Curcumin Reduces Hepatic IL-6 Expression in an L-NAME–Induced Preeclampsia Model in Wistar Rats (Rattus norvegicus)

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Abstract

Preeclampsia is a pregnancy complication after 20 weeks of gestation characterized by hypertension, proteinuria, and endothelial dysfunction driven by oxidative stress and inflammation. Elevated interleukin-6 (IL-6) contributes to hepatic injury and increases the risk of HELLP syndrome. Curcumin, the active compound of Curcuma longa, possesses antioxidant and anti-inflammatory effects via inhibition of the NF-κB pathway, potentially suppressing IL-6 expression in hepatic tissue. This study aimed to evaluate the effect of curcumin on hepatic IL-6 expression in an L-NAME–induced preeclampsia model in Wistar rats. A true experimental post-test-only control group design was used with 25 pregnant rats (n = 5/group) divided into a healthy control (K–), a disease model control (K+; L-NAME 125 mg/kg BW), and three curcumin-treated groups receiving 30, 50, and 100 mg/kg BW (P1, P2, P3). IL-6 expression in hepatic tissue was assessed immunohistochemically and quantified using ImageJ software. Data were normally distributed (Shapiro–Wilk p = 0.288) and homogeneous (Levene p = 0.277), allowing one-way ANOVA and Pearson correlation analyses (α = 0.05). Mean ± SD hepatic IL-6 expression (% area) was K– = 5.04 ± 2.32, K+ = 62.97 ± 2.71, P1 = 55.45 ± 2.57, P2 = 28.49 ± 4.08, and P3 = 16.46 ± 2.60 (p < 0.001, η² = 0.94). Post-hoc HSD analysis showed significant reductions in all curcumin-treated groups compared with K+, with the highest dose (P3) showing the greatest reduction and values approaching normal levels. A strong negative correlation (r = –0.962, p < 0.001; 95% CI = [–0.99, –0.86]) indicated a clear dose-related trend between curcumin administration and decreased IL-6 expression. These findings suggest that curcumin attenuates hepatic IL-6 expression in an L-NAME–induced preeclampsia model in a dose-related manner, supporting its potential hepatoprotective and anti-inflammatory roles against preeclampsia-associated oxidative injury.

Keywords: Curcumin, Immunohistochemistry, Liver, L-NAME, Pregnancy

INTRODUCTION

Preeclampsia is a hypertensive disorder of pregnancy occurring after 20 weeks of gestation and remains a major contributor to maternal and perinatal morbidity and mortality worldwide (World Health Organization, 2020). Despite advances in obstetric care, preeclampsia remains a major cause of maternal morbidity due to its complex pathophysiology and limited therapeutic options beyond delivery (Nirupama et al., 2021). In Indonesia, preeclampsia accounts for approximately 25–30% of maternal deaths, highlighting its significant public health impact and the need for effective preventive and therapeutic strategies (Kementerian Kesehatan Republik Indonesia, 2022). Maternal deaths associated with hypertensive disorders of pregnancy are often exacerbated by delays in diagnosis and management, underscoring the importance of early pathophysiological intervention (Dafroyati

et al., 2023). Clinically, preeclampsia is characterized by hypertension, proteinuria, and systemic endothelial dysfunction, which may progress to multiorgan involvement, including hepatic impairment (Ives et al., 2020).

Inflammation and oxidative stress are central mechanisms in the pathophysiology of preeclampsia, contributing to endothelial injury and organ dysfunction (Guan et al., 2023). Oxidative stress–induced inflammatory responses, including increased pro-inflammatory cytokines, have been consistently associated with preeclampsia (Ibrahim et al., 2024). IL-6 has been widely recognized as a key inflammatory mediator in pregnancy-related disorders, with elevated levels observed across various pathological gestational conditions (Kadhim & Khazaali, 2023). Among pro-inflammatory cytokines, interleukin-6 (IL-6) plays a critical role in amplifying inflammatory responses, endothelial activation, and vascular dysfunction in preeclamptic pregnancies (Nawaz & Kumar Verma, 2020). Elevated IL-6 levels have been associated with disease severity and increased risk of maternal complications, including hepatic involvement and HELLP syndrome (Kusuma et al., 2024). However, most existing studies focus on circulating IL-6 levels, while local hepatic IL-6 expression remains insufficiently explored, limiting understanding of liver-specific inflammatory responses in preeclampsia (Naruse, 2024).

The liver is particularly vulnerable to inflammatory injury in preeclampsia due to microvascular dysfunction, oxidative stress, and altered nitric oxide bioavailability (Ives et al., 2020). Hepatic inflammation may manifest as elevated liver enzymes, hepatocellular stress, and, in severe cases, progression to HELLP syndrome, which significantly increases maternal morbidity and mortality (Nana et al., 2025). Despite this clinical relevance, experimental evidence addressing inflammatory modulation specifically within hepatic tissue in preeclampsia models remains limited (Naruse, 2024).

Curcumin has been reported to exert anti-inflammatory effects in preeclampsia through modulation of inflammatory mediators and endothelial function (Fadinie et al., 2020). Curcumin, a bioactive polyphenolic compound derived from *Curcuma longa*, exhibits potent antioxidant and anti-inflammatory properties through inhibition of nuclear factor-κB (NF-κB) signaling and modulation of endothelial nitric oxide synthase (eNOS) activity (Tossetta et al., 2021). Curcumin has been shown to improve endothelial function by modulating eNOS activity and reducing oxidative stress, as demonstrated in experimental rat models exposed to environmental toxins (Aminuddin et al., 2023). Experimental studies have demonstrated that curcumin reduces oxidative stress, suppresses pro-inflammatory cytokines such as IL-6, and improves endothelial function in pregnancy-related disorders (Naemi et al., 2021). In L-

NAME–induced preeclampsia models, curcumin has been reported to ameliorate hypertension, proteinuria, and endothelial dysfunction, suggesting its potential as a protective agent against inflammation-mediated organ damage (Dewi et al., 2024).

Despite growing evidence supporting curcumin's systemic anti-inflammatory effects, data regarding its impact on hepatic IL-6 expression, particularly across different therapeutic doses, remain scarce (Zanganeh et al., 2020). Furthermore, the dose-dependent relationship between curcumin administration and liver-specific inflammatory modulation in preeclampsia models has not been comprehensively clarified, representing an important knowledge gap (Naemi et al., 2021). Therefore, this study aimed to evaluate the effect of curcumin on hepatic IL-6 expression in an L-NAME–induced preeclampsia model in Wistar rats and to determine whether this effect exhibits a dose-dependent pattern.

METHODS

This study employed a true experimental design with a post-test-only control group approach using pregnant Wistar rats (Rattus norvegicus). Twenty-five confirmed-pregnant rats (n = 5 per group) were randomly allocated into five groups using a simple randomization method. Pre-induction biochemical measurements (such as MDA and catalase) were not collected. Simple randomization was applied to ensure comparable baseline conditions across all groups; therefore, only post-test data are presented in this study. Based on random number generation: negative control (K–), positive control (K+; L-NAME only), and three treatment groups receiving L-NAME plus curcumin at doses of 30 mg/kg BW (P1), 50 mg/kg BW (P2), and 100 mg/kg BW (P3). The unit of analysis was the animal (n = 5/group); ten microscopic fields per liver section were analyzed and averaged to yield one value per animal, preventing pseudo-replication. Sample size (n = 5/group) was determined based on prior studies (Rahardjo et al., 2022; Rahardjo et al., 2024) and a minimum detectable effect size ($f = 0.8$, $\alpha = 0.05$, power = 0.8) using G*Power software, confirming adequate statistical power.

Animals were housed under controlled environmental conditions (temperature 22 ± 2°C, relative humidity 50–60%, 12:12 h light–dark cycle) with ad libitum access to standard chow and water. Pregnancy was confirmed by the presence of sperm in vaginal smears (gestational day 0). To induce preeclampsia, L-NAME (Nω-Nitro-L-arginine methyl ester) was administered intraperitoneally at 125 mg/kg BW daily from gestational day 13 to day 19. Curcumin (Sigma-Aldrich, St. Louis, MO, USA) was suspended in 0.5% carboxymethyl cellulose sodium (CMC-Na) and given orally 1 hour after each L-NAME injection during the same period. The negative control received only vehicle (0.5% CMC-Na).

Systolic blood pressure, as a secondary endpoint, was measured on gestational days 13 and 19 using a noninvasive tail-cuff system (CODA™, Kent Scientific, USA) after animal acclimatization. Urine samples were collected on day 19 using individual metabolic cages, and urinary protein concentration was quantified using a Colorimetric Protein Assay Kit (BioAssay Systems, USA) following the manufacturer's protocol. These parameters confirmed the successful establishment of the preeclampsia model prior to tissue collection.

At gestational day 20, rats were anesthetized and euthanized; liver tissues were excised and fixed in 10% neutral-buffered formalin for 24 hours. Tissues were processed into paraffin blocks and sectioned at 4–5 µm thickness. Immunohistochemical staining for IL-6 was performed using a monoclonal anti–IL-6 primary antibody (clone H-183, Santa Cruz Biotechnology, Cat. No. sc-130326, USA). The detection system used a commercial DAB Substrate Kit (Vector Laboratories, USA). All sections were counterstained with hematoxylin and mounted using DPX mounting medium (Sigma-Aldrich, USA). IL-6 expression was visualized as brown DAB staining and quantified using ImageJ software version 1.53c.

Microscopic evaluation was performed under a light microscope (Olympus CX43) at 400× magnification. The assessor was blinded to treatment allocation throughout image capture and analysis. Images were taken from 10 random, non-overlapping fields per specimen within periportal and centrilobular regions. Quantitative analysis was performed using ImageJ version 1.53c with color deconvolution to isolate the DAB channel. The threshold for brown-stained (positive) areas was standardized across all samples based on negative control calibration. IL-6 expression was expressed as the percentage of DAB-stained area per total field.

Data normality (Shapiro–Wilk, $p = 0.288$) and homogeneity (Levene, $p = 0.277$) assumptions were met, permitting parametric testing. Group means were compared by one-way ANOVA followed by Tukey's HSD post hoc test ($\alpha = 0.05$). Pearson correlation analysis was used to examine the association between curcumin dose and IL-6 expression. IL-6 immunoexpression was the primary endpoint, whereas blood pressure and urinary protein concentration were secondary endpoints. All analyses were performed in SPSS 25.0 (IBM Corp., USA). Ethical approval was obtained from the Health Research Ethics Committee, Faculty of Medicine, Universitas Brawijaya (No. 75/EC/KEPK-52/04/2025). The research was conducted from April to May 2025 at the Pharmacology Laboratory, Faculty of Medicine, Universitas Brawijaya.

RESULT

Blood Pressure and Urinary Protein Analysis

Systolic blood pressure was measured on gestational days 13 and 19. At baseline (day 13), all groups showed comparable blood pressure values due to simple randomization applied at allocation; therefore, only post-test values (day 19) are presented. On day 19, the negative control group (K–) showed normal systolic blood pressure (114.60 ± 2.41 mmHg), while the positive control group (K+) exhibited a marked increase (159.40 ± 2.12 mmHg), confirming successful preeclampsia induction by L-NAME.

Curcumin administration reduced systolic blood pressure in a dose-dependent manner: P1 (154.60 ± 1.72 mmHg), P2 (140.80 ± 2.28 mmHg), and P3 (122.40 ± 1.67 mmHg), with P3 showing values approaching normal pregnancy levels. A similar pattern was observed in urinary protein concentration. The K– group demonstrated the lowest level (3.13 ± 0.16 mg/mL), while K+ showed the highest (7.57 ± 0.15 mg/mL). Curcumin treatment reduced proteinuria in a graded response: P1 (5.94 ± 0.18 mg/mL), P2 (4.62 ± 0.21 mg/mL), and P3 (3.36 ± 0.14 mg/mL), indicating attenuation of renal inflammation and endothelial dysfunction.

IL-6 Expression

Assumption Testing

IL-6 expression data met statistical assumptions. The Shapiro–Wilk test confirmed normal distribution ($p = 0.29$), and the Levene test confirmed homogeneity of variance ($p = 0.28$), allowing parametric analysis.

Table 1. Normality and Homogeneity Test Results for IL-6 Expression

Variable	p-value	Distribution	Homogeneity	Interpretation
IL-6	0.29	Normal	0.28	Homogeneous

Quantitative Analysis of IL-6 Expression

Curcumin administration resulted in a dose-dependent reduction in hepatic IL-6 expression. Quantitative ImageJ analysis of the DAB-stained area (%) showed the following:

Table 2. One-way ANOVA

Group	N	Mean ± SD	p-Value
K-	5	5.04 ± 2.32^{a}	
K+	5	62.97 ± 2.71^{e}	
P1	5	55.45 ± 2.57^{d}	**0.000<α**
P2	5	28.49 ± 4.08^{c}	
P3	5	16.46 ± 2.60^{b}	

Different superscripts (a–e) indicate statistically significant differences between groups (Tukey's HSD, $p < 0.05$).

Based on the ANOVA results ($p < 0.001$), IL-6 expression significantly differed among groups. The highest IL-6 expression was observed in the positive control group (62.97 ± 2.71),

while the lowest was found in the negative control (5.04 ± 2.32), confirming the success of inflammation induction by L-NAME.

Curcumin administration led to a dose-dependent reduction in IL-6 expression. P1 (30 mg/kg BW) showed a modest yet significant decrease (55.45 ± 2.57; p = 0.005 vs. K+), while P2 (50 mg/kg BW) demonstrated a more pronounced reduction (28.49 ± 4.08; p = 0.000). The lowest IL-6 level was found in P3 (100 mg/kg BW, 16.46 ± 2.60; p = 0.000), approaching normal control values.

These findings confirm that curcumin exhibits a dose-dependent anti-inflammatory and hepatoprotective effect, effectively suppressing hepatic IL-6 expression in preeclampsia models.

Correlation Between Curcumin Dose and IL-6 Expression

Table 3. Correlation Test Result Between Curcumin Dose and IL-6 Expression

Variable	Test Type	r	p-value	Interpretation
Curcumin dose vs. IL-6 expression	Pearson	–0.96	0.000	Significant negative correlation

A Pearson correlation test revealed a strong, statistically significant negative correlation (r = –0.96, p < 0.001) between curcumin dose and IL-6 expression. The negative coefficient indicates that higher curcumin doses were associated with lower IL-6 expression levels, confirming a clear dose–response relationship.

The average IL-6 expression in the hepatic tissue of the preeclampsia rat model is illustrated in the histogram below.

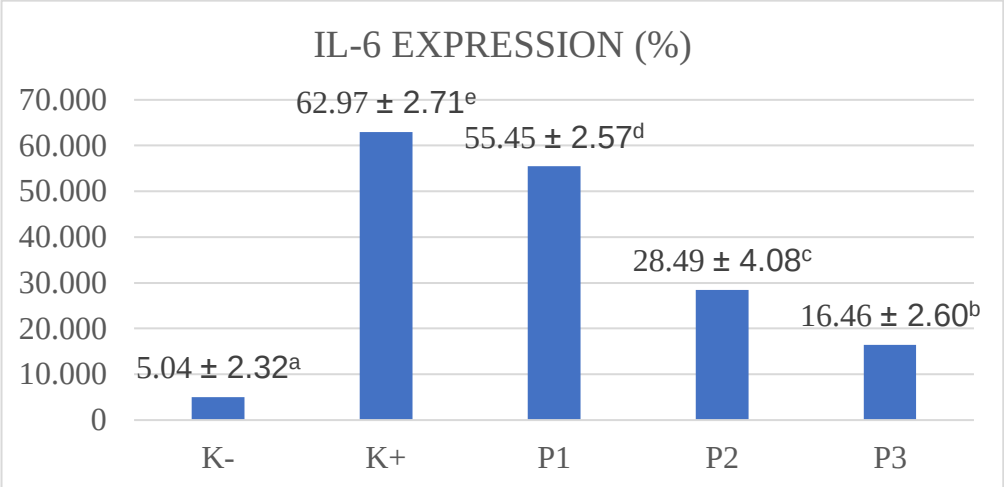

Figure 1. Expression of IL-6 Levels in Hepatic Tissue of Preeclamptic Rats. Black arrows indicate IL-6 expression in hepatic tissue, visualized as brown staining under a light microscope at 400× magnification; scale bar: 5 µm. (A) K(–): hepatic tissue of normal pregnant rats. (B) K(+): hepatic tissue of preeclamptic rats. (C) P1: hepatic tissue of preeclamptic rats + curcumin 30 mg/kg BW. (D) P2: hepatic tissue of

preeclamptic rats + curcumin 50 mg/kg BW. (E) P3: hepatic tissue of preeclamptic rats + curcumin 100 mg/kg BW.

Figure 1 shows that the highest mean IL-6 expression was observed in the positive control group. Mean IL-6 expression appeared lower in the P1, P2, and P3 groups compared with the positive control group. IL-6 expression tended to decrease with increasing curcumin dose. Statistical analysis revealed significant differences among the three curcumin doses; however, curcumin administration was able to reduce IL-6 expression in the preeclampsia rat model, with the 100 mg/kg BW dose (P3) producing a significant reduction.

Immunohistochemistry revealed dose-dependent reductions in IL-6 expression with curcumin treatment. Quantitative analysis (ImageJ 1.53c) showed:

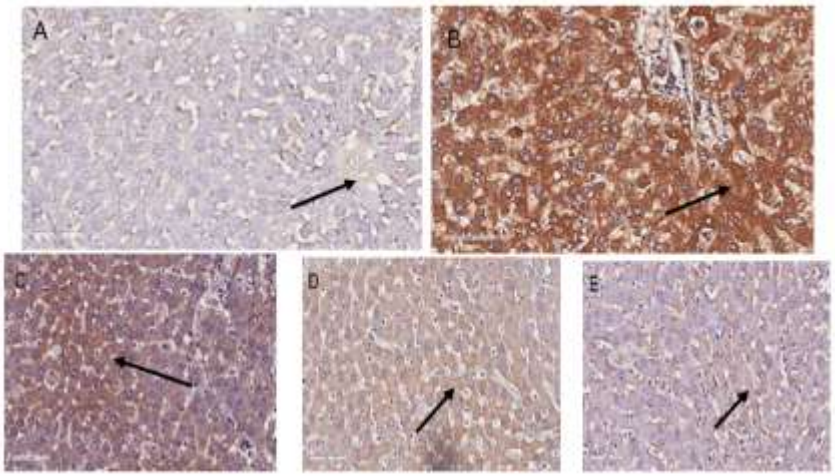

Figure 2. Immunohistochemical Expression of IL-6 in Hepatic Tissue of Preeclamptic Rats. Black arrows indicate IL-6 expression in hepatic tissue, visualized as brown staining under a light microscope at 400× magnification; scale bar: 5 µm. (A) K(–): hepatic tissue of normal pregnant rats. (B) K(+): hepatic tissue of preeclamptic rats. (C) P1: hepatic tissue of preeclamptic rats + curcumin 30 mg/kg BW. (D) P2: hepatic tissue of preeclamptic rats + curcumin 50 mg/kg BW. (E) P3: hepatic tissue of preeclamptic rats + curcumin 100 mg/kg BW.

Figure 2 presents the analysis results of IL-6 expression in the hepatic tissue of the preeclampsia rat model obtained through the immunohistochemistry method. Data were collected by capturing images from 10 randomly selected fields of view without consideration of specific cell types. Imaging was performed across all regions of the liver, followed by analysis using ImageJ software version 1.53c. The analysis utilized the *color deconvolution* feature to separate color components and identify the expression areas (indicated by brown staining), which were subsequently quantified as a percentage using the measurement feature. The measurement results were exported to an Excel file and analyzed using a one-way ANOVA test to evaluate the effect of curcumin administration on IL-6 expression in the hepatic tissue of the preeclampsia rat model.

DISCUSSION

Preeclampsia is a multifactorial disorder involving abnormal placentation, oxidative stress, endothelial dysfunction, and systemic inflammatory activation, which collectively contribute to maternal organ damage (Lian et al., 2022). The present study demonstrated that L-NAME administration successfully induced a preeclampsia-like condition in pregnant Wistar rats, as evidenced by elevated systolic blood pressure and increased urinary protein levels. These findings are consistent with previous studies reporting that chronic inhibition of nitric oxide synthase leads to endothelial dysfunction, hypertension, and renal impairment, which closely resemble the pathophysiological features of preeclampsia in humans (Naruse, 2024). The disruption of nitric oxide signaling observed in experimental models is consistent with clinical evidence demonstrating oxidative stress–mediated eNOS dysfunction in preeclampsia (Guerby et al., 2021). Endothelial nitric oxide synthase dysfunction plays a critical role in the development of hypertension and vascular abnormalities in preeclampsia (Ssengonzi Rebecca et al., 2024). Similar improvements in clinical and biochemical features have been reported in L-NAME-induced preeclampsia-like rat models following targeted molecular interventions (Zeng et al., 2023). The confirmation of this model provides a valid foundation for evaluating inflammatory responses and therapeutic interventions targeting organ-specific damage, including hepatic involvement.

A marked increase in hepatic IL-6 expression was observed in the positive control group, indicating a strong inflammatory response following L-NAME induction. Elevated IL-6 has been widely recognized as a key mediator of systemic inflammation in preeclampsia, contributing to endothelial activation, oxidative stress, and multiorgan dysfunction (Guan et al., 2023; Nawaz & Kumar Verma, 2020). Consistent with clinical observations, increased IL-6 levels have been reported in pregnant women with preeclampsia and are often accompanied by elevated inflammatory markers such as hsCRP (Yuniarti Ekasaputri Burhanuddin & Afrianty, 2021). The liver is particularly susceptible to such inflammatory insults due to microvascular disturbances and reduced nitric oxide bioavailability, which may progress to hepatocellular injury and, in severe cases, HELLP syndrome (Ives et al., 2020; Nana et al., 2025). The substantial increase in hepatic IL-6 expression observed in this study supports previous evidence that preeclampsia is not solely a placental disorder but also involves significant liver-specific inflammatory processes (Naruse, 2024).

Curcumin administration resulted in a significant reduction in hepatic IL-6 expression across all treatment groups, with the magnitude of reduction increasing in a dose-related manner. These findings are in line with prior experimental studies demonstrating curcumin’s

potent anti-inflammatory effects through suppression of pro-inflammatory cytokines, including IL-6, in pregnancy-related and inflammatory disease models (Naemi et al., 2021; Zanganeh et al., 2020). Experimental studies in Wistar rats have demonstrated that curcumin administration can modulate IL-6 levels without inducing acute toxicity, supporting its safety and anti-inflammatory potential (Lubis et al., 2023). The observed dose-dependent response suggests that higher curcumin doses exert more pronounced biological effects, particularly in conditions characterized by severe oxidative stress and inflammation.

The greatest reduction in IL-6 expression was observed in the group receiving the highest curcumin dose (100 mg/kg BW), indicating that this dosage was the most effective in attenuating hepatic inflammation. This finding is consistent with evidence that higher curcumin doses more effectively inhibit NF-κB signaling, a central transcription factor regulating IL-6 production and other pro-inflammatory mediators (Tossetta et al., 2021). At higher concentrations, curcumin has been shown to prevent NF-κB nuclear translocation, enhance endogenous antioxidant defenses, and stabilize hepatocyte membranes, thereby reducing inflammatory signaling within hepatic tissue (Bertoncini-Silva et al., 2024; Zanganeh et al., 2020). These mechanisms align with the near-normal IL-6 expression levels observed in the high-dose curcumin group in the present study and support the conclusion that 100 mg/kg BW represents an effective therapeutic dose in this experimental model.

In addition to its direct anti-inflammatory effects, curcumin is known to modulate oxidative stress pathways that are closely linked to cytokine production. Previous studies have demonstrated that curcumin reduces malondialdehyde levels while increasing antioxidant enzyme activity, such as catalase and superoxide dismutase, thereby limiting reactive oxygen species–induced inflammatory amplification (Naemi et al., 2021; Tossetta et al., 2021). At the cellular level, curcumin has been shown to influence trophoblast viability and apoptotic pathways, suggesting its broader regulatory role in pregnancy-related tissues (Nurseta et al., 2018). Although oxidative stress markers were not directly assessed in this study, the established interplay between oxidative stress reduction and cytokine suppression provides a plausible mechanistic explanation for the significant decrease in hepatic IL-6 expression observed, particularly at higher curcumin doses.

The strong negative correlation identified between curcumin dose and IL-6 expression further supports the presence of a clear dose–response relationship. While the curcumin dose variable is ordinal rather than continuous, this correlation reflects a consistent monotonic trend, reinforcing the conclusion that increasing curcumin doses are associated with progressively greater anti-inflammatory effects. Similar dose-dependent trends have been reported in other

experimental studies evaluating curcumin's effects on inflammatory and endothelial markers in preeclampsia and related models (Dewi et al., 2024; Kusuma et al., 2024).

The implications of these findings are clinically relevant, as hepatic involvement in preeclampsia is associated with increased maternal morbidity and adverse pregnancy outcomes. Therapeutic strategies capable of reducing liver-specific inflammation may help mitigate disease severity and prevent progression to severe complications such as HELLP syndrome (Nana et al., 2025; Naruse, 2024). Although curcumin is not currently part of standard preeclampsia management, its favorable safety profile and multi-target anti-inflammatory properties suggest potential as an adjunctive therapeutic agent, particularly if bioavailability-enhanced formulations are considered (Bertoncini-Silva et al., 2024).

Several limitations of this study should be acknowledged. First, the use of an animal model limits direct translation of the findings to human preeclampsia, as the L-NAME model does not fully capture the complex placental and immunological interactions present in clinical disease. Second, IL-6 expression was assessed using semi-quantitative immunohistochemistry rather than molecular techniques such as Western blot or RT-qPCR, which may provide more precise quantification. Third, biochemical markers of hepatic injury and oxidative stress were not measured, restricting deeper mechanistic interpretation of curcumin's hepatoprotective effects.

Future studies should incorporate molecular assays to confirm cytokine expression and explore upstream signaling pathways, including NF-κB and eNOS. The inclusion of oxidative stress markers and liver function parameters would further elucidate curcumin's protective mechanisms. Additionally, investigations using bioavailability-enhanced curcumin formulations and clinical studies in preeclamptic populations are warranted to determine translational relevance and therapeutic potential.

CONCLUSION

Curcumin administration in L-NAME–induced preeclamptic Wistar rats was associated with a significant, dose-dependent reduction in hepatic IL-6 expression, as confirmed by ANOVA and Tukey post hoc analysis. The highest curcumin dose (100 mg/kg BW) produced IL-6 levels approaching the normal control, indicating a clear attenuation of inflammatory activity. These findings suggest that curcumin may serve as a potential hepatoprotective and anti-inflammatory agent in preeclampsia; however, the small sample size and semi-quantitative assessment of IL-6 warrant further molecular validation and inclusion of additional oxidative stress markers in future studies.

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