

The Effect of Curcuma to Dysmenorrhea: A Systematic Review

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ABSTRACT

Background: Department of Nursing, Universitas Pesantren Tinggi Darul Ulum (Unipdu), Indonesia
Dysmenorrhea or menstrual pain is a common health problem among reproduction women. The prevalence of dysmenorrhea was high in many countries including in Indonesia. Some previous studies showed that curcumin was effective reduced menstrual pain.

Purpose: The aim of this study was to determine the effect of curcumin to dysmenorrhea.

Method: This study used systematic review method with Randomize Control Trial (RCT) design. The data was collected by using electronic databases such as Google Scholar, Science Direct, Pubmed, Scopus, Web of Science, SpringerLink and EBSCOhost in last 10 years, or in 2013-2023. The keywords used curcumin, turmeric, curcuma longa, dysmenorrhea, menstrual pain.

Results: There were 7 selected articles in this literature study. Curcumin reduced intensity and duration of dysmenorrhea; the increasing of vitamin D; the reducing of serum IgE, serum aspartate transaminase (AST) and direct bilirubin levels among women with dysmenorrhea.

Conclusion: Curcumin was affected to reducing the severity and symptoms of dysmenorrhea.

Keywords: curcumin, dysmenorrhea, systematic review, vitamin D

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BACKGROUND

Dysmenorrhea is one of health common problem among reproductive women, about 20 % – 90 % of disminorhea prevalence occurred among young women (Marjoribanks et al., 2015), with 2% -29% felt severe pain (Windastiwi et al., 2017). During the luteal and menstrual phases prostaglandin F₂-alpha (PGF₂-α) was secreted. Excessive PGF₂-α released the high amplitude and frequency of uterine contractions and causes vasospasm of uterine arterioles, leading to ischemia and cramping in lower abdomen (Lowdermilk et al., 2013). If it untreated, the pain will spread to waist and thighs, nausea and vomiting, headaches, diarrhea and irritability.

The prevalence of dysmenorrhea was occurred in several countries. Some data showed that 85.1% was occurred among students in Palestine University; 83.6% occurred among students at the University of Northern Ghana; 64.7% occurred in Ethiopia with pain characteristics were 61% in moderate level and 50.7% felt pain in lower abdominal, and 65% of participants said that they was absent from school because of their menstrual pain. Irregular menstrual cycles and a family history of dysmenorrhea were significantly associated with primary dysmenorrhea; 92.3% among reproductive women in Saudi Arabia had non-pathological (primary) dysmenorrhea, while 7.7% had pathological (secondary) dysmenorrhea; 80.9% among young Lebanese women. The majority of women with primary dysmenorrhea described that 56% of them at moderate level, 34.6% at severe level of menstrual pain and it was significantly affected their daily activities and school abilities (P<0.001). The main risk factors associated with primary dysmenorrhea include heavy menstrual flow, family history of primary dysmenorrhea, history of weight loss at tempts, and medical specialties (Abu Helwa et al., 2018; Ameade et al., 2018; Azagew et al., 2020; Bakhsh et al., 2022; Karout et al., 2021). The pathogenesis of primary dysmenorrhea was related with the increasing of prostaglandin F₂α and leukotrienes (Harel, 2012). The increasing of prostaglandins induced uterine contractions, decreased blood flow in myometrium and it caused ischemia and increasing of peripheral nerve sensitivity (Berek, 2011; Haidari et al., 2011). However, leukotrienes can increasing the sensitivity of uterine pain nerve fibers (Hillard, 2006). Dysmenorrhea affected adolescents' daily lives and limited of their social and academic activities. A study said that dysmenorrhea affected students' daily activities among 65% of student university in Mexico (Ortiz, 2010). Dysmenorrhea also influenced student's daily activities, poor sleep quality, and has a negative effects on mood, anxiety and depression (Bernardi et al., 2017). Dysmenorrhea also affects students' academic performance, absent from school and lost work days, and economic impact (Chongpensuklert et al., 2008).

The common treatment for dysmenorrhea can use non-steroidal anti-inflammatory drugs (NSAIDs). But a study said that medication drugs was given cause side effects including drug addicted (Chen et al., 2013; Shahla Gharloghi et al., 2012), diarrhea, abdominal pain, nausea (Kashefi et al., 2010), kidney complications, liver complications, sleep disturbances (Wang et al., 2013), digestive disorders (Nasehi et al., 2013). Pharmacological treatment for dysmenorrhea almost successful, but failure rate was 20%-25% (Navvabi Rigi et al., 2012). Because the incident of dysmenorrhea occurred in every month so best treatment with low risk impact was needed. One of the non-pharmacological treatment that can reduce menstrual pain is by using Curcumin. Curcumin is an active compound contained in turmeric, works by inhibiting the cyclooxygenase (COX) reaction so that it can inhibit and reduce inflammation, reduce uterine contractions which cause menstrual pain (Wulandari et al., 2018). Research conducted by (Astuti et al., 2020), shows

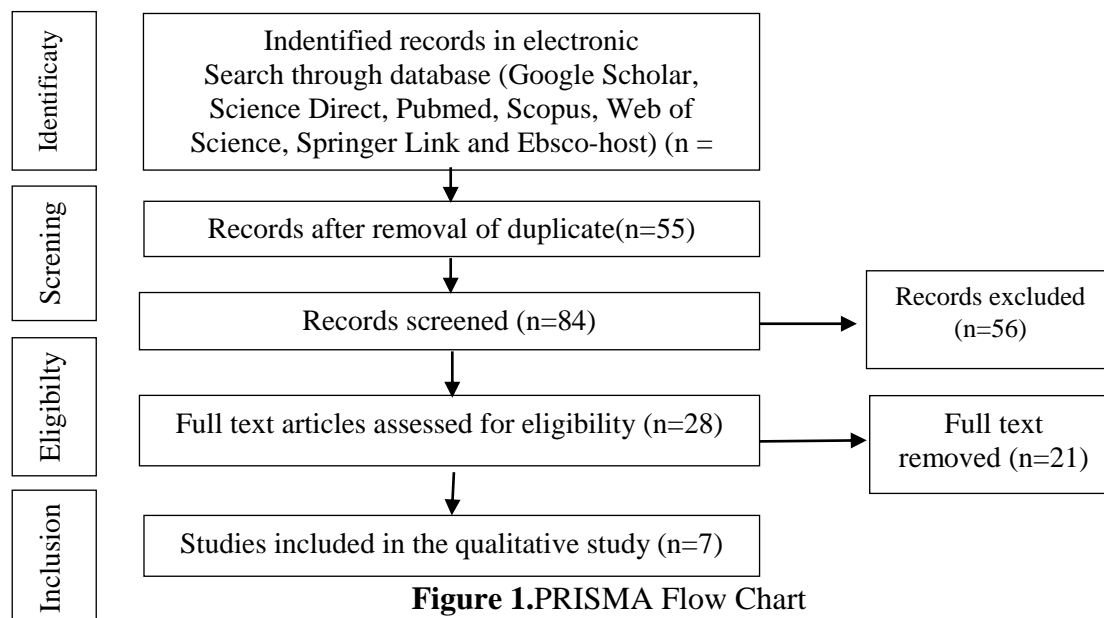
that giving tamarind turmeric has a significant effect on reducing the intensity of menstrual pain. Other research also shows that giving tamarind turmeric drinks had a significant effect on reducing menstrual pain. Based on some of this literature, the aim of this systematic review is to collect evidence that curcumin has an effect on dysmenorrhea.

METHOD

This systematic review was carried out by the author by searched literature from various databases, namely Google Scholar, Science Direct, Pubmed, Scopus, Web of Science, Springer Link and Ebsco-host in the last 10 years, from 2013-2023. The keywords used curcumin, turmeric, curcuma longa, dysmenorrhea, menstrual pain. Inclusion criteria in this literature review were RCT design, articles in English, women with primary dysmenorrhea, regular menstrual cycles (21-35 days). The randomized controlled trial (RCT) design was the gold standard for evaluating experimental studies. Case reports, review articles, abstracts from symposiums and congresses were not included in this literature review. All articles that met the inclusion criteria were included in the study. Duplications were also checked and unrelated articles were excluded (Figure 1). The search results in the electronic database found 139 articles that matched the keywords and there were 7 articles that matched the criteria and were analyzed.

The analysis was carried out using a systematic literature review method by examining, identifying, reviewing, and presenting it. Before presenting data, the researcher was merging, reviewing the material, and comparing the results in each article so the conclusion can be drawn in accordance with the topic of this journal.

The characteristics of the data were the subject, sample size, research design, type of treatment, dose and research results (Table 1).



RESULTS

This systematic review was conducted on 7 RCT articles. These articles were including 3 articles compared curcumin with placebo, 1 article compared curcuma longa drink home industry with curcuma longa drink prepared by researchers, 1 article compared turmeric with mefenamic acid given separately and together with the placebo group, and 2 articles compared the effects Curcumin plus Piperine with placebo.

A study conducted by Tabari *et al.* (2020), with the subject of Iranian University Medical Science Students showed a significant difference between the intervention group and the placebo group in terms of the severity and duration of menstrual pain ($p < 0.001$). Respondents in this study were adolescents who have dysmenorrhea for the last 2 months. The intervention group was given curcumin with containing 500 mg of turmeric extract, 2 capsules with food for the first three days of menstruation used for two cycles and the placebo group took capsules of the drug containing 10 grams of cornstarch, which looked similar to the intervention group. Observation of the severity and duration of pain used a visual analog scale (VAS), observed before and 3 hours and after the intervention in both cycles (Tabari *et al.*, 2020).

Other study conducted by Utami *et al.* (2020), there was a significant decreasing of the intensity of dysmenorrhea after received the curcuma intervention ($p \leq 0.001$). The statistical result showed there were no significant differences of curcuma longa drink home industry intervention and curcuma longa drink made by researchers ($p > 0.05$). Observation of pain used the Numeric Rating Scale (NRS) (Utami *et al.*, 2020).

Pichardo *et al.* (2020), conducted his research among primary dysmenorrhea women. The total sample was 108 respondents who were divided into 2 groups, the intervention group who was given curcumin and the control group was given placebo. Curcumin capsules (500 mg) or placebo were administered every 12 hours beginning 7 days before menstruation and continuing until 2 days after menstruation began for three consecutive menstrual cycles. Observation of pain used Visual Analog Scale (VAS). The results showed that curcumin was effective reduced the severity and symptoms of dysmenorrhea (Pichardo *et al.*, 2020).

Hesami *et al.* (2021), subjects were divided into four groups and taken randomly, namely the turmeric group ($n=32$), the mefenamic acid group ($n=32$), the turmeric and mefenamic acid groups ($n=32$), the placebo group ($n=32$). Observation of pain scale used VAS. The results of the analysis showed that turmeric and mefenamic acid were effectived in reducing the intensity of dysmenorrhea ($p < 0.05$). The combination of turmeric and mefenamic acid was more effective than intervention of turmeric with out mefenamic acid or vice versa ($p < 0.05$) (Hesami *et al.*, 2021).

Bahrami *et al.* (2021), the results of his study found that giving one curcuminoid capsule (500 mg) everyday, from 7 days before to 3 days after menstruation for three consecutive menstrual cycles resulted in a significant decreased in dysmenorrhea pain (Bahrami *et al.*, 2021).

The results of Arabnezhad *et al.* (2022), intervention of 500 mg curcuminoid + 5 mg piperine) everyday, from 7 days before to 3 days after menstruation for three consecutive menstrual cycles can increase serum vitamin D levels, decrease serum levels of aspartate transaminase (AST) and direct bilirubin in women with PMS and dysmenorrhea (Arabnezhad *et al.*, 2022).

Based on study by Bahrami *et al.* (2022), showed that daily intervention of curcumin 500 mg plus piperine, from 7 days before to 3 days after menstruation for three consecutive menstrual cycles significantly reduced mean serum IgE levels without significant changes in serum IL-10 and IL-12 in healthy young women with PMS and PD (Bahrami *et al.*, 2022).

Table 1. Characteristic sof Include Studies

Author/ Year	Sampel	Interventi on	Dosis	Results
Tabari <i>et al.</i> (2020)	74 adolesce	Curcumin	500mg, 2 capsules/	Curcumin decreased the severity and duration of menstrual pain

) nt		day, given everyday on the first three days of menstruation for three cycles and the placebo group consumed capsules containing 10 grams of cornstarch		
Utami <i>etal.</i> (2020) (Utami et al., 2020)	32 young women (18-35 tahun)	Curcuma longa drink home industri dan Concoction	100 cc given at the first 3 days of menstruation	There was no significant difference of the intervention of curcuma long drink home industry with curcuma long drink made by researchers (Concoction) ($p > 0.05$)
Pichard <i>oetal.</i> (2020) (Pichard o et al., 2020)	108 women (18-35 year)	Curcumin	Curcumin (500 mg) or placebo given every 12 hours starting 7 days before menstruation and continuing until 2 days after menstruation begins for three consecutive menstrual cycles.	The results of this study showed that curcumin was effective in reducing the severity and symptoms of dysmenorrhea

Hesami <i>et al.</i> (2021) (Hesami <i>et al.</i> , 2021)	128 respondent. Turmeric group (n=32), mefenamic acid group (n=32), turmeric group and mefenamic acid group (n=32), placebo group (n=32)	Turmeric	Turmeric contains 500 mg of turmeric powder. The placebo capsules contained wheat flour in the same shape, size and packaging. Turmeric capsules or mefenamic acid are taken for 5 days, two days before and the first 3 days of menstruation.	Turmeric and mefenamic acid were effective to reducing the intensity of dysmenorrhea ($p<0.05$). The combination of turmeric and mefenamic acid are more effective than giving turmeric with out mefenamic acid or vice versa ($p<0.05$)
Bahrami <i>et al.</i> (2021) (Bahrami <i>et al.</i> , 2021)	104 respondent	Curcumin oil capsules	500 mg/day, from 7 days before to 3 days after menstruation for three consecutive menstrual cycles	Curcumin significantly reduced menstrual pain
Arabnezhad <i>et al.</i> (2022) (Arabnezhad <i>et al.</i> , 2022)	76 respondent (38 each groups)	Curcumin	500 mg curcuminoid + 5 mg piperine) daily, from 7 days before	Curcumin increased vitamin D levels, decrease serum levels of aspartate transaminase (AST) and direct bilirubin among women with PMS and dysmenorrhea.

			and 3 days after menstruati on for three consecutiv e menstrual cycles	
Bahrami <i>et al.</i> (2022) (Bahram i et al., 2022)	38 Respon dent	Curcumin and piperin	500 mg of curcu min plus piperine daily, from 7 days before and 3 days after menstruati on for three consecutiv e menstrual cycles	Intervention of curcumin significantly reduced the mean of IgE serum levels with out significant changes in serum IL-10 and IL-12 among healthy young women with PMS and PD

DISCUSSION

Our systematic review focused on RCTs, especially on the effect of curcumin to dysmenorrhea, from 2013 – 2023. We identified 7 articles that met inclusion criteria and analyzed them. The results of the analysis showed that curcumin can reduce the intensity and duration of dysmenorrhea; increase vitamin D; reduced serum IgE, serum aspartate transaminase (AST) and direct bilirubin levels among women with dysmenorrhea. Curcumin does not cause side effects and is safe for consumption at repeated exposure to high concentrations (Pichardo et al., 2020; Tabari et al., 2020). Curcumin can be given 7 days before and 3 days after menstruation at a dose of 500 mg, 1-2 times a day for 3 menstrual cycles.

Dysmenorrhea is menstrual pain and it commonly occurred among adolescences, and it begins with 48 – 72 hours of bleeding (Ricci, 2017). Dysmenorrhea can occurred for few days before menstruation period and last for several hours in menstrual period. Primary dysmenorrhea begins at menarche or within one year of menarche, while secondary dysmenorrhea begins several years after menarche. Primary dysmenorrhea occurred frequently among adolescent with no pathological association (Wallace et al., 2010).

The pathogenesis of primary dysmenorrhea was closely related with the increasing of prostaglandin F2 α , leukotrienes (Harel, 2012), inflammation and large amounts of oxygen free radicals in typical tissue and endothelial injury in dysmenorrhea (Dikensoy et al., 2008; Turhan et al., 2012). Dysmenorrhea caused myometrial contractions, because of the secretion of prostaglandins in endometrium. The secretory endometrium contains largest of eicosanoids, it was converted prostaglandin F2 α (PGF2 α), prostaglandin E2 (PGE2),

and leukotrienes during menstruation. Other symptoms associated with dysmenorrhea included headache, nausea and vomiting, back pain and diarrhea associated with high levels of circulating prostaglandins (PGF2 α , PGE2). The posterior pituitary peptides and vasopressin and oxytocin have been implicated in pain. Most of the prostaglandin release during menstruation occurs within the first 48 hours (Turhan et al., 2012). Arachidonic acid is metabolized via cyclooxygenase and 5-lipoxygenase pathway. The first produces prostaglandins (PGF2 α and PGE2), prostacyclin and thromboxane. Leukotrienes are formed in the 5-lipoxygenase pathway (Evans & Salamonsen, 2012). Increased prostaglandins induce uterine contractions, decrease blood flow to the myometrium caused ischemia and increase peripheral nerve sensitivity (Berek, 2011; Haidari et al., 2011). Meanwhile, leukotrienes increased the sensitivity of uterine pain nerve fibers (Hillard, 2006). Cyclooxygenase inhibitors decreased menstrual prostaglandin levels and reduced pain (Lobo et al., 2017).

Curcumin has anti-inflammatory, antioxidant, anti-tumor and other biological activities. The anti-inflammatory properties of curcumin is the basis of various biological activities and play an important role in the diseases treatment (Peng et al., 2021). The mechanism of curcumin in reducing the severity and symptoms of primary dysmenorrhea is through its anti-inflammatory activity and analgesic effect. This is consistent with the pathophysiology of primary dysmenorrhea (Pichardo et al., 2020). Curcumin's anti-inflammatory is a media to inhibit the cyclooxygenase-2 (COX-2), lipoxygenase (LOX), and inducible nitric oxide synthase (iNOS). COX-2 and LOX are important enzymes to mediate inflammatory processes (Menon & Sudheer, 2007). Cyclooxygenase-2 (COX-2) and lipoxygenase (LOX) can inhibit the formation of prostaglandins (PGF2 α and PGE2), prostacyclin, thromboxane, leukotrienes and reduced the severity and duration of dysmenorrhea.

Low levels of vitamin D and calcium as a trigger of dysmenorrhea by increasing prostaglandin genesis or decreasing intestinal calcium absorption (Abdi et al., 2021). In addition, high intake of vitamin D may reduced the risk of PMS, with effects on sex steroid hormones and neuro transmitter activity (Bertone-johnson, 2010). Results from a number of in vitro studies indicated that curcumin was potential to directly or indirectly interact with vitamin D receptors (VDR/ vitamin D receptors) and their molecular targets. VDR as a nuclear transcription factor can modulate 1,25-(OH)2D3 activity, so that it has an important effect on calcium absorption, bone regeneration, and mineralization level. VDR is also expressed in endometrial, ovarian tissue, fallopian tube epithelial cell and placenta. Intervention of curcumin can increase serum vitamin D levels in women with pre menstrual syndrome and dysmenorrhea (Arabnezhad et al., 2022). Xin et al. (2015), reported that, curcumin intervention did not have a appreciable effect on serum 1,25-(OH)2D3 concentrations, it induced over expression of VDR in femur and osteoblasts, which might implicate curcumin's protective effect of bone. Porous (Xin et al., 2015). The increasing of serum levels of vitamin D decreased the genesis of prostaglandins there by reducing the severity and symptoms of dysmenorrhea.

Intervention of curcumin can also decreased serum aspartate aminotransferase (AST) and direct bilirubin in women with dysmenorrhea (Arabnezhad et al., 2022). There were several possible mechanism speculated about the ultimate beneficial effect of curcumin on liver function. Curcumin can prevent hepatic steatosis, liver damage, insulin resistance (Tabrizi et al., 2018), liver inflammation and fatty liver disease (Egashira et al., 2012). In addition, curcumin suppresses the induction of high mobility group box 1 (HMGB1) and nuclear factor kappa B (NF- κ B), down regulates ICAM-1, cyclo oxygenase-2 and MCP-1, reduces gene

expression of pro-inflammatory cytokines, CD11b, pro collagen type I, and metalloproteinase-1 tissue inhibitors and induction of peroxisome proliferator-activated receptor-gamma (PPAR- γ) which lead to improved development and increased inflammation in liver tissue and fibrosis. The antioxidant capacity of curcumin was related with several anti-oxidant enzyme activities such as glutathione transferase, catalase and heme-oxygenase-1 (Arabnezhad et al., 2022).

The anti-inflammatory and immunomodulatory effects of CUM increased with longer treatment duration, the maximal effect was observed almost after 13 weeks of intervention (Adamczak et al., 2020). The results of a study giving curcumin significantly lowered mean serum IgE levels in women with primary dysmenorrhea and PMS (premenstrual syndrome) (Bahrami et al., 2022). Turmeric treatment (100 mg/kg) in a rat model of allergic asthma reduced food allergy symptoms by lowering IgE, IgG, IL-4, IL5, and IL-13 values and finally regulating Th1/Th2 balance. Curcumin significantly reduces IgE formation by decreasing IL-4 and IgE expression; while overexpression of IFN- γ (Eyles et al., 2013).

CONCLUSION

Curcumin was affected to reduced the severity and symptoms of dysmenorrhea. Although, it is advisable to conduct clinical trials at different doses and of longer duration to assess the benefits of curcumin on Vitamin D status and liver enzyme function.

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CONFLICTS OF INTEREST

The authors declare that they have no conflict of interests regarding the publication of this paper.

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