology and toxicology study. *J Ethnopharmacol*. 2001;76(3):299-304. doi: 10.1016/s0378-

4. Lira Plascencia J, Simon Pereira LA, Amor Calleja L, García Lara E, Ibarra Chavarria V, Grosso Espinoza JM, et al. [Clinical practice guidelines. Diagnosis and treatment of primary dysmenorrhea in teenagers]. *Ginecol Obstet Mex.* 2009;77(8):S211-29.
5. Namavar Jahromi B, Tartifizadeh A, Khabnadideh S. Comparison of fennel and mefenamic acid for the treatment of primary dysmenorrhea. *Int J Gynaecol Obstet.* 2003;80(2):153-7. doi: 10.1016/s0020-7292(02)00372-7.
6. Rahimi R, Ardekani MR. Medicinal properties of *Foeniculum vulgare* Mill. in traditional Iranian medicine and modern phytotherapy. *Chin J Integr Med.* 2013;19(1):73-9. doi: 10.1007/s11655-013-1327-0.
7. Ghodsi Z, Asltoghiri M. The effect of fennel on pain quality, symptoms, and menstrual duration in primary dysmenorrhea. *J Pediatr Adolesc Gynecol.* 2014;27(5):283-6. doi: 10.1016/j.jpag.2013.12.003.
8. Modarresnejad V, Motamedi B, Asadipour M. Comparison of the effect of fennel and mefenamic acid in relieving pain of primary dysmenorrhea. *Journal of Rafsanjan University of Medical Sciences.* 2006;5(1):1-6. [Persian].
9. Zahrani ST, Amjadi MA, Mojab F, Majd HA. The effect of Fennel (*Foeniculum Vulgare*) on Dysmenorrhea. *Fertility and Infertility.* 2007;8(1):45-51. [Persian].
10. Nazarpour S, Azimi H. Comparison of therapeutic effects of fennelin and mefenamic acid on primary dysmenorrhea. *Journal of Mazandaran University of Medical Sciences.* 2007;17(61):54-61. [Persian].
11. Moslemi L, Bekhradi R, Hasani S, Khaleghi K. Effect of fennel extract on primary dysmenorrhea. *Family Health Quarterly.* 2013;1(4):15-20. [Persian].
12. Delaram M, Forouzandeh N. The effect of fennel on the primary dysmenorrhea in students of Shahrekord university of medical sciences. *Jundishapur Scientific Medical Journal.* 2011;10(1):81-88. [Persian].
13. Zeraati F, Shobeiri F, Nazari M, Araghchian M, Bekhradi R. Comparative evaluation of the efficacy of herbal drugs (fennelin and vitagnus) and mefenamic acid in the treatment of primary dysmenorrhea. *Iran J Nurs Midwifery Res.* 2014;19(6):581-4.
14. Motavalli R, Shahbazzadegan S. Comparative study of the effects of fennel with Gelofen on the severity of primary dysmenorrhea: a randomized clinical trial. *The Iranian Journal of Obstetrics, Gynecology and Infertility.* 2018;21(7):36-42. doi: 10.22038/ijogi.2018.11795. [Persian].