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Effective reduction of primary dysmenorrheal symptoms through concurrent use of n-3 fatty acids and Rosa damascena extract (RDE)

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Abstract

Background: Primary dysmenorrhea (PD) is characterized by painful cramps of lower abdomen without abnormal pelvic pathology. PD begins some hours before or simultaneously with the onset of menstrual bleeding.

Objectives: The purpose of this study was to investigate the effects of separate and concurrent supplementation of fish oils (FO) containing n-3 fatty acids and Rosa Damascena extract (RDE) on PD symptoms.

Methods: In this double blind clinical trial in 2015, through convenience sampling, 105 university students with primary menstrual pain in most recent years, without abnormal pathology, and with moderate/severe dysmenorrheal symptoms according to visual analogue scale (VAS) were randomly assigned into one of four groups: 1. FO 1000 mg/day (n=26), 2. RDE 1000 mg/day (n=27), 3. FO and RDE concurrently, with the same dose (n=27), and 4. Control group (n=25). All measurements were performed three times, at the beginning, 30th day, and 60th day. Symptoms including nausea, vomiting, diarrhea, bloating, cramp, low back pain, headache, fatigue, anxiety, sweat, weakness, dizziness, drowsiness, and feeling cold were measured by VAS.

Results: After 2-month treatment, supplementation with RDE significantly reduced severity of bloating ($p<0.001$) and sweat ($p<0.001$), but FO supplementation had no significant effect on PD symptoms. The concurrent use of FO and RDE significantly decreased severity of diarrhea ($p=0.038$), weakness ($p<0.001$), dizziness ($p=0.003$), and feeling cold ($p=0.049$).

Conclusion: Our results suggest that the concurrent supplementation of omega-3 fatty acids and RDE could be more effective than their separate use in decreasing PD symptoms; however, larger trials are warranted to confirm these preliminary findings.

Key words: dysmenorrhea, rosa damascena, fish oils, symptoms

Introduction

Dysmenorrhea means painful menstruation and has two types: primary and secondary (1). Primary dysmenorrhea (PD) is characterized by painful cramps of lower abdomen without abnormal pelvic pathology. PD begins some hours before or simultaneously with the onset of bleeding and takes up to 72 hours. Secondary dysmenorrhea is defined as pelvic pain associated with pathological conditions such as endometriosis and adenomyosis [1,2].

The prevalence of dysmenorrhea is estimated to be 45-90% in different countries [3]. For example, its prevalence has been reported to be 87.7%, 67% and more than 70% (59%-82%) in Turkey, Mexico and Iran, respectively [1,3].

Dysmenorrhea is a major cause of impaired quality of social activities of women at childbearing age [4], especially if it is associated with symptoms such as headache, fatigue, nausea, vomiting, diarrhea, irritability, chills, and muscle cramps. Because of dysmenorrhea complaints,

about 1% of women at childbearing age may take time off from work for three days in a month. This leads to a waste of 600 million work hours and economically 2 billion dollars annually in some communities like the USA (2, 4).

The inflammatory response initiated by the prostaglandins (PGs) and leukotrienes (LTs) results in vasoconstriction, myometrial contraction, and ischemia that cause pain, gastrointestinal symptoms such as nausea, vomiting and bloating, and headache [5]. Causes of cramps and systemic symptoms of PD may be psychological, endocrine, cervical factors, abnormally increased uterine activity, and excessive synthesis and secretion of PGs. Uterine cramps are associated with 50% of cases with one or several systemic symptoms including nausea and vomiting 90%, fatigue 85%, diarrhea 60%, lower back pain 60%, and headache 45% [6].

Various treatments including non-invasive methods such as psychotherapy, yoga, hypnotic, prescription vitamins and food supplements and aggressive treatments such as surgery, acupuncture, and medical treatments such as PG synthesize inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs) and oral contraceptives have been tried to treat dysmenorrhea [4]. Among these treatment methods, the most commonly used are drugs, but given their side effects such as gastrointestinal problems and kidney failure [7,8], many people with dysmenorrhea keep looking for alternative remedies like herbal and nutritional ones. The beneficial effects of nutritional supplements such as Valerian, FO, vitamin B_{12}, Cinnamon, cumin, and wheat germ extract on symptoms of dysmenorrhea have been reported [6,9-11].

Supplementation with omega-3 fatty acids, which are found mainly in fish oil, mediates the production of less potent PGs and LTs, resulting in a reduction in the severity of myometrial contractions and uterine vasoconstriction, a decrease in the formation of inflammatory mediators, and subsequently reduced ischemia and improved blood flow [7], thereby relieving pain and probably other dysmenorrheal symptoms (12-15). Sampalis et al evaluated the effects of omega-3 fatty acids on premenstrual syndrome and dysmenorrhea. Supplementation with omega-3 fatty acids significantly decreased the severity of symptoms such as weight gain ($p<0.01$) and swelling ($p<0.001$) after 90 days (7). Supplementation with omega-3 fatty acids reduced the symptom intensity of primary dysmenorrhea and the ibuprofen rescue dose [12].

Rosa Damascena (RD) or damask rose is one of the most important species of the Rosacea family [16]. RD has commonly been applied in traditional medicine to treat pains of abdomen and chest, strengthen the heart, and also treat menstrual bleeding, digestion problems as well as inflammation, especially on the throat [16,17].

According to the beneficial effects of omega-3 fatty acids and Rosa Damascena extract (RDE) in relieving menstrual pain severity, and since only a few previous studies have evaluated the effects of n-3 fatty acids (FO) on reducing some systemic symptoms of dysmenorrhea in combination with anti-inflammatory and relaxant effects of RD (flavonoid compounds), the purpose of this study was to investigate the effects of separate and concurrent supplementation of n-3 fatty acid and Rosa Damascena extract (RDE) on some of the PD symptoms.

Methods

This double blind clinical trial investigated the effects of fish oil (FO) and RDE supplementation on severity of common systemic dysmenorrhea symptoms such as nausea, vomiting, diarrhea, bloating, cramp, low back pain, headache, fatigue, anxiety, sweat, weakness, dizziness, drowsiness, and feeling cold among female university students with PD. The study design was explained to participants living in the dormitories in Tabriz University of Medical Sciences (Tabriz, Iran). Inclusion criteria were as follows: 1- primary menstrual pain in most recent years, without abnormal pathology, 2- having moderate and severe dysmenorrhea based on visual analogue scale (VAS), 3- regular menstrual cycles (21-35 day), 4- body mass index (BMI)=18.5-24.9 kg/m^2. The validity and reliability of VAS and IPAQ have already been approved in various studies [4-6,12,18]

Whole-counting method was used for initial sampling, that is the total female students of Tabriz University of Medical Sciences living in

student dormitories were included in the study considering inclusion and exclusion criteria.

The severity of dysmenorrhea was determined on a 10-point scale [1,3]. In this method, the scores of the pain classified as mild (1-3), moderate (4-7), and severe (8-10). Visual analogue scale (VAS) was used to measure the severity of the symptoms.

This trial was approved by the Ethics Committee of Tabriz University of Medical Sciences, and written consent was obtained from those who were willing to participate in the study. This study is registered at the Iranian Registry of Clinical Trials (IRCT registration number: (IRCT201403105670N8) and the Code of Ethics applies to: No.92212 in the department of research and technology of Tabriz University of Medical Sciences.

The participants who agreed to take part in this study were interviewed and requested to complete questionnaires including information on demographic characteristics, consumption frequency of major dietary resources of n-3 fatty acids including fish, nuts, fruit, and vegetables (time/week) by a Qualitative- Food Frequency Questionnaire (FFQ) and physical activity levels (PAL) by International Physical Activity Questionnaire (IPAQ). These were checked only before the study, in order to match and adjust the major confounding factors in the studied groups. Some of the menstrual characteristics included pain and symptoms of dysmenorrhea [1,3,11].

After a primary examination (n=1200 students), 120 women who met the above inclusion criteria were registered to participate in the present study. A diagnosis of dysmenorrhea was made with the assistance of a gynecologist. Subjects were assigned into one of the four groups using simple randomized method: 1) Fish oil with Rosa Damascena extract placebo (FO+RDEP): 1000 mg/day soft gel capsules of fish oil (FO) containing 180 mg Eicosapentaenoic acid (EPA), 120 mg of Docosahexaenoic acid (DHA) (n=30); 2) Rosa Damascena extract with Fish oil placebo(RDE+FOP): 1000 mg/day capsules containing 200 mg of RDE (n=30); 3) Fish oil with Rosa Damascena extract (FO+RDE): 1000 mg/day FO capsules and 1000 mg/day RDE concurrently (n=30); and 4)Fish oil placebo and Rosa Damascena extract placebo(FOP+RDEP) (n=30). For blinding the study an epidemiologist student as third party was asked to pack and number the supplements based on the proposed groupings from 1 to 4. The main capsules and placebos were of similar size and shape. Patients were not informed about which group they were in. In order to make the investigator and final evaluator unaware of the type of treatment in each group, the distribution of supplements and placebos was prescribed by a fourth person who did not know the details of the study and capsules packs contents. Finally, the patients, the researcher and the final evaluator were not aware of the type of treatment patients and the allocation of the groups.

At the beginning of the study, the groups had no significant difference in terms of variables such as diet and physical activity. Symptoms intensity was measured by VAS [28] at the beginning, and 30th and 60th days after the interventions. The sample size was determined based on the formula below.

$$n = \frac{a\sigma^2}{\sum T_i^2}\emptyset^2 = \frac{4 * 531.3}{532.71}(2.5)^2 = 24.93 \cong 25$$

n demonstrates sample size (25) for each group

a demonstrates the number of groups (4)

σ demonstrates the total variance (23.05)

T_i demonstrates the deferent mean of group i from total mean (T_1=11.22, $T_2 = 10.11$, $T_3 = 12.96$, $T_4 = 11.69$, $\sum T_i^2$ =532.71)

$\emptyset$ demonstrates carve characteristic (2.5)

The influential variables were adjusted between the two groups (one with one-gram soft gel capsule of FO and the other without it) in two sub-groups (one with one-gram capsules of RDE and the other without it) at the 1st day before starting the experimental procedures. For quantitative data, normality was evaluated by Q-Q test, and outlier data were removed. Then, two-way repeated measures of ANCOVA were used to compare pain severity, bleeding days, and quantity of bleeding between RDE factor and FO factor. For repeated measures data at first, Mauchly's W test was checked for identity covariance matrix, and repeated measures test applied using Minitab Software, version 17. The results included four p values, the first p value

was used to compare RDE and non- RDE groups, the second was p value treatment for comparing FO and non-FO groups, the third was p-value interaction for recognizing interaction effects between RDE factor and FO factor and the final p value for comparing variations at three time points of the interventions. Sidak test was used for multiple comparisons. The level of significance was set at 0.05, and all results were expressed as Mean±SEM (standard error of mean).

Results

Of the 120 female students who enrolled, 15 discontinued as subjects of the study: 3 from group 1, 4 from group 2, 3 from group 3, and 5 from group 4 (Figure 1).

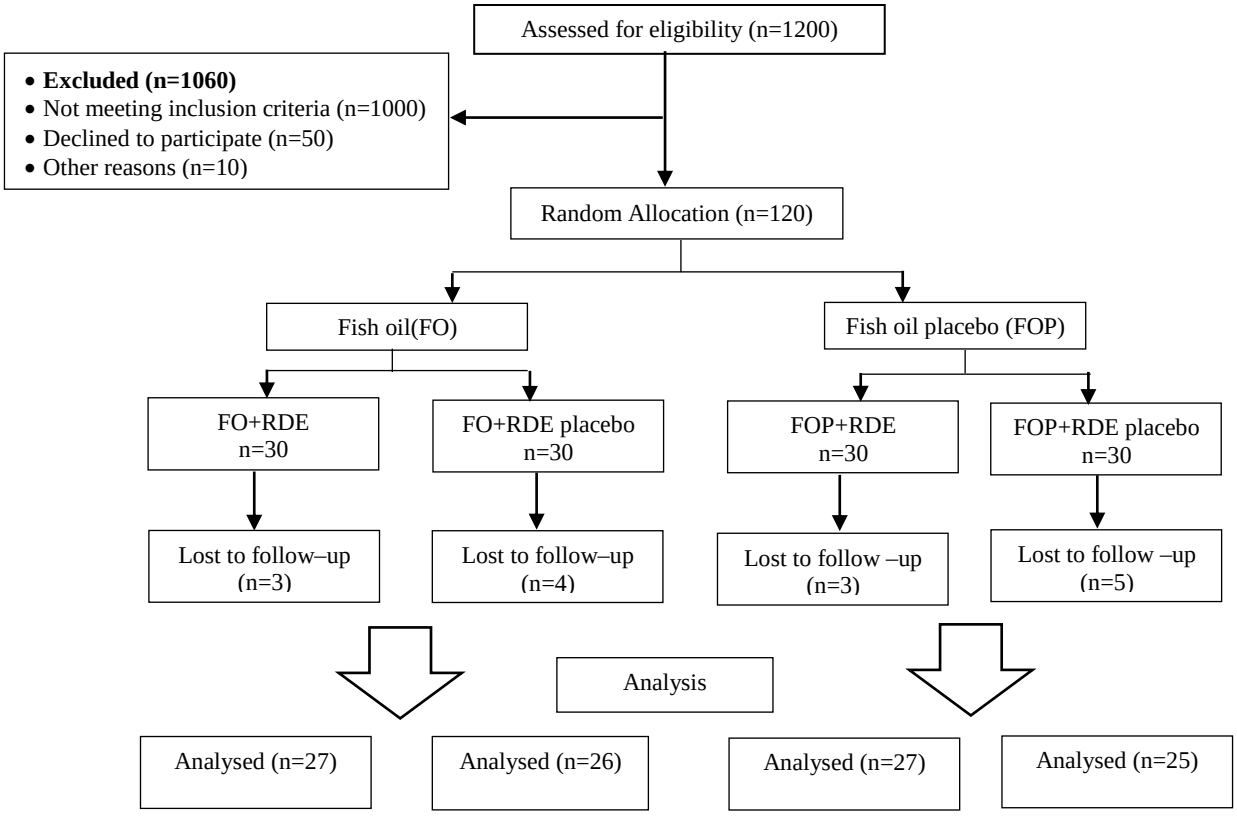

Figure 1: Flow diagram of study selection and data collection process

As shown in Tables 1 and 2, no significant difference was observed for baseline characteristics including the mean pain severity score (p=0.069), BMI (p=0.880), menarche age (p=0.70), consumption frequency (time/week) of major dietary resources of n-3 fatty acids: fish (p=0.98), nuts (p=0.67), fruits (p=0.24), and vegetables (p=0.88) between groups. The mean of menstrual cycle days (p=0.01) and PAL (p=0.04) was significantly different between the study groups. Statistical analyses were adjusted for the effect of confounding variables such as age, menarche age, BMI, menstrual cycle days, family history of dysmenorrhea, PAL, the number of analgesic drugs such as gelofen-200, gelofen-400, acetaminophen-325, acetaminophen-500, acetaminophen codeine, mefenamic acid, suppository, and frequency of fish, nuts, and fruit and vegetables consumption.

Table 1: Mean±Sd of baseline characteristics of study groups

Group	RDE + FOP (n=27)	FO + RDE (n=27)	FO + RDEP (n=26)	RDEP + FOP (n=25)	P value*
Age (year)	22.63±0.47	21.96±0.56	21.15±0.40	22.08±0.39	0.15
BMI (kg/m^2)	21.35±0.43	20.97±0.46	21.30±0.46	21.45±0.43	0.88
PAL (1-3)	1.15±0.09	1.40±0.13	1.46±0.11	1.60±0.13	0.04
Menarche age (year)	13.19±0.26	13.00±0.23	13.08±0.27	13.40±0.24	0.70
Menstrual cycle (day)	27.37±0.53	29.56±0.52	28.65±0.38	28.88±0.43	0.01
Pain severity (VAS=0-10)	7.52±0.23	6.68±0.33	7.15±0.26	6.64±0.26	0.06

FO=Fish oil; RDE= Rosa Damascena extract; RDEP= Rosa Damascena extract placebo; FOP=Fish oil placebo; *One Way Anova test, PAL=Physical activity level; VAS=Visual analogue scale.

Table 2: Mean±Sd of baseline characteristics of study groups

Group	RDE + FOP (n=27)	FO + RDE (n=27)	FO + RDEP (n=26)	RDEP + FOP (n=25)	P value
Fish (times/wk)	0.13±0.02	0.12±0.01	0.12±0.02	0.12±0.01	0.980
Nuts (times/wk)	0.23±0.05	0.19±0.07	0.15±0.04	0.22±0.05	0.670
Fruits (times/wk)	0.85±0.09	0.85±0.09	1.11±0.11	1.00±0.13	0.240
Vegetables (times/wk)	0.22±0.07	0.27±0.06	0.20±0.08	0.21±0.05	0.880

FO=Fish oil; RDE= Rosa damascena extract; RDEP= Rosa damascena extract placebo; FOP=Fish oil placebo; *One Way Anova test,

As shown in Table 3, after two months of supplementation with RDE, the severity of bloating ($p<0.001$) and sweat ($p<0.001$) significantly reduced, but FO supplementation had no significant effect on dysmenorrhea symptoms. Diarrhea ($p=0.038$), weakness ($p<0.001$), dizziness ($p=0.003$) and feeling cold ($p=0.049$) had diminished significantly following the concurrent use of FO and RDE (table 3). Time had a significant effect on nausea ($p=0.016$), vomiting ($p=0.038$), diarrhea ($p=0.043$), bloating ($p=0.004$), cramp ($p<0.001$), anxiety ($p<0.001$), headache ($p=0.002$), dizziness ($p=0.009$), sweat ($p=0.001$), low back pain ($p<0.001$), and fatigue ($p<0.001$; Table 3).

RDEP and FOP had no significant effect on systemic symptoms of primary dysmenorrheal.

Table 3: Mean(Sd) of systemic symptoms of primary dysmenorrhea in study groups

Fish Oil Factor	Yes						No						P value*			
RDE[1] Factor	Yes			No			Yes			No			FO	RDE	FO + RDE	Time
systemic symptoms	begin	30th day	60th day	Begin	30th day	60th day	begin	30th day	60th day	begin	30th day	60th day				
Nausea	1.40 (0.41)	2.40 (0.71)	1.72 (0.54)	3.70 (0.73)	3.11 (0.66)	1.40 (0.39)	2.00 (0.39)	1.38 (0.32)	1.07 (0.32)	2.52 (0.44)	2.72 (0.56)	2.48 (0.49)	0.68	0.17	0.84	0.016
Vomiting	0.72 (0.40)	1.76 (0.71)	1.12 (0.45)	1.92 (0.73)	1.00 (0.43)	0.44 (0.14)	0.23 (0.84)	0.30 (0.10)	0.76 (0.53)	0.44 (0.33)	0.64 (0.29)	1.12 (0.40)	0.06	0.86	0.19	0.038
Diarrhea	1.96 (0.53)	2.52 (0.59)	1.72 (0.46)	2.40 (0.56)	2.07 (0.48)	1.33 (0.38)	2.88 (0.62)	1.84 (0.48)	1.38 (0.31)	1.68 (0.37)	1.16 (0.33)	0.72 (0.21)	0.62	0.08	0.03	0.043
Bloating	2.96 (0.56)	1.64 (0.35)	0.92 (0.25)	4.92 (0.59)	3.96 (0.53)	2.74 (0.43)	3.15 (0.59)	2.88 (0.68)	1.96 (0.55)	4.60 (0.44)	4.28 (0.58)	3.84 (0.55)	0.22	0.00	0.25	0.004
Cramp	4.00 (0.36)	3.28 (0.44)	2.00 (0.30)	3.66 (0.51)	3.11 (0.56)	1.85 (0.41)	3.42 (0.54)	2.11 (0.45)	1.69 (0.45)	3.60 (0.51)	2.72 (0.54)	2.56 (0.53)	0.75	0.88	0.29	0.001
Headache	4.08 (0.51)	3.48 (0.44)	2.12 (0.30)	3.62 (0.70)	2.22 (0.44)	1.74 (0.38)	4.07 (0.65)	2.50 0.43	2.30 (0.47)	4.04 (0.61)	3.08 (0.59)	2.60 (0.57)	0.11	0.42	0.49	0.002
Low back pain	6.28 (0.36)	5.64 (0.38)	3.64 (0.37)	6.80 (0.46)	5.88 (0.42)	3.77 (0.47)	5.88 (0.53)	4.03 (0.50)	4.07 (0.60)	5.36 (0.55)	3.68 (0.63)	3.00 (0.59)	0.348	0.166	0.269	0.00
Anxiety	3.44 (0.47)	3.36 (0.46)	2.48 (0.38)	4.85 (0.62)	3.70 (0.62)	2.33 (0.45)	4.88 (0.59)	3.50 (0.45)	2.76 (0.44)	5.00 (0.57)	3.36 (0.66)	3.04 (0.60)	0.425	0.779	0.981	0.00
Weakness	3.80 (0.48)	3.80 (0.53)	2.56 (0.40)	4.96 (0.56)	3.74 (0.53)	2.74 (0.46)	2.74 (0.46)	4.07 (0.56)	3.50 (0.44)	4.84 (0.58)	2.88 (0.53)	2.52 (0.54)	0.514	0.828	·0.00	0. 719
Fatigue	5.04 (0.31)	4.76 (0.37)	2.60 (0.35)	6.55 (0.44)	4.62 (0.61)	3.62 (0.50)	6.15 (0.60)	4.88 (0.58)	4.42 (0.52)	5.84 (0.62)	4.52 (0.56)	4.16 (0.61)	0.125	0.859	0.117	0.00
drowsiness	5.08 (0.12)	4.80 (0.43)	2.88 (0.36)	5.37 (0.58)	4.74 (0.51)	3.81 (0.46)	5.11 (0.55)	5.00 (0.57)	4.03 (0.52)	5.08 (0.62)	4.48 (0.60)	3.72 (0.67)	0.840	0.644	0.328	0.063
Dizziness	3.96 (0.44)	2.88 (0.32)	1.96 (0.41)	2.44 (0.56)	2.25 (0.44)	1.37 (0.31)	2.50 (0.53)	1.23 (0.37)	1.07 (0.35)	3.24 (0.58)	2.56 (0.55)	1.92 (0.58)	0.408	0.325	0.003	0.009
Feeling cold	4.64 (0.43)	4.08 (0.45)	2.80 (0.42)	4.11 (0.63)	4.55 (0.59)	2.88 (0.48)	3.96 (0.57)	3.15 (0.48)	2.73 (0.48)	5.24 (0.47)	5.08 (0.50)	4.12 (0.56)	0.946	0.916	0.049	0.277
Sweat	3.20 (0.60)	3.24 (0.68)	1.80 (0.44)	4.81 (0.57)	3.22 (0.43)	2.44 (0.40)	2.34 (0.46)	1.53 (0.43)	1.61 (0.46)	4.28 (0.60)	2.96 (0.55)	2.28 (0.42)	0.647	0.001	0.811	0.001

Discussion

Our study revealed that RDE had analgesic effects on some PD symptoms such as bloating and sweating. These results are in line with the studies of Cinnamon and Valerian on the symptoms of PD (6). RD is a plant used as a flavoring agent in yogurt in diets of Persians and also as a laxative. Due to its side-effect-free characteristic, this plant could be a good candidate for PD management.

To the best of our knowledge, only a few studies have been conducted on the effect of RD on the pain severity of dysmenorrhea. They have not evaluated its effects on PD symptoms. For example, Tseng et al. showed a significant positive effect of rose tea consumption on relieving pain severity, stress, and anxiety of dysmenorrhea (19). The effects of RDE can be attributed to its compounds including flavonoid, geraniol, eugenol, terpene, and saponin (16, 20 and 21). Studies have confirmed the anti-inflammatory effects of its flavonoid compounds on the metabolism of AA in the enzymatic peroxidation reactions (17). Due to their anti-inflammatory properties, and by decreasing PGs in blood flow, these compounds have a positive impact on the reduction of pain and the severity of the symptoms.

A plethora of studies have been conducted on the health benefits of FO and its components in the literature; however, very few studies have examined the effect of these substances on PD symptoms. Positive effects of omega-3 fatty acid supplementation in relieving pain in dysmenorrhea have been shown in several studies (7, 12, 22). Wu et al suggested that the conversion of linoleic acid to gamma linoleic acid in subjects with dysmenorrhea was slower when they received omega-3 fatty acid supplements (22). The omega-3 fatty acids present in FO possess anti-inflammatory activities that might relieve the symptoms of PD, presumably by influencing the metabolism of prostaglandins (PGs) and other factors involved in pain and inflammation (23). Sampalis et al showed the positive effect of supplementation with omega-3 fatty acids on relieving some dysmenorrhea symptoms including abdominal pain, weight gain, and swelling (7); our results were not in accord with these findings.

In this study, concurrent supplementation of RDE and omega-3 fatty acids had a positive effect on relieving some symptoms of dysmenorrhea such as diarrhea, weakness, dizziness, and feeling cold. This was in agreement with the increasing evidence on the effects of n-3 fatty acid supplementation in combination with vitamins B_{12}, E (antioxidant effect) (16). Although no studies have evaluated the effect of RD on dysmenorrheal symptoms, it seems that antioxidant compounds of RDE reduced PG due to their anti-inflammatory effects, and fish oil improved blood flow, thereby improving symptoms. Nevertheless, detailed studies are warranted to explain the precise mechanisms of this interaction.

The strengths of this study include controlling for the potential confounding factors of age, BMI, menarche age, and intakes of major dietary sources of n-3 fatty acids and phytochemicals. PALs of the subjects were significantly different across the groups that may impact the results. The limitations of this study are as follows. We did not repeat the measurement of the level of physical activity at the end of the study, nor did we evaluate the side effects of supplements. Further studies with a wider range of age, BMI, and inclusion of subjects from different population groups could provide more accurate, accountable, and generalizable results.

In conclusion, based on our results, the supplementation of RDE had positive effects on bloating and sweat in PD patients, but the concurrent use of omega-3 fatty acids and RDE as nutritional supplements was more effective in relieving some systemic symptoms of PD although the mechanisms are yet to be discovered.

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Conflict of interest: The authors declare that there is no conflict of interest associated with this study.

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