The Effect of Curcumin on 5-Lipoxygenase (5-LO) Levels in the Hearts of Wistar Rats (Rattus norvegicus) as a Preeclampsia Model

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Abstract

Excessive activation of the 5-lipoxygenase (5-LO) pathway plays a pivotal role in promoting inflammation and endothelial dysfunction, thereby aggravating cardiovascular complications in preeclampsia. Curcumin, a natural polyphenolic compound with well-established anti-inflammatory and antioxidant properties, has been suggested to suppress 5-LO activity. This study aimed to evaluate the effect of curcumin administration on cardiac 5-LO levels in pregnant Wistar rats with an L-NAME–induced preeclampsia model. A true experimental post-test–only control group design was conducted using 25 pregnant Wistar rats divided into five groups, consisting of a negative control, a positive control receiving L-NAME, and three treatment groups administered curcumin at doses of 30, 50, or 100 mg/kg body weight alongside L-NAME. Preeclampsia was induced by L-NAME administration at a dose of 125 mg/kg body weight from gestational day 13 to 19, while curcumin was given orally during the same period. Cardiac 5-LO levels were measured from serum samples using enzyme-linked immunosorbent assay (ELISA) and analyzed using one-way ANOVA followed by Tukey's post hoc test with a significance level of $p < 0.05$. The results showed a marked elevation of cardiac 5-LO levels in the positive control group compared to the negative control. Curcumin administration significantly reduced 5-LO levels at all tested doses, with the most pronounced effect observed at 100 mg/kg body weight. Furthermore, a very strong negative correlation was identified between curcumin dose and cardiac 5-LO levels ($r = -0.871$), indicating a clear dose-dependent response. These findings demonstrate that curcumin effectively suppresses cardiac 5-LO levels in a dose-dependent manner in a preeclampsia rat model and highlight its potential clinical relevance as a natural adjunct therapy for mitigating cardiovascular inflammation and endothelial dysfunction associated with preeclampsia

Keywords: Curcumin, 5-Lipoxygenase, Inflammation, Heart, Preeclampsia

INTRODUCTION

Preeclampsia is one of the most serious pregnancy complications, characterized by new-onset hypertension after 20 weeks of gestation accompanied by proteinuria or signs of organ damage. It remains a major cause of maternal morbidity and mortality worldwide, affecting approximately 5–8% of pregnancies (Ives et al., 2020). Its pathophysiology involves endothelial dysfunction, oxidative stress, and a heightened inflammatory response, all of which contribute to impaired organ perfusion and tissue injury (Rana et al., 2019). These mechanisms highlight that inflammation plays a central role in the progression and severity of preeclampsia (Veri et al., 2024).

Among the inflammatory pathways implicated in this condition, the 5-lipoxygenase (5-LO) pathway has received increasing attention. Activation of 5-LO leads to the synthesis of proinflammatory leukotrienes that contribute to vasoconstriction, increased vascular permeability, and endothelial dysfunction all hallmarks of preeclampsia (Abbas et al., 2014; Liu et al, 2025). Although leukotriene-mediated inflammation has been studied in preeclampsia, its specific impact on cardiac tissue during pregnancy complications remains insufficiently explored (Wang et al., 2022).

Activation of 5-LO also enhances oxidative stress and promotes vascular inflammation by increasing leukotrienes such as LTB4 and LTC4, which are known to exacerbate vascular injury and raise blood pressure (Nugroho et al., 2018). Given that cardiac involvement in preeclampsia through hypertrophy, diastolic dysfunction, and microvascular injury is increasingly recognized, understanding inflammatory mediators such as 5-LO in the heart has become an important emerging research priority (Chang et al., 2022).

Curcumin, the active compound in *Curcuma longa*, possesses well-documented anti-inflammatory and antioxidant properties (Panahi et al., 2015). It exerts inhibitory effects on 5-LO through both direct and indirect mechanisms, including suppression of the FLAP–5-LO interaction and downregulation of ALOX5 gene expression via NF-κB inhibition (Du et al., 2019; Fadine et al., 2020). Additionally, curcumin improves endothelial function by enhancing nitric oxide bioavailability and reducing oxidative stress, supporting its potential role in ameliorating preeclamptic pathology (Rahnavard et al., 2019).

Despite extensive evidence regarding curcumin's anti-inflammatory activity, no previous study has specifically examined its effect on 5-LO levels in cardiac tissue or serum derived from cardiac circulation in a preeclampsia model. This represents a critical research gap because understanding cardiac inflammatory changes could provide new mechanistic insights into maternal cardiovascular risk associated with preeclampsia.

Therefore, this study was designed to evaluate the effect of curcumin on cardiac-related 5-LO levels in pregnant Wistar rats induced with L-NAME to model preeclampsia. Addressing this gap is urgent, as elucidating the relationship between curcumin, 5-LO modulation, and cardiac inflammation may help identify novel adjunct therapeutic strategies to mitigate the cardiovascular complications of preeclampsia.

METHODS

This study employed a true experimental design using a post-test only control group. A total of 25 healthy female Wistar rats (10–12 weeks old; 150–200 g) were randomly allocated into five groups (n = 5 per group). Although a sample size of five animals per group is commonly used in rodent inflammatory and molecular studies, this sample size was additionally justified based on previous L-NAME–induced preeclampsia studies demonstrating measurable differences in inflammatory biomarkers with similar group sizes (Nugroho et al., 2018; Rahardjo et al., 2024). This approach aligns with the 3Rs principles, particularly Reduction, while maintaining adequate statistical power for one-way ANOVA.

This study employed a true experimental design with a post-test only control group. Healthy Wistar rats aged 10–12 weeks and weighing 150–200 grams were used as experimental subjects. The preeclampsia model was induced using L-NAME at a dose of 125 mg/kgBW. The animals were then divided into five groups. The negative control group (K–) consisted of pregnant rats without any intervention, while the positive control group (K+) consisted of pregnant rats administered L-NAME without curcumin. The remaining three treatment groups received L-NAME at the same dose followed by curcumin at different doses: 30 mg/kgBW (P1), 50 mg/kgBW (P2), and 100 mg/kgBW (P3) (Rahardjo et al., 2024).

The preeclampsia model was established using L-NAME dissolved in water for injection (WFI). The L-NAME solution was administered intraperitoneally to pregnant rats from gestational day 13 to day 19 at a dose of 125 mg/kgBW per day. Dose calculation was based on an estimated rat body weight of 200 grams, resulting in the following requirement per rat: (125/1000)×200=25 mg/rat/day.

The curcumin extract used in this study was Curcumin Natural C0434 (Tokyo Chemical), provided in powder form. The curcumin powder was dissolved and administered to the animals using an oral feeding apparatus. Following Rahardjo et al. (2024), the doses administered were 30 mg/kgBW, 50 mg/kgBW, and 100 mg/kgBW. The curcumin solution was diluted with distilled water to a final volume of 1 mL for each administration.

At gestational day 20, animals were anesthetized, and cardiac blood serum was collected via cardiac puncture of the left ventricle using a sterile syringe. This technique allows the collection of blood directly from the heart, providing serum that reflects cardiac-associated systemic inflammatory activity. The collected blood was allowed to clot at room temperature and centrifuged at 3,000 rpm for 10–15 minutes at 4 °C to obtain cardiac serum.

5-lipoxygenase (5-LO) concentrations in cardiac serum were measured using a rat-specific 5-LO ELISA kit according to the manufacturer’s protocol. Serum samples and

standards were added to wells pre-coated with capture antibodies, followed by incubation with enzyme-conjugated detection antibodies. After TMB substrate development, absorbance was measured at 450 nm using a microplate reader. 5-LO concentrations were calculated from a standard curve and expressed in ng/mL.

Rationale for sample type: Although the study focuses on cardiac involvement, 5-LO was measured in *cardiac blood serum* because serum collected directly from the heart reflects systemic inflammatory status associated with cardiac dysfunction in L-NAME–induced preeclampsia. This method is widely accepted in cardiovascular inflammation studies while avoiding the variability of tissue homogenate processing.

Descriptive statistics were performed to summarize the data. Normality of distribution was evaluated using the Shapiro–Wilk test, and homogeneity of variance using Levene's test. If assumptions were met, one-way ANOVA was used to assess differences in 5-LO levels among groups, followed by Tukey's post-hoc test for pairwise comparisons.

Pearson correlation analysis was conducted to analyze the relationship between curcumin dose (independent variable) and 5-LO concentration (dependent variable). A significance level of $\alpha = 0.05$ was applied for all analyses

This study obtained ethical clearance from the Health Research Ethics Committee, Faculty of Medicine, Universitas Brawijaya, Indonesia. The protocol was reviewed according to the principles of the Declaration of Helsinki and approved under Ethical Approval Number No. 76 / EC / KEPK – S2 / 04 / 2025. The approval is valid from 10 April 2025 to 10 April 2026. All procedures involving experimental animals were carried out in accordance with institutional guidelines for the care and use of laboratory animals.

RESULTS

Table 1. Normality and Homogeneity Test Results for 5-LO Levels

Group	Shapiro–Wilk p-value	Distribution	Levene's Test p-value (Homogeneity)
Negative Control	0.059	Normal	
Positive Control	0.133	Normal	
Treatment 1	0.455	Normal	0.113
Treatment 2	0.370	Normal	
Treatment 3	0.767	Normal	

Normality testing was performed using the Shapiro–Wilk test because each group consisted of five rats ($n < 50$). The results of the normality test were then used to determine the appropriate statistical analysis. Since the data were normally distributed, the analysis was carried out using one-way ANOVA followed by Tukey's post hoc test. The Shapiro–Wilk test showed that all groups had significance values of $p > 0.05$, with the Negative Control at 0.059,

Positive Control at 0.133, Treatment 1 at 0.455, Treatment 2 at 0.370, and Treatment 3 at 0.767. These results indicate that the 5-lipoxygenase levels in all groups were normally distributed.

The Shapiro–Wilk test showed that all groups had p-values greater than 0.05, indicating that the data were normally distributed. Homogeneity of variances was then assessed using Levene's Test, yielding a significance value of 0.113 ($p > 0.05$). This result confirmed that the variances of 5-Lipoxygenase levels across groups were homogeneous. Therefore, the data met the assumptions required for parametric analysis and could be further examined using a One-Way ANOVA.

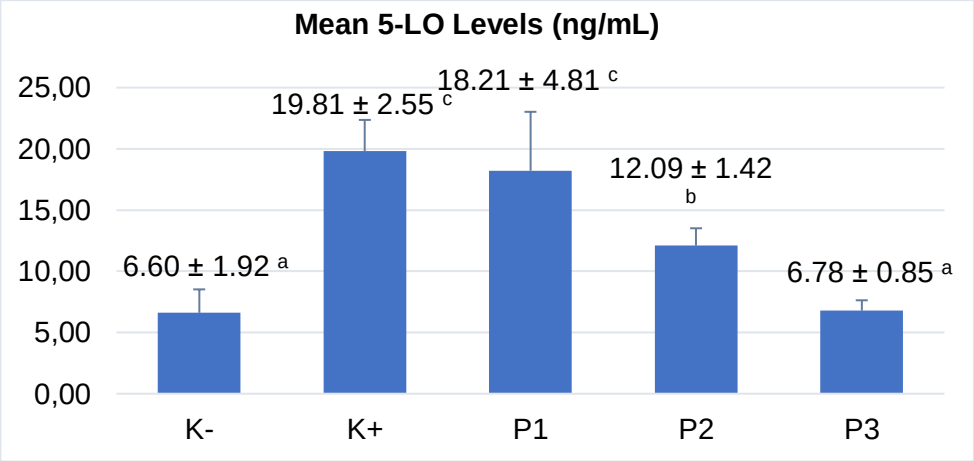
Table 2. ANOVA and Post Hoc Test Results for 5-LO Levels

Group	n	Mean ± SD (ng/mL)	Tukey Subset	p-value (One-Way ANOVA)
K–	5	6.60 ± 1.92	a	
K+	5	19.81 ± 2.55	c	
P1	5	18.21 ± 4.81	c	0.000
P2	5	12.09 ± 1.42	b	
P3	5	6.78 ± 0.85	a	

The One-Way ANOVA demonstrated a statistically significant difference in 5-LO levels among groups ($p = 0.000$). Tukey HSD post hoc analysis assigned letter subsets (a, b, c), where groups sharing the same letter are not significantly different, and groups with different letters differ significantly.

The Positive Control group and Treatment Group 1 were placed in subset **c**, indicating the highest 5-LO concentrations. Treatment Group 2 formed an intermediate subset b, significantly different from both subset c (higher 5-LO) and subset a (lower 5-LO). The Negative Control and Treatment Group 3 shared subset a, reflecting the lowest 5-LO levels.

These findings confirm that curcumin at 100 mg/kgBW/day (P3) produced the greatest reduction in 5-LO levels, reaching values comparable to the healthy Negative Control.



Histogram of Mean 5-LO Levels (ng/mL) in Each Group

Description: K− = Negative control (healthy pregnant), K+ = Positive control (preeclampsia), P1 = Curcumin 30 mg/kgBW/day, P2 = Curcumin 50 mg/kgBW/day, P3 = Curcumin 100 mg/kgBW/day.

The histogram showed a clear dose-dependent decrease in 5-LO levels with increasing curcumin doses. The Positive Control group exhibited the highest mean level (19.813 ng/mL), followed by P1 (18.209 ng/mL). Curcumin at 50 and 100 mg/kgBW/day (P2 and P3) resulted in markedly lower 5-LO levels (12.089 and 6.783 ng/mL, respectively). Notably, P3 nearly matched the Negative Control (6.604 ng/mL), supporting curcumin's dose-dependent anti-inflammatory effect.

Table 3. Correlation Test Results Between Curcumin Dose and 5-LO Levels

Variable	Test Type	Correlation Coefficient (r/ρ)	p-value	Correlation Strength & Direction
5-LO Levels with Dose Groups	Pearson	-0.871	0.000	Very strong, negative, significant

Pearson correlation analysis revealed a very strong and significant negative correlation between curcumin dose and 5-LO levels ($r = –0.871$, $p = 0.000$). This indicates that higher curcumin doses are consistently associated with lower 5-LO concentrations, further reinforcing the dose-dependent therapeutic effect.

DISCUSSION

The present study demonstrated that induction of preeclampsia using L-NAME significantly increased cardiac-related 5-lipoxygenase (5-LO) levels compared with the negative control group. This finding confirms that inhibition of nitric oxide synthase induces a proinflammatory state characterized by endothelial dysfunction and oxidative stress, which are central features of preeclampsia pathophysiology (Rana et al., 2019; Sun et al., 2019). Elevated 5-LO levels in the positive control group reflect enhanced leukotriene synthesis, which contributes to vasoconstriction, increased vascular permeability, and inflammatory amplification commonly observed in preeclampsia (Ortega et al., 2024).

The significant increase in 5-LO levels following L-NAME administration supports previous findings that reduced nitric oxide (NO) bioavailability promotes activation of inflammatory lipid pathways, including the arachidonic acid–5-LO cascade (Mulyani et al., 2021). In preeclampsia, diminished NO production disrupts endothelial homeostasis, leading to increased oxidative stress and upregulation of inflammatory mediators such as leukotrienes, which further aggravate cardiovascular dysfunction (Kahnt et al., 2024).

Administration of curcumin at doses of 30, 50, and 100 mg/kgBW resulted in a significant reduction in 5-LO levels compared with the positive control group. This finding

indicates that curcumin effectively suppresses inflammatory activation in the L-NAME–induced preeclampsia model. The most pronounced reduction was observed at the highest dose (100 mg/kgBW), where 5-LO levels approached those of the negative control group. These results are consistent with previous studies reporting the anti-inflammatory effects of curcumin through inhibition of inflammatory enzymes and signaling pathways involved in preeclampsia (Gadnayak et al., 2022; Zanganeh et al., 2020).

The dose-dependent reduction in 5-LO levels observed in this study suggests that curcumin exerts its effects through direct modulation of the 5-LO pathway. Curcumin has been shown to inhibit the interaction between 5-LO and 5-LO–activating protein (FLAP), suppress ALOX5 gene expression, and downregulate NF-κB signaling, thereby reducing leukotriene production and inflammatory amplification (Mulyani et al., 2021; Winardi et al., 2023). These mechanisms provide a biological explanation for the progressive decline in 5-LO levels across increasing curcumin doses observed in the present study.

The very strong negative correlation between curcumin dose and 5-LO levels ($r = -0.871$) further confirms the dose-responsive nature of curcumin's anti-inflammatory effect. This finding aligns with previous experimental studies demonstrating that higher doses of curcumin yield stronger suppression of inflammatory biomarkers in preeclampsia models (Rahardjo et al., 2024). Such a correlation indicates that curcumin's effect is not incidental but reflects a consistent pharmacological response.

Cardiac involvement in preeclampsia has been increasingly recognized as a contributor to both short- and long-term maternal cardiovascular risk. Persistent inflammation and leukotriene-mediated vascular injury promote myocardial remodeling, increased afterload, and impaired cardiac function (Yang et al., 2023). The reduction of cardiac-associated 5-LO levels observed in this study suggests that curcumin may exert cardioprotective effects by attenuating inflammatory pathways that contribute to cardiac stress and dysfunction in preeclampsia.

Although 5-LO levels were measured in cardiac serum rather than heart tissue, serum obtained via cardiac puncture reflects inflammatory activity closely associated with cardiac circulation and systemic cardiovascular stress (Santos et al., 2021). This approach is commonly used in cardiovascular inflammation studies and provides meaningful insight into inflammatory changes related to cardiac involvement in preeclampsia (Guan et al., 2023).

The modest reduction in 5-LO levels observed at the lowest curcumin dose (30 mg/kgBW) compared with the more substantial reductions at 50 and 100 mg/kgBW underscores the importance of adequate dosing. This finding is consistent with previous reports indicating that low-dose curcumin may be insufficient to counteract the intense inflammatory

burden associated with preeclampsia (Pourbagher-Shahri et al., 2021; Tossetta et al., 2021). Therefore, the dose-dependent effect observed in this study highlights the need for careful dose optimization when considering curcumin as a potential adjunct therapy.

Despite the promising findings, this study has limitations that should be acknowledged. The relatively small sample size may limit generalizability, although statistically significant differences were observed across groups. Additionally, the absence of direct cardiac tissue analysis limits the ability to fully characterize localized myocardial inflammation. Future studies should incorporate heart tissue homogenates, histopathological analysis, and additional biomarkers to further elucidate the cardioprotective mechanisms of curcumin in preeclampsia.

Overall, the findings of this study provide novel evidence that curcumin effectively suppresses 5-LO activity in a preeclampsia rat model in a dose-dependent manner. These results support the potential role of curcumin as a natural anti-inflammatory and cardioprotective adjunct in preeclampsia management, particularly in mitigating inflammation-driven cardiovascular complications.

CONCLUSION

Curcumin demonstrates potential as a natural adjunctive preventive approach for preeclampsia, particularly in reducing cardiovascular-related inflammation through suppression of the 5-lipoxygenase (5-LO) pathway in a dose-dependent manner. Among the evaluated doses (30, 50, and 100 mg/kg body weight), curcumin at 100 mg/kg body weight was the most effective, significantly lowering cardiac 5-LO levels to values approaching those of normal physiological conditions in pregnant Wistar rats (Rattus norvegicus) with an L-NAME–induced preeclampsia model.

This study focused on a single inflammatory biomarker (5-LO); therefore, further research is warranted to correlate these findings with cardiac histopathological changes and additional biomarkers of endothelial dysfunction and cardiovascular injury. Although animal models provide valuable mechanistic insights, physiological differences between rodent models and human pregnancy should be considered when interpreting these results. Moreover, other molecular pathways potentially influenced by curcumin were not investigated in this study and may represent important directions for future research to further elucidate the cardioprotective mechanisms of curcumin in preeclampsia.

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