ANALYSIS

23(96), March - April, 2019

ISSN
2321–7359
EISSN
2321–7367

Medical Science

Comparison of the effects of *Nigella sativa* and Mefenamic acid on the severity, duration, and systemic symptoms of primary Dysmenorrhea

Fatemeh Mohanazadeh Falahieh[1], Farzaneh Jafarnejad[2,✉], Hassan Rakhshandeh[3], Mohammad-Taghi Shakeri[4], Malihe Motavasselian[5]

Background: **Dysmenorrhea is the most prevalent pelvic cyclic pain and the most common complaint of gynecologic patients due to causing many personal and social problems. Since the use of physiotherapy has become commonplace, this study was conducted to evaluate the effects of *Nigella sativa* compared to *Mefenamic acid* on primary dysmenorrhea. *Materials and methods:* This double-blind randomized clinical trial was conducted on 70 single female students aged between 18 and 30, who were living at the dormitory of Mashhad University. The students were allocated randomly into two groups; the *Nigella sativa* group (n=35) took 1gr of *Nigella sativa* powder q8h in the first 3 days of menstruation for two cycles. The second group (n=35) received 250mg of *Mefenamic acid* q8h in the first 3 days of menstruation. The pain severity (measured on the visual analog scale) and duration (measured on cox) were measured at the baseline and during the two cycles. *Results:* The two groups had no significant difference in the severity and duration of pain at the baseline; however, after the intervention, the severity and duration of the pain were significantly lower in the *Nigella sativa* group than in the *Mefenamic acid* group (P< 0/05). *Conclusion:* The results of this study showed that *Nigella sativa* could reduce the severity and duration of menstrual pain by exerting anti-inflammatory effects; thus, it is recommended to be used in the treatment of this common gynecologic disorder in women.**

INTRODUCTION

Dysmenorrhea is defined as painful uterine contractions that occur during menstrual bleeding and in 15% of the cases, it leads to absence from school and work, and also reduces the quality of life (1, 2). It usually starts a few hours before bleeding and lasts for 48-72 hours. The labor-like pain and cramps of dysmenorrhea startin the lower abdomen and reaches the upper abdomen, waist, and thighs, sometimes coinciding with systemic symptoms, such as nausea, vomiting, diarrhea, headaches, and dizziness (3). This condition is due to the increased prostaglandins, vasopressin, and leukotrienes in the endometrium; therefore, a treatment involving the reducing of the production of prostaglandin is supposed to be effective. Current treatments include prostaglandin synthesis inhibitors and non-steroidal anti-inflammatory drugs (NSAIDs). In addition, oral contraceptives have been suggested for dysmenorrhea, which can be associated with side effects, such as headaches, dizziness, dysuria, sleepiness, the loss of appetite, nausea, acne, increased acute asthma, vomiting, and gastrointestinal bleeding. However, these medicines have the failure rates of 20% to 25% (4). Complementary treatments, such as massage, aromatherapy, heating or cooling therapy, and medicinal plants with minimal side effects have been used for the treatment of dysmenorrhea across the world (5, 21, 22). *Nigella sativa*, a dicotyledon fromthe family *Ranunculaceae*, is a grassy plant with green to blue flowers and small black seeds, which grows in temperate and cold climates. The seeds of *Nigella sativa* are also called black cumin and contain thymoquinone and monoterpenes, such as *p*-Cymene and α-Pinene, Nigellidine, Nigellimine, and a Saponin (6, 23). The seed oil has anti-inflammatory, analgesic, anti-hypertensive, antimicrobial, and antineoplastic properties (7). The main active ingredient is isolated from the volatile oil of *N.sativa* is thymoquinone (8). *N.sativa* and pure thymoquinone inhibit cyclooxygenase and 5-lipoxygenase pathways of arachidonate metabolism, thereby leading to the inhibition of prostaglandins (9). Components of *N.sativa* have also shown major anti-inflammatory effects in several inflammatory diseases, such as experimental allergic encephalomyelitis, colitis, and arthritis (10, 24). Since along history of human experiences supports the traditional and classic uses of black cumin seeds, this plant can be considered a valuable source of several potential drugs. The evaluation of analgesic and anti-inflammatory effects of black cumin seeds has been the subject of several recent studies, having been focused mostly on pure thymoquinone (11). The present study was done aimed at comparing the

[1]M.Sc. in Midwifery, School of Nursing and Midwifery, Mashhad University of Medical Sciences, Mashhad, Iran; [2]Department of Midwifery, School of Nursing and Midwifery, Mashhad University of Medical Sciences, Mashhad, Iran; [3]Pharmacological Research Center of Medicinal Plants, Mashhad University of Medical Sciences, Mashhad, Iran; [4]Department of Biostatistics, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran; [5]Department of Persian Medicine, School of Persian and Complementary Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

✉*Corresponding author:* Farzaneh Jafarnejad; Department of Midwifery, School of Nursing and Midwifery, Mashhad University of Medical Sciences, Mashhad, Iran

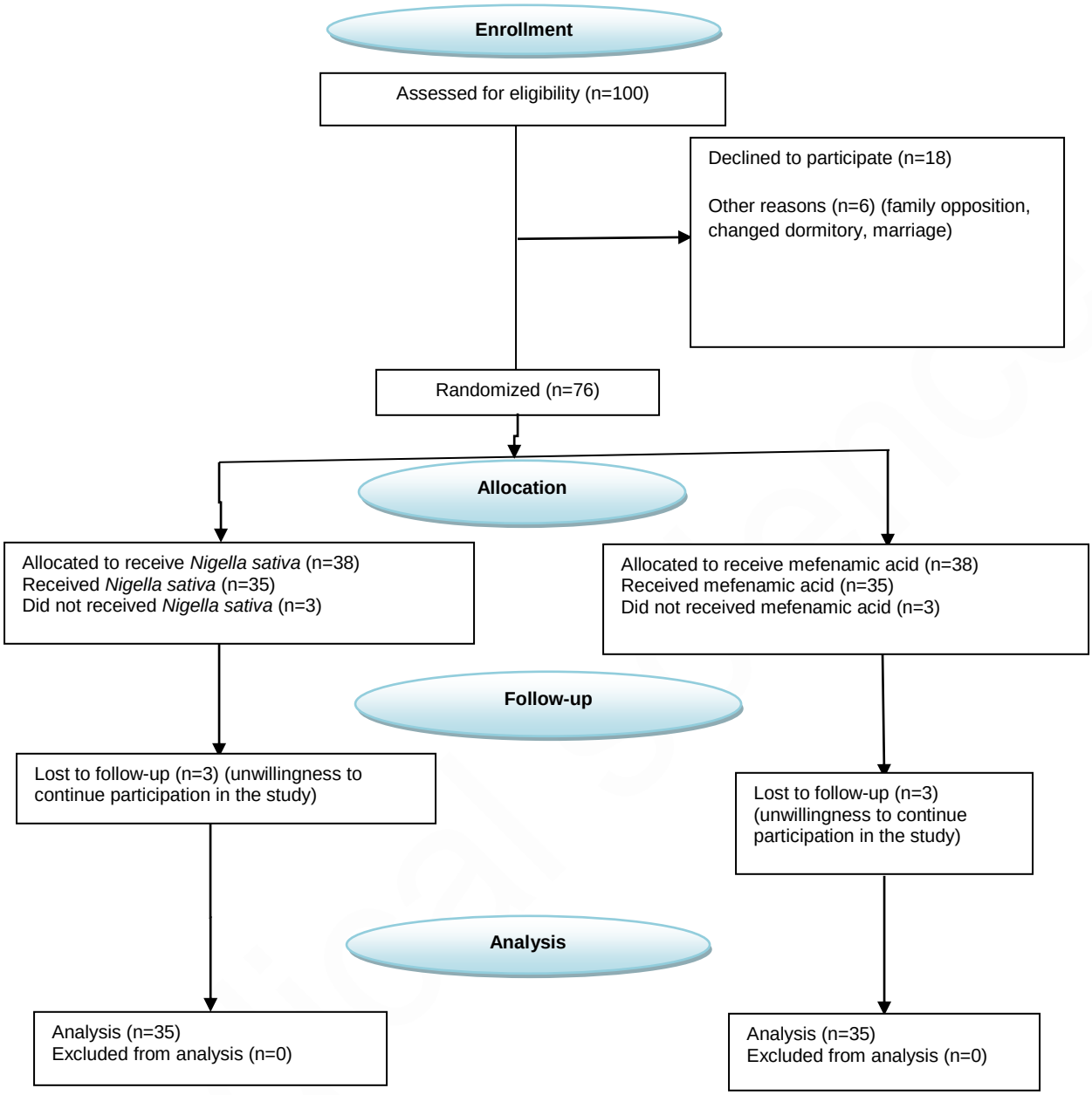

Figure 1 The flow of participants through the study

effects of *Nigella sativa* and those of mefenamic acid on the severity, duration, and systemic symptoms of dysmenorrhea.

MATERIALS AND METHODS

Procedures

Nigella sativa was collected from Torbat Heydarieh (a northeastern Iranian city), with its seeds dried at room temperature in the absence of sunlight. The botanists in theherbarium of Ferdowsi University of Mashhad identified theplant with the specimen number of 293-0303-1. *N.sativa* seeds were processed into a powder encapsulated in pharmaceutical-grade capsules. Each capsule contained 500mg of the *N.sativa* seed powder, with the prescribed dose for each participant having been two capsules, three times a day (TDS) (n=38). The dosage and treatment period were selected based on previous studies (15). The mefenamic acid capsules of 250mg (two 500mg capsules with 125mg of effective materials) were purchased from Razac Pharmaceuticals company (Tehran, Iran) and used as TDS (n=38).

Participants

The present study was a double-blind randomized placebo-controlled trial, consisted of voluntary single students with moderate-to-severe dysmenorrhea experiences living at the dormitory of Mashhad University of Medical Sciences (Mashhad, Iran). The trial started in October 2014 and ended in December 2014. Based on statistical estimates, 70 participants were required to reach the statistical significance at a 95% confidence interval. Computer-generated random numbers were employed to divide participants into two groups for taking *Nigella sativa* (n=35) or mefenamic acid (n=35). Both participants and researchers were kept blinded in allocating the treatment (Fig. 1). The inclusion criteria were aging 18-30, having a

Table 1 Demographic characteristics of the participants

Variation	*Nigella sativa*	Mefenamic Acid	P(Man-Whitney)
Age (year)	22/9±3/54	22/14±3/02	0/38
BMI (Kg/m^2)	21.39 ± 1.28	21.75 ± 1.62	0.199
Age at menarche(year)	13/22±1/21	13/25±1/19	0/87
Age of dysmenorrheal(year)	14/32±1/30	14/25±1/55	0/53
Length of Menstrual Cycle(day)	29/05±2/74	28/7±3/43	0/57

Table 2 Severity of Dysmenorrhea before and After the Intervention in Study Groups

Treatment Round	Before Treatment $\overline{X} \pm SD$	Four Weeks After Treatment $\overline{X} \pm SD$	Eight Weeks After Treatment $\overline{X} \pm SD$	P(Friedman)
Nigella sativa	7/31±1/30	1/59±1/17	1/50±0/98	P<0/001
Mefenamic Acid	7/85±1/39	2/21±1/06	1/91±102/	P<0/001
P(Man-Whitney)	1/884	0/024	0/045	

normal body mass index (19.8-25 kg/m^2), and experiencing regular menstrual periods with moderate to severe primary dysmenorrhea. Students who used any supplements or medicines, including those who had used herbal medicines during the past 3 months, those who had chronic diseases or symptoms of genital tract infections, and the ones who had experienced stressors, such as the separation of parents and the death of first-degree relatives in the past six months were not included. The exclusion criteria were unwillingness to continue participation at any stages of the research, the development of pelvic pathology (myoma, pelvic tumors, endometriosis, and pelvic infections) during the study, the improper use of medicines, and taking other medicines during the study. Written informed consent was obtained from all students before their participation. It was supposed that some people might develop an allergy to *Nigella sativa*; however, no case was found with allergic reactions to *Nigella sativa* and mefenamic acid. Eligible individuals were assessed for the severity, duration, and systemic symptoms of the menstrual pain and placed in separate blocks (with either moderate or severe dysmenorrhea). Next, they were allocated randomly to the *Nigella sativa* and mefenamic acid groups to receive *Nigella sativa* and *Mefenamic acid*, respectively. At the beginning of the study, the participants' weight and height were measured, with their demographic data, including age, menarche age, and dysmenorrhea agecollected. The subjects were then asked to maintain their normal diet and physical activities during the study. All capsules were nameless, coded, and similar in shape and packaging. All subjects were instructed to take 2 capsules every 8 hours in the first three days of menstruation, for two consecutive cycles. A menstrual status questionnaire about the severity, duration, and systemic symptoms of the menstrual pain was distributed at the baseline and end of each period. The pain severity duration and systemic symptoms were assessed in 24, 48, and 72 hours after the intervention. During the first three days of each menstrual flow, the subjects were asked to mark their maximum daily pain severity on a visual analogue scale (VAS), which ranged from 1 to 10, with the scores 1-3, 4-7, and 8-10 implying mild pain, moderate pain, and severe pain. The VAS was developed at McGill University, with its validity and reliability approved (12). The duration of pain was measured using the cox menstrual symptom scale (CMSS) during the first three days of menstrual bleeding (13). Based on this scale, the pain duration was divided into5 scales, i.e. 0= no pain, 1= pain shorter than 0.5 hour, 2= pain lasting between 0.5 and 1 hour, 3= pain lasting for a few hours, and 4=pain lasting for a few days. In addition, the number of the times of systemic symptoms, including fatigue, diarrhea, syncope, nausea and vomiting, lack of energy, headaches, and mood swings, was counted. To determine the validity of the questionnaire, content validity was used. The questionnaire was distributed among10 faculty members of Mashhad University of Medical Sciences and utilized after revision. To determine the reliability of the questionnaire, a Cronbach's alpha test was used. The reliability of the questionnaire was determined to be 0.89.

Statistical analysis

The collected data were analyzed using SPSS statistical software, version 16 (SPSS Inc., Chicago, IL., USA). Descriptive statistics, the independent t-test, the chi-square test, repeated measurements, the Friedman test, and the Man-Whitney U test were utilized to analyze the results. P<0.05 was considered significant.

Ethical considerations

The study protocol was approved by the Research and Ethics Committee of Mashhad University of Medical Sciences and registered with the Iranian Registry of Clinical Trials under code 'IRCT2014040117111 N1'.

RESULTS

The length of the menstrual period in all participants ranged from three to 10 days, and the interval between the periods ranged from 21 to 35 days. In order to control the confounding factors, both groups were matched in terms ofthe factors of age, BMI, menarche age, the length of the menstrual cycle, with no statistically significant difference found between the two groups concerning these variables (Table 1), (Fig.2).

The mean severity of pain in the *Nigella sativa* group decreased from 7.31±1.30 before the intervention to 1.50±0.98 during the second cycle. The mean value of pain in the mefenamic acid group was 7.85±1.39 before the intervention, which decreased to 1.91±1.02 in the second cycle. Before the intervention, the mean durations of pain were

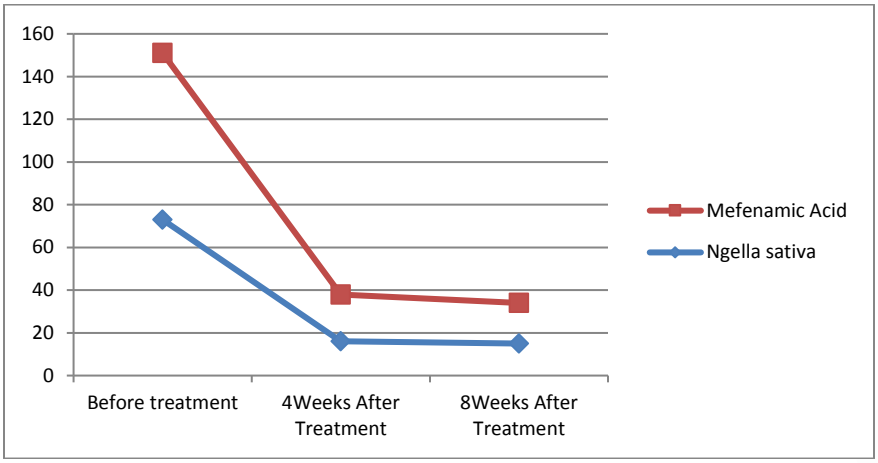

Figure 2 Severity of Dysmenorrhea Before and After the Intervention in Study Groups

Table 3 Duration of Dysmenorrhea Before and After the Intervention in Study Groups

Treatment Round	Before Treatment $\overline{X} \pm SD$	4 Weeks After Treatment $\overline{X} \pm SD$	8 Weeks After Treatment $\overline{X} \pm SD$	P-value (Friedman)
Nigella sativa	3/34±0/48	1/19±0/47	1/45±0/45	P<0/001
Mefenamic Acid	3/45±0/50	1/45±0/50	1/46±0/45	P<0/001
P(Man-Whitney)	0/336	0/023	0/001	

Table 4 Severity of Systemic Signs Associated with Dysmenorrhea

Systemic sign	Before Treatment			Four Weeks After Treatment			Eight Weeks After Treatment		
	Percentage			Percentage of recovery			Percentage of recovery		
	Nigella sativa	Mefenamic Acid	P-Value	*Nigella sativa*	Mefenamic Acid	P-Value	*Nigella sativa*	Mefenamic Acid	P-Value
Nausea and vomiting	65/7	42/9	0/05	95/7	93/3	0/754	95/7	93/3	0/754
Lack of energy	28/6	17/1	0/251	90	83/3	0/696	90	83/3	0/696
Headache	68/6	57/1	0/326	90	83/3	0/583	90	83/3	0/583
Diarrhea	42/6	37/1	0/468	94/1	100	0/81	94/1	94/3	0/629
Fatigue	88/6	91/4	0/692	100	50	P<0/001	100	59/4	P<0/001
Mood swings	77/1	82/9	0/552	86/3	48/3	P<0/001	86/3	51/7	P<0/001
Syncope	42/9	28/6	0/281	93/3	70	0/075	93/3	70	0/068

3.34±0.48 and 3.45 ±0.50 in the *Nigella sativa* and mefenamic acid groups, respectively. The corresponding values were 1.11±0.36 and 1.46 ±0.45 on the second cycle (Tables 2 and 3). The two groups were not significantly different in the mean severity and duration of pain before the intervention. However, during the first and second menstrual cycles, the mean severity and duration of pain were significantly lower in the *Nigella sativa* group than in the mefenamic acid group (P< 0/05). The severity of the systemic symptoms, like fatigue and mood swings, in each of the two treatment groups before the intervention and the two cycles after the treatment revealed that the *Nigella sativa* and the mefenamic acid groups had a statistically significant difference (P<0/001). In addition, the variables, like nausea and vomiting, lack of energy, headaches, diarrhea, and syncope demonstrated no significant difference between the *Nigella sativa* and mefenamic acid groups after the treatment (Table 4). Besides, no side effect was reported in both *Nigella sativa* and mefenamic acid groups.

DISCUSSION

The results of the present study showed an improvement in severity, duration, and systemic symptoms, such as fatigue and mood swings in patients receiving *Nigella sativa* compared to the mefenamic acid group. The severity of dysmenorrhea was improved from severe to mild according to the VAS results. This was the first report of a comparative study on the effects of *Nigella sativa* and mefenamic acid on the alleviation of pain in primary dysmenorrhea. Traditionally, *Nigella sativa* is used for treating medicinal properties such as bronchodilatory, hypotensive, antibacterial, antifungal, analgesic, anti-inflammatory and immune-potentiating (14). *Nigella sativa* was found to be able to relieve the symptoms of or cure patients with several diseases, such as

hypertension, dyslipidemia, metabolic syndrome, diabetes, asthma and convulsion (15). The study by Mahmoud Aqel et al. showed that Nigella sativa seeds inhibited the spontaneous movements of uterine smooth muscles in rats and guinea pigs as well as the contractions induced by oxytocin stimulation (16). In another study, Huseini et al. confirmed that *Nigella sativa* showed significant analgesic effects on patients with cyclic mastalgia (17). In addition, Oysu et al. confirmed some of the nasal symptoms for example, nasal dryness, obstruction, and crusting, can be significantly improved by using Nigella sativa oil (18). A study by Mahboubi et al. demonstrated that *Nigella sativa* inflammatory effects on rat acute sinusitis (19). In addition, Tamer A. Gheita et al. suggested the use of *Nigella sativa* as supplementation therapy for the treatment of rheumatoid arthritis and inflammatory diseases (20).

CONCLUSION

All studies described above demonstrated that natural remedies were more effective treatments than synthetic ones, with no significant side effect. *Nigella sativa*appeared to have beneficial effects onthe severity and duration of the systemic symptoms of dysmenorrhea, due to its anti-inflammatory, analgesic, and relaxating impacton smooth muscles.The results showed that *Nigella sativa* was as effective as mefenamic acid in decreasing pain in the subjects with primary dysmenorrhea.

REFERENCES

1. Adib Rad H, Basirat Z, Bakouei F, Moghadamnia AA, Khafri S, Farhadi Kotenaei Z, et al. Effect of Ginger and Novafen on menstrual pain: A cross-over trial. Taiwanese journal of obstetrics & gynecology. 2018 Dec;57(6):806-9.
2. Blodt S, Pach D, Eisenhart-Rothe SV, Lotz F, Roll S, Icke K, et al. Effectiveness of app-based self-acupressure for women with menstrual pain compared to usual care: a randomized pragmatic trial. on American journal of obstetrics and gynecology. 2018 Feb ;e1- e9.
3. Shetty GB, Shetty B, Mooventhan A. Efficacy of Acupuncture in the Management of Primary Dysmenorrhea: A Randomized Controlled Trial. Journal of acupuncture and meridian studies. 2018 Aug;11(4):153-8.
4. Yang M, Chen X, Bo L, Lao L, Chen J, Yu S, et al. Moxibustion for pain relief in patients with primary dysmenorrhea: A randomized controlled trial. PloS one. 2017;12(2):e0170952.
5. Uysal M, Doğru HY, Sapmaz E, Tas U, Çakmak B, Ozsoy AZ, et al. Investigating the effect of rose essential oil in patients with primary dysmenorrhea. Complementary therapies in clinical practice. 2016;24:45-9.
6. Aljabre SH, Alakloby OM, Randhawa MA. Dermatological effects of Nigella sativa. Journal of Dermatology & Dermatologic Surgery. 2015;19(2):92-8.
7. Kooti W, Hasanzadeh-Noohi Z, Sharafi-Ahvazi N, Asadi-Samani M, Ashtary-Larky D. Phytochemistry, pharmacology, and therapeutic uses of black seed (Nigella sativa). Chinese journal of natural medicines. 2016;14(10):732-45.
8. Shanmugam MK, Arfuso F, Kumar AP, Wang L, Goh BC, Ahn KS, et al. Modulation of diverse oncogenic transcription factors by thymoquinone, an essential oil compound isolated from the seeds of Nigella sativa Linn. Pharmacological research. 2018;129:357-64.
9. Gholamnezhad Z, Havakhah S, Boskabady MH. Preclinical and clinical effects of Nigella sativa and its constituent, thymoquinone: A review. Journal of ethnopharmacology. 2016;190:372-86.
10. Majdalawieh AF, Fayyad MW. Immunomodulatory and anti-inflammat International immunopharmacology. 2015;28(1):295-304.
11. Ijaz H, Tulain UR, Qureshi J, Danish Z, Musayab S, Akhtar MF, et al. Nigella sativa (Prophetic Medicine): A Review. Pakistan journal of pharmaceutical sciences. 2017;30(1).
12. McMahon SB, Koltzenburg M, Tracey I, Turk D. Wall & Melzack's Textbook of Pain E-Book: Elsevier Health Sciences; 2013
13. Cox DJ, Meyer RG. Behavioral treatment parameters with primary dysmenorrhea. Journal of behavioral medicine. 1978;1(3):297-310.
14. Khan MA, Afzal M. Chemical composition of Nigella sativa Linn: part 2 recent advances. Inflammopharmacology. 2016;24(2-3):67-79.
15. Tavakkoli A, Mahdian V, Razavi BM, Hosseinzadeh H. Review on Clinical Trials of Black Seed (Nigella sativa) and Its Active Constituent, Thymoquinone. Journal of pharmacopuncture 2017 Sep;20(3):179-93.
16. Aqel M, Shaheen R. Effects of the volatile oil of Nigella sativa seeds on the uterine smooth muscle of rat and guinea pig. Journal of Ethnopharmacology. 1996;52(1):23-6.
17. Huseini HF, Kianbakht S, Mirshamsi MH, Zarch AB. Effectiveness of topical Nigella sativa Seed Oil in the treatment of cyclic Mastalgia: a randomized, triple-blind, active, and placebo-controlled clinical trial. Planta Med. 2016;82(4):285-8.
18. Oysu C, Tosun A, Yilmaz HB, Sahin-Yilmaz A, Korkmaz D, Karaaslan A. Topical Nigella sativa for nasal symptoms in elderly. Auris Nasus Larynx. 2014;41(3):269-72.
19. Mahboubi M. Natural therapeutic approach of Nigella sativa (Black seed) fixed oil in management of Sinusitis. Integrative medicine research. 2018 Mar;7(1):27-32.
20. Gheita TA, Kenawy SA. Effectiveness of Nigella sativa oil in the management of rheumatoid arthritis patients: a placebo-controlled study. Phytotherapy Research. 2012;26(8):1246-8.
21. Zeinab Younes Barani, Maryam Shahraki. Comparison of the effect of ice massage in the LI4 and SP6 on Primary Dysmenorrhea: A blinded clinical trial. Medical Science, 2018, 22(94), 544-548
22. Fatimatuz Zahra, Mahbubur Rahman AHM. Medicinal uses of angiosperm weeds in and around Rajshahi metropolitan city of Bangladesh. Science & Technology, 2018, 4, 52-70
23. Hamedeh Bagheri, Parichehreh Yaghmaei, Mohamadhosein Modaresi, Azadeh Ebrahim-Habibi, Marjan Sabbaghian. Role of Cymene in the attenuation of fatty liver and UCP2 gene expression. Medical Science, 2018, 22(90), 232-242
24. Mst. Mabia Khatun, Mahbubur Rahman AHM. Traditional knowledge of medicinal plants used by the local people in Bagmara Upazila of Rajshahi district, Bangladesh. Discovery Nature, 2018, 12, 5-31

Article Keywords

Nigella sativa, Mefenamic acid, Primary dysmenorrhea, Physiotherapy

Funding/Support

This study was supported by Mashhad University of Medical Sciences.

Article History

Received: 2 January 2019
Accepted: 15 February 2019
Published: March-April 2019

Citation

Fatemeh Mohanazadeh Falahieh, Farzaneh Jafarnejad, Hassan Rakhshandeh, Mohammad-Taghi Shakeri, Malihe Motavasselian. Comparison of the effects of *Nigella sativa* and Mefenamic acid on the severity, duration, and systemic symptoms of primary Dysmenorrhea. *Medical Science*, 2019, 23(96), 233-237