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Original Article

Dose-dependent effects of curcumin on writhing response: A study in a Balb/c mouse model with dysmenorrhea

[Efectos dependientes de la dosis de curcumina sobre la respuesta de contorsión: Un estudio en un modelo de ratón Balb/c con dismenorrea]

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Abstract

Context: Primary dysmenorrhea negatively affects adolescents' quality of life. Curcumin, an active turmeric compound, inhibits the cyclooxygenase reaction to inhibit and reduce inflammation.

Aims: To determine the effects of varying doses of curcumin on the writhing response in a mouse model of primary dysmenorrhea.

Methods: We performed an experiment using a post-test only and a control-group design approach with random sampling. The research subjects were non-pregnant female Balb/c mice (*Mus musculus*) as models of primary dysmenorrhea induced by estradiol benzoate and oxytocin. Forty mice met the inclusion criteria and were divided into five groups: the negative control group was administered corn oil, the positive control group was administered ibuprofen 100 mg/kg and corn oil (0.5 mL of corn oil), and three intervention groups were administered curcumin (100 mg/kg, 200 mg/kg, or 400 mg/kg). The writing number and latency were evaluated 30 minutes after the oxytocin injection.

Results: The writhing number significantly decreased after curcumin administration ($p<0.05$). Writhing latency was also significantly longer after curcumin administration ($p<0.05$). Curcumin (400 mg) provided the best response in the treatment of primary dysmenorrhea in mice.

Conclusions: The relationship between the curcumin dose and writhing response was dose-dependent. A 50% efficacy was observed at the optimal dose of 166 mg/kg, whereas maximum effect was observed at a dose of 1541 mg/kg.

Keywords: curcumin; dose-dependent; dysmenorrhea; sexual and reproductive health; writhing response.

Resumen

Contexto: La dismenorrea primaria afecta negativamente la calidad de vida de los adolescentes. La curcumina, un compuesto activo de la cúrcuma, inhibe la reacción de la ciclooxigenasa para inhibir y reducir la inflamación.

Objetivos: Determinar los efectos de diferentes dosis de curcumina en la respuesta de retorcimiento en un modelo murino de dismenorrea primaria.

Métodos: Realizamos un experimento utilizando solo un diseño de prueba posterior y un enfoque de grupo de control con muestreo aleatorio. Los sujetos de investigación fueron ratones Balb/c hembras no preñadas (*Mus musculus*) como modelos de dismenorrea primaria inducida por benzoato de estradiol y oxitocina. Cuarenta ratones cumplieron los criterios de inclusión y se dividieron en cinco grupos: al grupo de control negativo se le administró aceite de maíz, al grupo de control positivo se le administró ibuprofeno 100 mg/kg y aceite de maíz (0,5 ml de aceite de maíz) y a tres grupos de intervención se les administró curcumina (100 mg/kg, 200 mg/kg o 400 mg/kg). Se evaluó el número de retorcimientos y la latencia durante 30 minutos después de la inyección de oxitocina.

Resultados: El número de retorcimientos disminuyó significativamente después de la administración de curcumina ($p<0,05$). La latencia de los retorcimientos también fue significativamente más larga después de la administración de curcumina ($p<0,05$). La curcumina (400 mg) proporcionó la mejor respuesta en el tratamiento de la dismenorrea primaria en ratones.

Conclusiones: La relación entre la dosis de curcumina y la respuesta de retorcimientos fue dependiente de la dosis. Se observó una eficacia del 50% con la dosis óptima de 166 mg/kg, mientras que el efecto máximo se observó con una dosis de 1541 mg/kg.

Palabras Clave: curcumina; dependiente de la dosis; dismenorrea; respuesta de retorcimiento; salud sexual y reproductiva.

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INTRODUCTION

The prevalence of primary dysmenorrhea worldwide is still relatively high, with approximately 90% in adolescents and >50% in menstruating women, with approximately 10–20% of the cases experiencing severe pain (Ongbayokolak et al., 2020). The pathophysiology of primary dysmenorrhea is associated with an increase in prostaglandin F2α and leukotrienes (Harel, 2012). Increased levels of prostaglandins induce uterine contractions and decrease blood flow to the myometrium, resulting in ischemia and increased peripheral nerve sensitivity (Barcikowska et al., 2020). Leukotrienes can increase the sensitivity of the uterine pain nerve fibers (Hillard, 2006). Dysmenorrhea negatively affects the quality of life, academic and professional performance, and social and recreational activities (Abu Helwa et al., 2018; Molla et al., 2022) and has significant economic consequences (Al-Matouq et al., 2019).

Dysmenorrhea commonly occurs in women of reproductive age and reduces the quality of life (Osonuga and Ekor, 2019). According to its etiology, dysmenorrhea is categorized as primary or secondary. Primary dysmenorrhea is characterized by menstrual pain that occurs in adolescence without accompanying pelvic anatomical abnormalities. It is characterized by cramping and pelvic pain that begin immediately after the onset of menstruation and last for one to three days. Primary dysmenorrhea often occurs six to 12 months after menarche. Secondary dysmenorrhea occurs owing to organ pathologies. Endometriosis is the most common cause of secondary dysmenorrhea. Other causes include leiomyoma, adenomyosis, ovarian cysts, fibroids, and pelvic inflammatory disease. Secondary dysmenorrhea begins later than primary dysmenorrhea, usually more than two years after menarche (Abu Helwa et al., 2018; Al-Matouq et al., 2019; Fasanghari et al., 2023; Molla et al., 2022; Osonuga and Ekor, 2019).

Commonly used treatments for dysmenorrhea are non-steroidal anti-inflammatory drugs (NSAIDs). The effectiveness of NSAIDs in the treatment of dysmenorrhea was confirmed in a review of 73 randomized controlled trials (Marjoribanks et al., 2010). Next to their benefits, these drugs cause side effects, including drug dependence (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), and gastrointestinal tract complications (Alhamadi et al., 2022). Pharmacological treatment of dysmenorrhea is usually successful, but the failure rate is 20–25% (Navvabi Rigi et al., 2012). Due to the complications and side effects of chemical drugs, non-pharmacological and herbal methods can be used as alternatives to treat dysmenorrhea.

Turmeric contains phenolic compounds that can be used as analgesic and anti-inflammatory agents. Several studies have shown that turmeric can reduce the pain intensity and duration of dysmenorrhea (Kiswati, 2021; Okuyan et al., 2021). Curcumin, an active compound contained in turmeric, works by inhibiting the occurrence of cyclooxygenase (COX) reactions to inhibit and reduce inflammation, uterine contractions, and the severity of dysmenorrhea (Mukhoirotin et al., 2024; Sharifipour et al., 2024). The in vivo model of mice administered with oxytocin administration is recognized as a pharmacodynamic experimental mouse model and is often used to study primary dysmenorrhea. Severe acute abdominal pain is the main clinical symptom of primary dysmenorrhea, and writhing response is the main indicator, whereas writhing time is used to evaluate model and drug test effects (Yang et al., 2015). Data and research results regarding appropriate curcumin dosage regimens for the treatment of dysmenorrhea are limited. This study aimed to determine the effects of varying doses of curcumin on the writhing response in a mouse model of primary dysmenorrhea.

MATERIAL AND METHODS

Animals

Female Balb/c mice *(Mus musculus)* (weight 20 ± 2 g and age 6–8 weeks) were obtained from the laboratory of the Faculty of Veterinary Medicine, Universitas Airlangga. Animals were housed in a 12-hour light/dark cycle chamber at a temperature of 23 ± 1°C with *ad libitum* access to food and water (Hong et al., 2022; Yang et al., 2015). All animal welfare and experimental procedures were performed in accordance with the Care and Use Guidelines of the Faculty of Veterinary Medicine Laboratory at Universitas Airlangga. The animal experiments were also approved by the Faculty of Veterinary Medicine Ethics Committee, Airlangga University, Surabaya (No. 2.KEH.109.07.2023).

Chemicals and reagents

The treatment materials used were as follows: 1) induction of primary dysmenorrhea with estradiol benzoate (E0329, Tokyo Chemical Industry Co. LTD, Japan) and oxytocin (Interchemie Werken, Holland); 2) curcumin (C1386, Sigma-Aldrich, USA); 3) ibuprofen (Novapharin, Gresik, Indonesia); 4) corn oil (CCO Corn Oil, CV. Surya Agung, Indonesia).

Animal treatment

Before treatment, 40 mice were acclimatized to laboratory conditions for one week with *ad libitum* access to food and water. The model mice were established by observing the estrous cycle using vaginal smears (Fig. 1). Mice in the estrous cycle were included in this study. The mice were randomly allocated to five groups: the negative control group (NG), positive control group (PG), first treatment group (DC100), second treatment group (DC200), and third treatment group (DC300). The NG, PG, DC100, DC200, and DC400 models are described below.

The mice were modeled for primary dysmenorrhea, and 40 mice were subcutaneously injected with estradiol benzoate for 10 days (10 mg/kg on days 1 and 10 and 5 mg/kg from day 2 to day 9). On the 11th day, the mice were intraperitoneally injected with oxytocin (100 U/kg) to induce dysmenorrhea (Peng et al., 2020). From day 4 to day 10, the negative control group was given 0.5 mL of corn oil. The positive control group was given ibuprofen (100 mg/kg) and corn oil (0.5 mL). In the DC100 group, curcumin (100 mg/kg) and corn oil (0.5 mL). In the DC200 group, curcumin (200 mg/kg) and corn oil (0.5 mL). The DC400 group was orally administered curcumin (400 mg/kg) and corn oil (0.5 mL). Each treatment was given two times a day by oral gavage. This study used corn oil because it is a solvent that increases the bioavailability of curcumin (Shishu and Maheshwari, 2010). On day 11, a writhing response was observed within 30 min after oxytocin injection (Liu et al., 2022; Peng et al., 2020; Yu et al., 2019).

Observation of writhing response

The writhing response was observed within 30 min of oxytocin injection. The writhing response mainly consists of abdominal wall contraction and pelvic rotation, followed by the stretching of the hind limbs (Hong et al., 2022; Yang et al., 2015). The parameters for the writhing response were writhing number and latency. The writhing number was defined as the number of writhes observed in each group within 30 min after oxytocin injection. The writhing latency is the time taken from the injection of oxytocin to the first writhing behavior (Li et al., 2017). The writhing responses were observed by at least two research teams and documented using video.

Statistical analysis

Data were tabulated and presented based on the data distribution. Data normality was tested using the Saphiro-Wilk test. Data were analyzed using One-way ANOVA and Kruskal–Wallis test, if significant, followed by a post hoc test with a significance level of $a \leq 0.05$. The software SPSS version 26.0. (IBM, New York, USA) was used for statistical analyses. Correlation analysis of the curcumin dose-response relationship on the writhing response using Spearman's rho with probability model analysis.

RESULTS

The writhing response parameters in this study were writhing number and latency. The effects of curcumin on the writhing response in the dysmenorrhea mouse model are presented in Table 1.

Table 1 shows that there are significant differences in writhing numbers in all groups vs the NG group ($p<0.05$). This analysis shows that the administration of ibuprofen at 100 mg/kg and curcumin at 100, 200, and 400 mg/kg twice a day are equally effective in reducing writhing numbers in dysmenorrhea mice models. The lowest average writing number was obtained for PG and DC400. The administration of curcumin at a dose of 400 mg/kg has the strongest effect in reducing writhing numbers and is comparable to the administration of ibuprofen at a dose of 100 mg/kg.

There were significant differences in writhing latency in all groups compared with the NG group ($p<0.05$). This analysis showed that the administration of ibuprofen at 100 mg/kg and curcumin at 100, 200, and 400 mg/kg twice a day affected the writhing latency in dysmenorrhea mice models. The longest average writhing latency was observed in the group administered 400 mg/kg curcumin.

The relationship between curcumin dose and its effect is depicted in Fig. 2.

Fig. 2. shows that a 50% effect of curcumin on the writhing response was observed at a dose of 166 mg/kg (ED_{50}), whereas the administration of a 400 mg/kg dose of curcumin had a maximum effect of 85% in inhibiting the writhing response. The maximum effect of curcumin was obtained at a dose of 1541 mg/kg, which was related to the weight of the mice and showed 99% inhibition of the writhing response in the mice models of primary dysmenorrhea.

The linearity of the dose-response relationship of curcumin to the writhing response in the primary dysmenorrhea mice models is shown in Fig. 3.

Fig. 3. shows a strong positive correlation between the dose and effect of curcumin on the writhing response, with a correlation value (R^2) of 0.976.

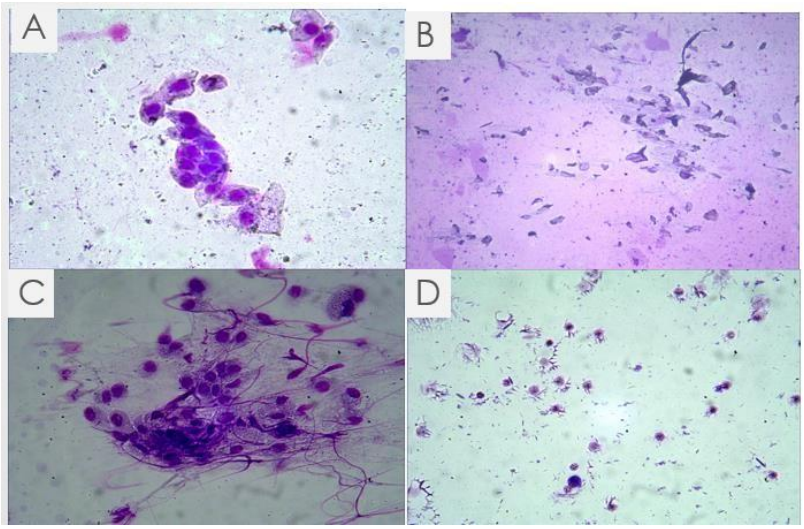

Figure. 1. Estrus cycle.
(**A)** Proestrus; **(B)** Estrus; **(C)** Metestrus; **(D)** Diestrus. Magnification 400×.

Table 1. Effects of curcumin on writhing response in a primary dysmenorrhea mouse model.

Group	Writhing number (frequency)		Writhing latency (minute)	
	(Mean ± SD)	p-value	Median (Max-Min)	p-value
NG	68.63 ± 31.93	Ref.	1.00 (1–2)	Ref.
PG	9.75 ± 9.60*	<0.001	3.50 (2–25)*	0.001
DC100	24.88 ± 15.63*	0.001	2.50 (1–28)*	0.024
DC200	25.13 ± 20.43*	0.001	2.00 (1–3)*	0.037
DC400	10.75 ± 7.78*	<0.001	9.00 (1–29)*	0.018

*Significant difference (p<0.05, n = 40). NG: Dysmenorrhea; PG: Dysmenorrhea + ibuprofen (100 mg/kg); DC100: Dysmenorrhea + curcumin (100 mg/kg); DC200: Dysmenorrhea + curcumin (200 mg/kg); DC400: Dysmenorrhea + curcumin (400 mg/kg).

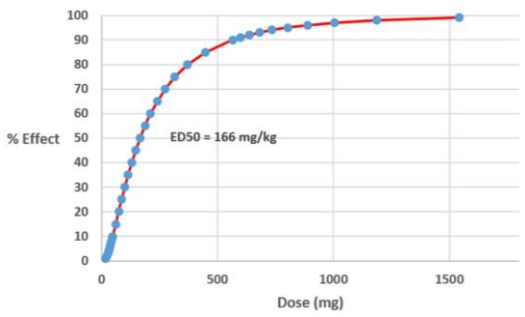

Figure 2. Graded dose-response curve of curcumin.
The effect indicates the percentage of writhing.

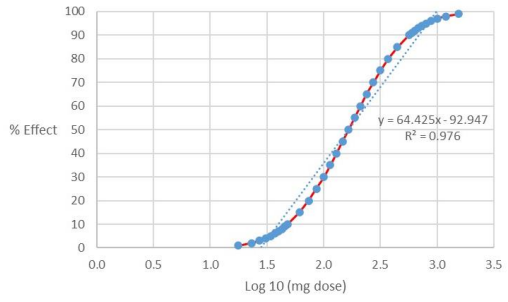

Figure 3. Log-dose response curve of curcumin.

DISCUSSION

Dysmenorrhea is severe lower abdominal pain that occurs during menstruation in women. The pain is often characterized by cramping and radiates to the thighs or lower spine. Lower abdominal pain may be accompanied by vomiting, headache, back pain, diarrhea, and fatigue (Barcikowska et al., 2020). Dysmenorrhea is the most frequently treated medical condition (Saha et al., 2016). Primary dysmenorrhea is defined as menstrual pain in the suprapubic region in the absence of pelvic abnormalities such as myomas, endometriosis, or ovarian cysts. The pain occurs just before or on the first day, lasts for 2–3 days, and is most severe during the first 24–36 h of menstruation, with or without nausea, vomiting, diarrhea, head-

ache, or syncope (Aksoy et al., 2017; Barcikowska et al., 2020).

In primary dysmenorrhea, there is an increase in endometrial secretions, namely PGF2α and leukotriene levels, during the menstrual phase (Gao et al., 2017). Increased prostaglandin and leukotriene levels induce uterine contractions and decrease blood flow to the myometrium, resulting in ischemia and increased peripheral nerve sensitivity, thereby lowering the pain threshold and resulting in pain (Harel, 2012). Cyclooxygenase inhibitors decrease menstrual prostaglandin levels and uterine contractility (Guimarães and Póvoa, 2020). Clinical trials have shown that abnormal contractions of the uterine smooth muscle can reduce the blood supply to the endometrium, causing temporary hypoxia and eventually leading to primary dysmenorrhea (Iacovides et al., 2015). Estradiol benzoate is often used to induce primary dysmenorrhea, and the writhing response triggered by oxytocin is used to simulate the main symptoms (Bi et al., 2021; Hong et al., 2022; Jesuíno et al., 2019; Ma et al., 2021; Peng et al., 2020; Pu et al., 2015; Yang et al., 2015).

The writhing response is a key indicator of pain in mice models of primary dysmenorrhea (Yang et al., 2015). The results of this study confirm that the administration of curcumin can reduce the number of writhing cycles and writhing latency. The administration of curcumin at a dose of 400 mg/kg had the strongest effect on the writhing response, with a maximum inhibition of 85%, which was comparable to the administration of ibuprofen. In primary dysmenorrhea, an increase in endometrial secretions, namely PGF2α and leukotriene levels, is observed during the menstrual phase (Harel, 2012). COX is involved in prostaglandin synthesis. Activation of COX-2 leads to the production of PGF2α (Yang et al., 2023). Increased prostaglandins and leukotrienes induce uterine contractions, decrease blood flow to the myometrium resulting in ischemia, and increase the sensitivity of peripheral nerves, lowering the pain threshold and resulting in pain (Harel, 2012).

Curcumin reduces the severity and symptoms of primary dysmenorrhea through anti-inflammatory and analgesic effects. This finding is consistent with the pathophysiology of primary dysmenorrhea (Pichardo et al., 2020). The anti-inflammatory effects of curcumin are mediated by its ability to inhibit COX-2, lipoxygenase (LOX), and inducible nitric oxide synthase (iNOS) (Menon and Sudheer, 2007). COX-2 and LOX are important enzymes that mediate the inflammatory processes (Menon and Sudheer, 2007). Inhibition of COX-2 and LOX can, in turn, inhibit the formation of prostaglandins (PGF2α and PGE2) and leukotrienes and thus reduce the uterine contractions and vasoconstriction, increase blood flow to the uterus, and reduce uterine ischemia, thereby reducing the severity and duration of menstrual pain and in this case the writhing response (writhing number and latency). The results of this study are in line with those of several previous clinical studies that showed that administration of 500 mg curcumin once or twice a day for three consecutive menstrual cycles can reduce the severity and duration of menstrual pain (Arabnezhad et al., 2022; Bahrami et al., 2021; 2022; Pichardo et al., 2020; Tabari et al., 2020).

The group administered 100 mg/kg ibuprofen also showed a significant decrease in the writhing response. Ibuprofen is a type of NSAID that works by blocking the production of prostaglandins through the inhibition of COX, the enzyme responsible for prostaglandin formation. NSAIDs cause menstrual cramps to be less painful and can prevent other symptoms, such as nausea and diarrhea, and reduce severe pain in women with primary dysmenorrhea (Bernardi et al., 2017). NSAIDs can also reduce menstrual blood volume and have a direct analgesic effect on the central nervous system (Motahari-Tabari et al., 2017). The results of this study are in line with those of Yang et al. (2016), which showed that the administration of ibuprofen at a dose of 0.12 g/kg significantly inhibited the oxytocin-induced writhing response with a maximum inhibition of 79%. Ge-Gen Decoction (GGD) at a dose of 14 mg/kg also significantly inhibited the writhing response with a maximum inhibition of 87% in mice models of primary dysmenorrhea (Yang et al., 2016). Other studies have also shown that the administration of ibuprofen at 100 mg/kg can significantly reduce writhing time and latency and that the administration of 200 and 400 mg/kg paeonol (PAE) can significantly reduce writhing time and latency in mice with primary dysmenorrhea (Peng et al., 2020).

The limitation of this study is that the inflammatory activity was not confirmed through examination. In the future, the anti-inflammatory activity should be measured, and the decrease in pain should be observed through the peripheral nerve pathways in the uterus.

CONCLUSION

Curcumin at 400 mg/kg was the superior dose, producing an 85% effect for treating primary dysmenorrhea in mice. The relationship between curcumin dose and the writhing response was dose-dependent. The optimal dose was 166 mg/kg, with a maximum dose of 1541 mg/kg.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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AUTHOR CONTRIBUTION:

Contribution	Mukhoirotin	Purba AKR	Purwanto B	Ernawati	Zainiyah H	Postma MJ
Concepts or ideas	x	x	x	x		
Design	x	x	x	x		x
Definition of intellectual content	x	x	x	x	x	x
Literature search	x	x	x	x	x	x
Experimental studies	x	x	x	x		
Data acquisition	x	x	x	x	x	x
Data analysis	x	x	x	x	x	x
Statistical analysis	x	x	x			
Manuscript preparation	x	x	x		x	
Manuscript editing	x	x	x	x	x	x
Manuscript review	x	x	x	x	x	x

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