JMCH Journal of Maternal and Child Health (2021), 06(03): 353-364
Masters Program in Public Health, Universitas Sebelas Maret

Meta-analysis

The Effectiveness of Fish Oil and Ginger Drink in Reducing Dysmenorrhea: A Meta Analysis

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ABSTRACT

Background: Dysmenorrhea causes 34-50% of women to be unable to work in the workplace and 40% of adolescent girls are absent from school. Fish oil and ginger are used as alternatives to NSAIDs, because although the use of NSAIDs is effective in reducing dysmenorrhea pain, they have side effects that are harmful to health after long-term conventional therapy. This study aims to estimate the magnitude of the effect of fish oil and ginger in reducing dysmenorrhea in women of reproductive age.
Subjects and Method: This was a meta-analysis and systematic study. The articles used were obtained from PubMed, Science Direct, ProQuest, Springer Link, and Google Scholar. The inclusion criteria used were full text articles with Randomized Control Trial (RCT). The study subjects are women of productive age. The treatment given was the consumption of fish oil or ginger with a placebo comparison, dysmenorrhea assessment using standardized measuring instruments such as VAS, Cox, questionnaires, etc. Articles published in English. The PICO Research Problem are population= women of reproductive age, intervention= fish oil or ginger, comparison= placebo, and outcome= dysmenorrhea. The study was assessed using an effect size (Standardized Mean Difference). Meta analysis was performed using RevMan 5.3 with Random Effect Model.
Results: A total of 14 articles were reviewed in a meta-analysis in this study. Meta-analysis of 6 articles showed that fish oil reduced dysmenorrhea pain in women of reproductive age higher than placebo (Standardized Mean Difference= -1.06; 95% CI= -1.76 to -0.36; p= 0.003). Meta-analysis of 8 articles showed that ginger reduced dysmenorrhea pain in women of childbearing age more than placebo (Standardized Mean Difference= -0.77; 95% CI= -1.26 to -0.27; p=0.002).
Conclusion: Fish oil and ginger are effective in reducing dysmenorrhea pain in women of reproductive age.

Keywords: fish oil, ginger, and dysmenorrhea

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Cite this as:
Novitasari I, Pamungkasari EP, Prasetya H (2021). The Effectiveness of Fish Oil and Ginger Drink in Reducing Dysmenorrhea: A Meta Analysis. 06(03): 353-364. https://doi.org/10.26911/thejmch.2021.06.03.10.

BACKGROUND

The prevalence of dysmenorrhea among women of reproductive age ranges from 16 to 91%, whereas, 10-12% of women suffer from severe dysmenorrhea (Chen et al., 2018). Dysmenorrhea causes 34-50% of women to be unable to work in the workplace and 40% of adolescent girls are absent from school. According to annual reports in the United States, dysmenorrhea causes the loss of about 600 million work hours or two million dollars every year and reduces the quality of women's performance (Ferries, 2020).

Dysmenorrhea not only has physical effects but also has psychological effects, such as depression, anxiety, and endangering social relationships. Dysmenorrhea also has a negative impact on sexual life and social relationships. Symptoms related to dysmenorrhea can control women's lives and sacrifice quality of life in all aspects, therefore the impact caused by dysmenorrhea should not be underestimated, both individually and for society, because it can cause loss of productivity in the workplace and use of large health resources (Corte et al., 2020).

The prevalence of primary dysmenorrhea is quite high, causing the importance of providing effective and timely treatment to women who experience dysmenorrhea (Kashefi et al., 2014). The use of non-steroidal anti-inflammatory drugs (NSAIDs) can provide effective pain relief for women with primary dysmenorrhea, but the use of these drugs also has severe side effects after long-term conventional therapy. The side effects of chronic NSAID use are impaired renal function and gastrointestinal bleeding that can limit their use in primary dysmenorrhea. Alternatives to the use of these drugs include several nutritional supplements, including omega-3 fatty acids, magnesium, zinc, vitamin B1 (thiamine), vitamin E, and ginger (Rahbar, et al., 2012).

Omega-3 polyunsaturated long-chain fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are the main active ingredients in fish oil dietary supplements and purified omega-3 fatty acids (Hilleman et al., 2020). Omega-3 fatty acids have many beneficial effects on health and taking fish oil supplements is an alternative way to increase your intake of essential fatty acids. Fish oil supplements improve chemical stability by preventing oxidation and ensuring good organoleptic properties. Some of the benefits of fish oil are to protect the heart so that it prevents coronary heart disease, lowers triglycerides, and is anti-inflammatory (Christophersen et al., 2016).

Ginger (from rizhome of *Zingiber officinale Roscoe*) has been widely used in ethnomedicine for the treatment of several diseases. The main active ingredient in ginger is a phenolic compound called gingerol. The composition contained in ginger is mostly used to treat nausea and vomiting in pregnant women in modern phytotherapy (Pagano et al., 2020).

Gingerol and shogaol can inhibit the synthesis of proinflammatory cytokines, in macrophages, shogaol can reduce inflammation and COX-2 gene expression. Ginger exhibits anti-inflammatory effects by suppressing prostaglandin synthesis as well as interference with cytokine signaling. Ginger powder is as effective as ibuprofen in the treatment of dysmenorrhea (Saha et al., 2020). Ginger reduces the duration of the severity of dysmenorrhea but the mechanism by which fish oil supplements treat dysmenorrhea has not been fully elucidated, so researchers are interested in investigating the effectiveness of using fish oil supplements in reducing dysmenorrhea in women of childbearing age.

SUBJECTS AND METHOD

1. Study Design

This was a systematic review and meta-analysis. The articles were collected from PubMed, Science Direct, ProQuest, Springer Link, and Google Scholar databases. The keywords used: “fish oil” AND “dysmenorrhea”, “ginger”, “randomized control trial.

2. Inclusion Criteria

The inclusion criteria were full paper randomized controlled trails (RCT) articles, using fish oil or ginger intervention, subjects are women of reproductive age and outcomes are measured using standardized

instruments.

3. Exclusion Criteria

The exclusion criteria were women of reproductive age who had a history of infectious diseases, endocrine disorders, chronic diseases or who had undergone major surgery and PID.

4. Operational Definition

Articles included in the study were PICO-adjusted. The search for articles was carried out by considering the eligibility criteria defined using the PICO model. The study population is women of productive age. Intervention group was women consume fish oil or ginger drink and control group was not consumed it. The outcome was dysmenorrhea reduction.

Fish oil is the oral administration of fish oil supplements.

Ginger is the oral administration of ginger supplements

Dysmenorrhea is pain in the abdomen, back or breasts that is felt either before or during menstruation.

5. Instruments

The study used the PRISMA flow diagram and the assessment of the quality of articles using the Critical Appraisal Checklist for RCT Study tools (CEBM, 2014).

6. Data Analysis

The data in this study were analyzed using the RevMan 5.3 application, to calculate the effect size and heterogeneity of the study. The results of data processing are presented in the form of forest plots and funnel plots.

RESULTS

The article review process using the PRISMA flow chart can be seen in Figure 1. The total articles obtained were 14 articles. For the distribution of articles, there are several countries with details 1 from India, 1 from Pakistan, and 12 from Iran.

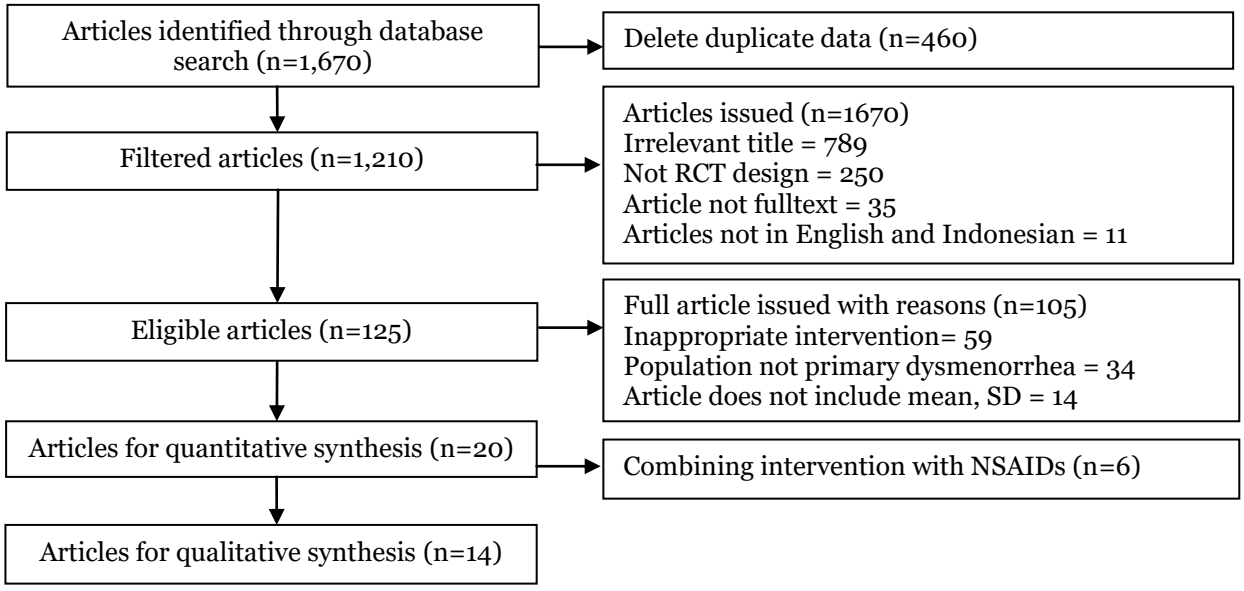

Figure 1. PRISMA flowchart

1. The effectiveness of fish oil in reducing dysmenorrhea

Table 1 shows 6 RCT articles on the effectiveness of fish oil in reducing dysmenorrhea that meet qualitative and quantitative requirements.

Table 1. The effectiveness of fish oil in reducing dysmenorrhea

Author, Year	Country	Population	Instru-ment	Intervention		Comparison		Outcome
Behboudi-G *et al.,* 2018	Iran	Women aged 20-35 years old	VAS	Fish oil	1 g	Placebo	1 g	Fish oil reduces the pain of dysmenorrhea.
Davaneghi et al.,, 2017	Iran	Women aged 20-35 years old	VAS	Omega-3	300 mg	Control	-	Omega-3 reduces dysmenorrhea.
Hosseinlou *et al.,* 2014	Iran	Female 18-25 years old	VAS	Fish oil	500 mg	Placebo	500 mg	Fish oil reduces dysmenorrhea.
Kheirkhah *et al.,* 2016	Iran	Female 18-35 years old	DSM-IV	Omega-3	2 g	Placebo	2 g	Omega-3 reduces dysmenorrhea.
Rahbar et al., 2012	Iran	Female 18-22 years old	Cox	Fish oil	1 g	Placebo	1 g	Fish oil reduces dysmenorrhea.
Sadeghi et al., 2018	Iran	Female 18-25 years old	VAS	Omega-3	300 mg	Placebo	300 mg	Omega-3 reduces dysmenorrhea.

a. Forest plot

Figure 2 shows the results of the analysis that giving fish oil reduces dysmenorrhea pain in women of reproductive age. The results were statistically significant (SMD = -1.01; 95% CI= -1.6 to -0.42; p=0.0007).

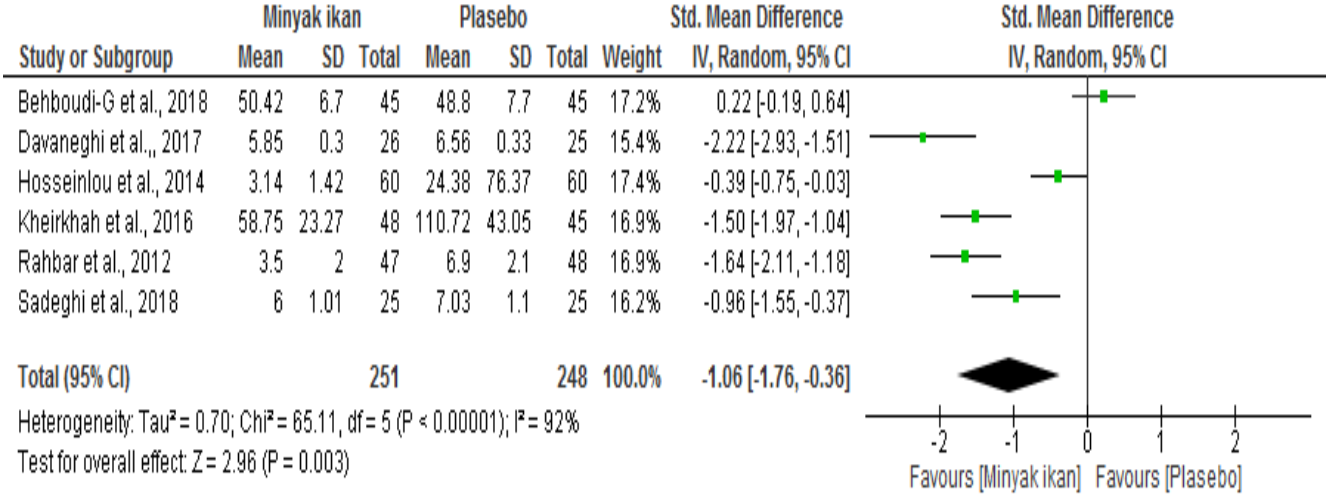

Figure 2. Forest plot meta analysis of the effectiveness of fish oil in reducing dysmenorrhea pain

b. Funnel plot

In Figure 3, the funnel plot graph shows no publication bias which is indicated by the symmetrical right and left plots and forms an inverted funnel where 3 plots are on the right and 3 plots are on the left. The plot on the left has a standard error between 0.2 and 0.4 while the plot on the right has a standard error between 0.1 and 0.4.

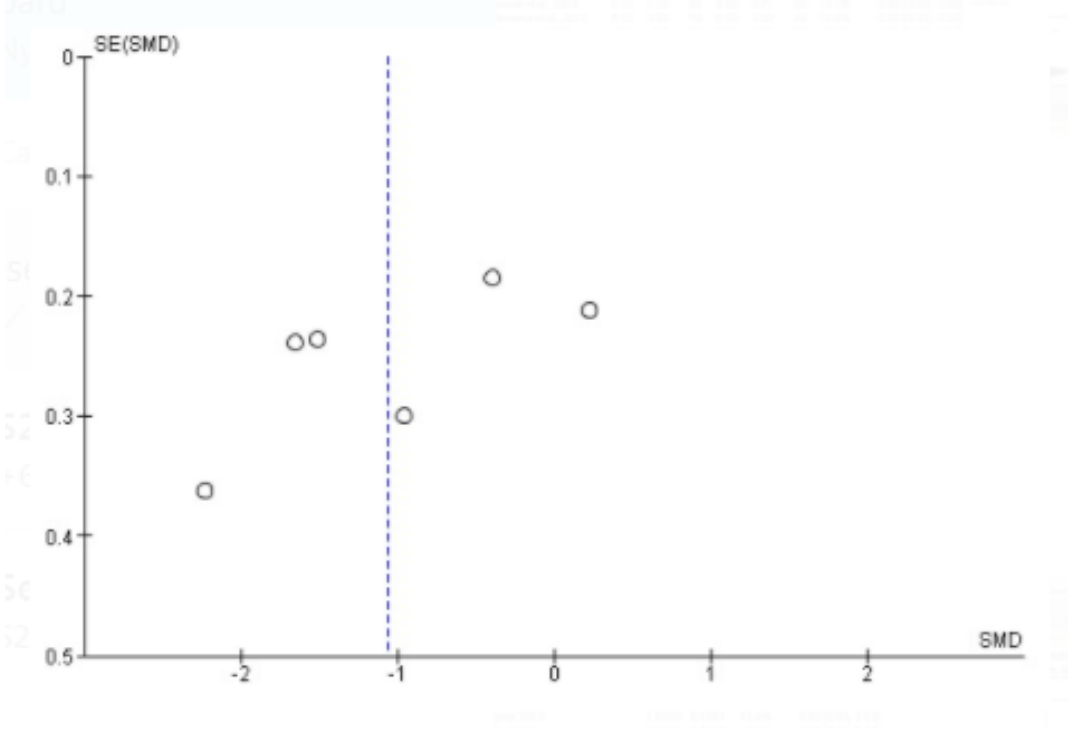

Figure 3. Funnel plot meta-analysis of the effectiveness of fish oil n reducing dysmenorrhea pain in women of reproductive age

2. Meta-analysis of ginger's effectiveness in reducing dysmenorrhea

Table 2 shows 8 articles in a randomized controlled trial (RCT) on the effectiveness of ginger in reducing dysmenorrhea pain in women of reproductive age who met qualitative and quantitative requirements..

Table 2. The effectiveness of ginger in reducing dysmenorrhea pain

Author, Year	Country	Population	Instrument	Intervention		Comparison		Outcome
Abadi et al., 2020	Iran	Women aged 20-30 years old	Likert scale	Ginger	250 mg	placebo	250 mg	Ginger does not reduce dysmenorrhea
Jenabi, 2013	Iran	Female 18-25 years old	VAS	Ginger	500 mg	placebo	500 mg	Ginger Reduces dysmenorrhea
Kashefi et al., 2014	Iran	Female aged 15-18 years old	VAS	Ginger	250 mg	placebo	250 mg	Ginger Reduces dysmenorrhea
Khayat et al., 2014	Iran	Women aged 20-35 years old	DSM-IV	Ginger	250 mg	placebo	250 mg	Ginger Reduces dysmenorrhea
Pakniati et al., 2019	Iran	Female 18-25 years old	Likert scale	Ginger	500 mg	placebo	500 mg	Ginger Reduces dysmenorrhea
Rahnama et al., 2012	Iran	Female 18-35 years old	Cox	Ginger	500 mg	placebo	500 mg	Ginger Reduces dysmenorrhea
Sultan et al., 2020	Iran	Female age 13-22 years old	Likert scale	Ginger	250 mg	placebo	250 mg	Ginger Reduces dysmenorrhea
Sutapa et al., 2017	Iran	Female 18-35 years old	Likert scale	Ginger	250 mg	Control	-	Ginger Reduces dysmenorrhea

a. Forest plot

Figure 4 shows the results of the analysis that the administration of ginger reduces the pain of dysmenorrhea in women of reproductive age. The results were statistically significant (SMD= -1.07; 95% CI= -1.73 to -0.40; p=0.002).

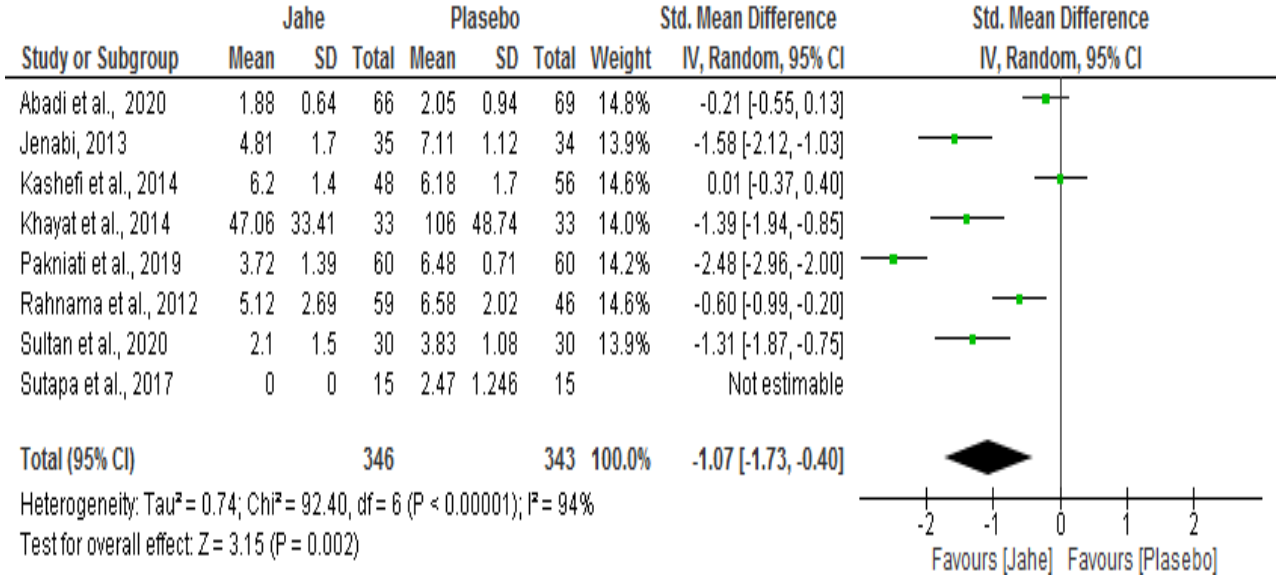

Figure 4. Forest plot meta-analysis of ginger's effectiveness in reducing dysmenorrhea pain

b. Funnel plot

In Figure 5, the funnel plot graph shows publication bias which is indicated by the asymmetry between the right and left plots where there are 3 plots on the right and 4 plots on the left so as not to form an inverted funnel. The plot on the left of the graph has a standard error between 0.2 and 0.3, while the plot on the right of the graph has a standard error between 0.1 and 0.3 ..

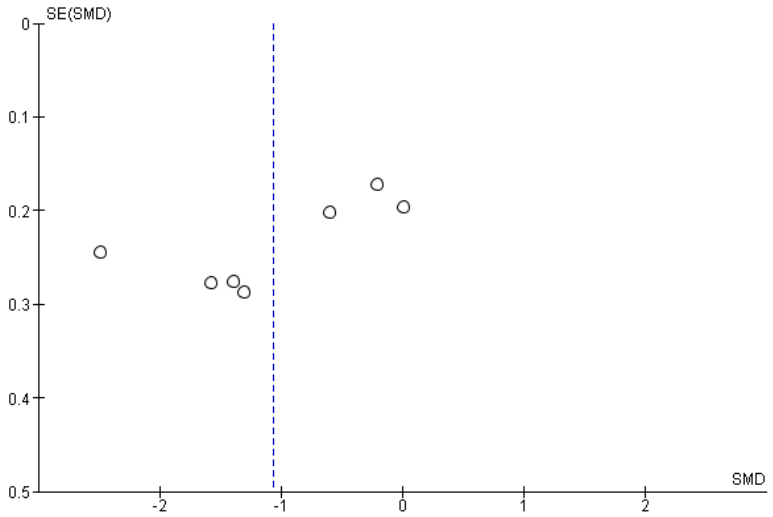

Figure 5. Funnel plot meta-analysis of ginger's effectiveness in reducing dysmenorrhea pain

DISCUSSION

Dysmenorrhea is not a non-life-threatening disorder, but dysmenorrhea can affect the quality of life and social relationships for women who are experiencing it (Najafi et al., 2018). Dysmenorrhea occurs mainly in the lower abdomen, but can spread to the lower back, waist, pelvis, upper thighs, to the calves.

Many studies have considered fish oil and ginger in reducing dysmenorrhea pain, this is as an alternative to NSAIDs, although these drugs can provide effective pain relief for women with primary dysmenorrhea, but the use of these drugs also has side effects that are very dangerous. severe after long-term conventional therapy. The side effects of chronic NSAID use are quite large, such as impaired kidney function and gastrointestinal bleeding that can limit their use in primary dysmenorrhea (Rahbar, et al., 2012).

Fish oil and ginger are reported to be effective as alternative treatments in reducing dysmenorrhea pain. This study is a systematic review and meta-analysis that aims to find a conclusion from the results of various similar studies that tested the administration of fish oil or ginger in reducing dysmenorrhea pain in various countries, races, and ethnicities, in order to obtain conclusions that can generally be used as a basis for giving therapy.

The results of the systematic review and meta-analysis are presented in the form of forest plots and funnel plots. The forest plot is a graphical representation of the meta-analysis that includes several tables and important information including the mean score, standard deviation, odds/ risk ratio, number of study participants and on the right side has one line representing each study in the meta-analysis, plotted according to the standard mean difference (SMD - very rough, this is the difference between the average score of participants in the intervention group, and the average score of the control group participants) (Akobeng, 2005 in Murti, 2018)

A funnel plot is a plot that depicts the approximate size of the effect of each study on the estimate of its accuracy which is usually the standard error. In this case a study with a large size (sufficient sample) and high precision (confidential interval) will approach the true effect (Murti, 2018).

1. Fish oil in reducing dysmenorrhea

Fish oil is oil that is consumed by humans and comes from raw fish (Anonymous, 2017). Raw fish oil contains 90% triglycerides, 2 - 5% unsaponified sterols, free fatty acids, esterified fatty acid cholesterol, small amounts of vitamins A, D, and E, minerals and water-soluble amino acids and peptides. The majority of fish oil triglyceride fatty acids are omega-3 long-chain polyunsaturated fatty acids (LC PUFAs). Omega-3 fatty acids consist of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and -linolenic acid (ALA) (Chatterjee and Judeh, 2016).

Omega-3 fatty acids (i.e., EPA and DHA) found in fish oil supplements produce anti-inflammatory and inflammatory mediators (e.g., protectin, resolvin, maresin), while reducing transcription of proinflammatory cytokine genes. Thus, fish oil supplements have the potential to reduce pain perception by indirectly decreasing nociceptor activation. Decreased proinflammatory cytokine genes prevent prostaglandin synthesis.

2. Ginger in reducing dysmenorrhea

Ginger exhibits significant anti-inflammatory effects but also exhibits side effects and side effects such as peptic ulcers. Ginger acts as an inhibitor of cyclooxygenase (COX) and lipoxygenase (Pratap et al., 2017). The inhibition of COX results in the inhibition of leukotrienes and prostaglan-

dins, therefore ginger can be an alternative as an analgesic in dysmenorrhea (Rahnama et al., 2012).

Systematic review and meta-analysis in this study was conducted with the aim of increasing the generalizability of the findings and obtaining convincing conclusions from the results of various similar studies regarding the effect of fish oil and ginger in reducing dysmenorrhea pain. In addition, systematic review and meta-analysis in this study also uses research that controls confounding factors which can be seen from the research inclusion criteria, using a Randomized Controlled Trial design, and the statistical results reported are Mean Difference (MD) and Standard Deviation (SD). Even so, there are still confounding factors from several primary studies that are able to influence the actual effect relationship.

Kashefi et al., (2014) stated that pain tolerance differs from person to person, participants may have different levels of response to pain reduction effects of zinc sulfate and ginger. Research subjects who experienced stressful events during history taking were excluded before the start of the intervention, but this did not control whether any of the study subjects were affected by stressful events during the intervention. Therefore, the value of dysmenorrhea for each study subject will be different compared to research subjects who experience stress during the intervention. The existence of differences in stress experienced by study subjects during the intervention will tend to affect the results of studies between each research.

AUTHOR CONTRIBUTION

Isnaini Novitasari is the main researcher who selects the topic, searches and collects research data. Eti Poncorini Pamungkasari and Hanung Prasetya analyzed data and review ed research documents.

FUNDING AND SPONSORSHIP

This study is self-funded.

CONFLICT OF INTEREST

There is no conflict of interest in this study.

ACKNOWLEDGMENT

We are very grateful to the database providers PubMed, Science Direct, AJOT, Springer Link, and Google Scholar.

LIST OF ABBREVIATIONS

ALA : Linoleic acid
COX : cyclooxygenase
DHA : Docosahexanoic acid
EPA : eicosapentaenoic
FDA : Food and Drug Administration
FEM : fixed effect model
MD : Mean Difference
NSAID: Nonsteroidal Anti-inflammatory Drug
OR : Odds Ratio
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PICO :Population, Intervention, Comparison, and Outcomes
REM : Random Effect Model
SD : Standard Deviation
VAS : Visual Analog Scale
WHO : World health Organization

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