Therapeutic Effect of Curcumin on Hepatic iNOS Expression in a Rat (Rattus norvegicus) Preeclampsia Model

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Track Record Article

Revised: 21 October 2025
Accepted: 10 December 2025
Published: 31 December 2025

How to cite :
Sururi, D. A., Rizki, M. P. N., Rahardjo, B., & Ariani, N. (2025). Therapeutic Effect of Curcumin on Hepatic iNOS Expression in a Rat (Rattus norvegicus) Preeclampsia Model. *Contagion: Scientific Periodical Journal of Public Health and Coastal Health*, *7*(3), 159–167.

Abstract

Preeclampsia is a pregnancy-specific disorder characterized by hypertension after 20 weeks of gestation and multisystem involvement, including hepatic dysfunction. Amplified oxidative stress and systemic inflammation contribute to liver damage, partly through the stimulation of inducible nitric oxide synthase (iNOS). Curcumin, a polyphenol derived from Curcuma longa, possesses strong antioxidant and anti-inflammatory properties and has been reported to inhibit iNOS expression in various disease models. The objective of this study was to evaluate the effect of curcumin on hepatic iNOS protein expression in a rat model of preeclampsia. A true experimental post-test-only control group design was employed. Twenty-five pregnant Wistar rats were randomly assigned to five groups: negative control, positive control (L-NAME–induced preeclampsia), and three treatment groups receiving curcumin at 30, 50, or 100 mg/kg body weight alongside L-NAME. Preeclampsia was induced by intraperitoneal administration of L-NAME (125 mg/kg body weight) from gestational day 13 to 19, during which curcumin was administered orally. Liver tissues were collected and subjected to immunohistochemical analysis to quantify iNOS expression. One-way ANOVA with post hoc testing ($p < 0.05$) revealed significant differences among groups. Quantitative ImageJ analysis iNOS expression (% positive area) showed: 5.06 (negative control), 77.00 (positive control), 64.34 (P1), 33.67 (P2), and 19.78 (P3), indicating a dose-dependent reduction in iNOS expression. Curcumin at 100 mg/kg body weight produced the most pronounced decrease in hepatic iNOS expression in preeclampsia-induced rats. These findings demonstrate that curcumin exerts hepatoprotective effects through the downregulation of iNOS in preeclamptic liver tissue and suggest its potential as an adjunctive therapeutic or preventive strategy for mitigating hepatic inflammation in preeclampsia. Further investigation in advanced preclinical and clinical studies is warranted.

Keywords: Curcumin, iNOS, Oxidative stress, Hepatic Inflammation, Preeclampsia.

INTRODUCTION

Preeclampsia is a serious condition that contributes to 3-8% of maternal and neonatal deaths worldwide (Deng et al., 2024). It accounts for about 30% of acute kidney injury (AKI) cases, roughly 20 per 100,000 pregnancy, and 0.8% of pregnant women (Burton et al., 2019). In Indonesia, hypertension during pregnancy is one of the leading drivers of AKI, resulting in 412 maternal deaths between 2021 and 2023 (Kementerian Kesehatan RI, 2024). At its core, preeclampsia is a complex disease marked by problems with the endothelium, reduced blood flow to the placenta, and inflammation in the blood vessels, which can harm multiple organ systems (Chiang et al., 2024). The liver, in particular, is highly vulnerable to oxidative stress

(Ives et al., 2020) triggered by preeclampsia, and this stress is closely tied to the development of HELLP syndrome.

The liver plays a central role in detoxifying the body and breaking down various compounds, some of which can produce free radicals. Normally, the liver maintains balance through its antioxidant defenses. But when the production of free radicals, especially reactive oxygen species (ROS), exceeds the body's ability to neutralize them, this balance is disrupted. Excess ROS can damage proteins, lipids, and DNA inside liver cells (Banerjee et al., 2023), eventually impairing both the structure and function of the liver.

In mothers with preeclampsia, the production of reactive oxygen species (ROS) increases, which triggers the release of pro-inflammatory cytokines such as IL-6 and TNF-α. These cytokines activate signaling pathways that include NF-κB, a key regulator that stimulates the expression of inducible nitric oxide synthase (iNOS). iNOS then drives the excessive and uncontrolled production of nitric oxide (NO) in response to oxidative stress and inflammation (Wang et al., 2019). The NO generated by iNOS reacts with superoxide to form peroxynitrite ($ONOO^-$) (Yang et al., 2020), a compound that further sustains the overproduction of ROS.

Under pathological conditions, iNOS produces large amounts of nitric oxide (NO), which is the main source of reactive nitrogen species (RNS). One of the most harmful products formed is peroxynitrite ($ONOO^-$). This compound can damage key cellular components such as DNA, lipids, and proteins. It also causes protein nitration, a process that drastically alters the structure and function of the affected proteins (Raguema et al., 2020). Because of this, regulating iNOS activity is crucial, as uncontrolled NO production can lead to significant tissue injury. Beyond its damaging potential, NO also plays important roles in normal physiology (Lee et al., 2019), including vasodilation and participation in immune and inflammatory responses.

Curcumin, also known as diferuloylmethane, is a natural compound with a wide range of biological activities. Research has shown that it can act as an antioxidant, anti-inflammatory, antiviral, antibacterial, antifungal, antiproliferative, neuroprotective, hepatoprotective, immunomodulatory, and even anticancer agent (Grafeneder et al., 2022). Its antioxidant effects are particularly important in pregnancy: curcumin helps protect placental trophoblast cells, reduces oxidative stress in other organs, and lowers cell death associated with preeclampsia (Tossetta et al., 2021). In this study, we aimed to explore how curcumin might suppress the expression of inducible nitric oxide synthase (iNOS) in the liver tissue of rats that were experimentally induced to develop a preeclampsia-like condition.

METHODS

This study used a true experimental design with a post-test-only control group to examine the effect of curcumin on iNOS expression in the liver tissue of preeclampsia-induced rats (Rattus norvegicus). A total of 25 female Wistar rats, aged 10–12 weeks and weighing 150–200 grams, were randomly divided into five groups. These included: a positive control group (K+, representing preeclampsia-induced rats), a negative control group (K−, representing healthy rats), and three treatment groups (P1, P2, and P3). Each group consisted of five rats.

Preeclampsia was induced by administering L-NAME intraperitoneally at a dosage of 125 mg/kg body weight from gestational day 13 to day 19. The success of the induction was confirmed by two markers: an increase in systolic blood pressure to ≥140 mmHg, measured using the CODA monitoring system, and proteinuria levels above 5.617 mg/mL, determined by the Bradford Assay. Curcumin, obtained in natural powder form, was dissolved in distilled water and administered orally by gavage. To achieve the target dosages of 30, 50, and 100 mg/kg body weight, a dilution formula was used to ensure accurate dose delivery per body weight. On gestational day 20, the rats were sacrificed and their liver tissues were collected for immunohistochemical analysis. The NOS-2/iNOS Polyclonal Antibody (bs-2072R, United States) was used as the primary antibody. To compare iNOS expression levels across the groups, a one-way ANOVA was performed. Post hoc testing was then applied to identify the specific treatment groups that showed significant differences. This research was conducted with approval from the Health Research Ethics Committee of the Faculty of Medicine, Brawijaya University (Approval No. 74/EC/KEPK-S2/04/2025). The study was reviewed in accordance with the principles of the Declaration of Helsinki. Ethical clearance was granted for the period from April 10, 2025, to April 10, 2026.

RESULT

Table 1. Analysis of Variance (One-Way ANOVA)

Group	N	Mean ± SD	p-value
K-	5	5.063 ± 2.42^{a}	
K+	5	77.00 ± 3.63^{e}	
P1	5	64.34 ± 4.69^{d}	0.000
P2	5	33.67 ± 5.90^{c}	
P3	5	19.78 ± 2.17^{b}	

In Table 1, the superscript letters (a, b, c, d, e) indicate statistically significant differences between groups at $p < 0.05$. The ANOVA test showed a p-value <0.001, confirming that the mean levels of iNOS expression differed significantly across all experimental groups. The highest average iNOS expression was observed in the K+ group (L-NAME–induced

preeclampsia), while the lowest was found in the K− group (healthy control). Tukey's HSD test further revealed a highly significant difference between these two groups ($p < 0.001$), highlighting the contrast between preeclampsia-model rats and normal pregnant rats. Additionally, the comparison between P1 and K- also produced a p-value <0.001, indicating a statistically significant difference. Similarly, the P2 group showed a significantly higher mean iNOS expression compared to the K− group, with a p-value <0.001. When compared to the K+ group (L-NAME–induced preeclampsia), all treatment groups demonstrated a marked reduction in iNOS expression. The difference between P1 and K+ was statistically significant ($p < 0.001$). In addition, the comparison between P2 and P3 yielded a p-value of 0.000, confirming a significant difference between these treatment groups. Overall, these findings suggest that curcumin, across low to high doses, can effectively reduce iNOS levels in preeclampsia-model rats.

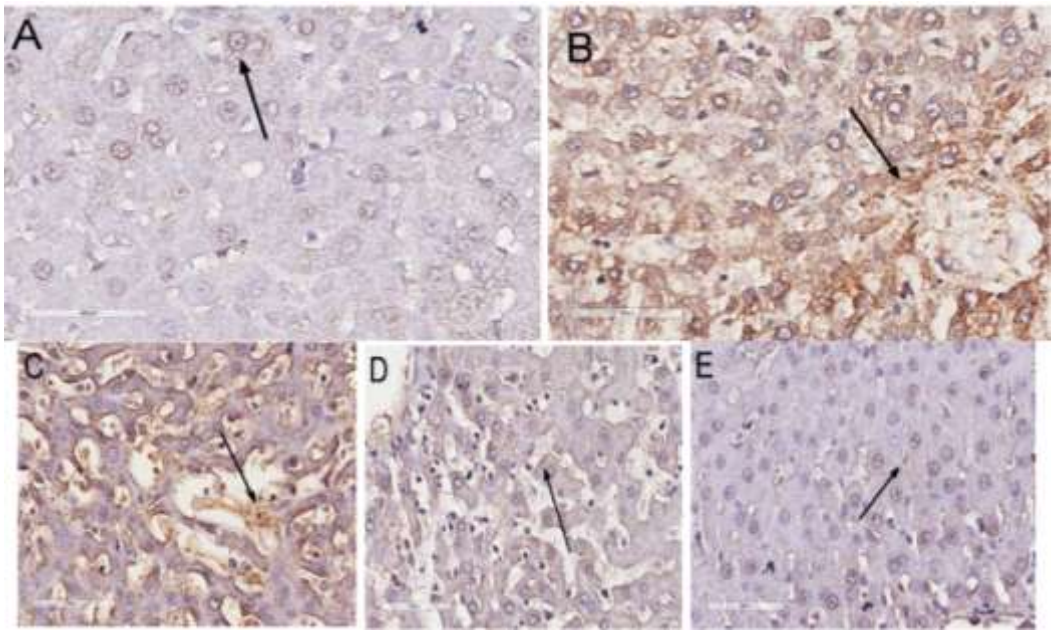

Figure 1. Immunohistochemistry of iNOS Expression in the Liver of Preeclampsia-Induced Rats. The black arrows indicate iNOS expression in the liver tissue of rats, visible as brown staining under a light microscope at 400× magnification, with a scale bar of 5 µm. (A) K- represents the liver of a normal pregnant rat. (B) K+ represents the liver of a preeclampsia-induced pregnant rat. (C) P1 represents the liver of a preeclampsia-induced pregnant rat treated with curcumin at 30 mg/kg body weight. (D) P2 represents the liver of a preeclampsia-induced pregnant rat treated with curcumin at 50 mg/kg body weight. (E) P3 represents the liver of a preeclampsia-induced pregnant rat treated with curcumin at 100 mg/kg body weight.

Figure 1 shows the outcomes of the immunohistochemistry (IHC) technique of the iNOS expression in the hepatic tissue of Wistar rats with preeclampsia model. Brown staining shows the regions where the antibody attaches to iNOS (target protein expression), the darker

the brown staining, the higher the iNOS expression. The cell nuclei are stained in blue, which gives contrast.

Image A shows that the background is largely blue and only slightly brown, which means that iNOS is barely expressed in normal tissue which does not experience high levels of oxidative stress. Conversely, image B presents a very strong and diffuse brown stain, which is the indicator of the high expression of iNOS, which is similar to the oxidative stress and inflammation that signifies preeclampsia.

Image C also shows that there is a presence of visible brown stain, but not as strong as in image B, implying that curcumin is starting to suppress iNOS expression, although not significantly. Likewise image D indicates that there is further decrease in brown staining than image C so that a higher amount of curcumin dosage of 50 mg/kg body weight is more effective in reducing the level of iNOS. Lastly, image E demonstrates the presence of the brown stain which is more akin to the image A but the brown stain has significantly reduced coloration which shows that the highest dosage of the curcumin is effective in the inhibition of the iNOS expression.

DISCUSSION

During a normal pregnancy, the body undergoes many physiological changes to support fetal growth, including adjustments in the circulatory system. Nitric oxide (NO) plays a central role in these adaptations. It helps maintain vascular elasticity and promotes healthy blood flow to the uterus (Aouache et al., 2018). As a natural vasodilator and anticoagulant, NO production increases during pregnancy, largely due to elevated estrogen levels (San Juan-Reyes et al., 2020). The primary pathway for NO synthesis in this period is through the activation of the enzyme nitric oxide synthase.

Because preeclampsia affects multiple organs, nitric oxide (NO) also plays a central role in both normal and abnormal liver pathways. NO is produced by three isoforms of nitric oxide synthase (NOS): neuronal NOS (nNOS/NOS1), inducible NOS (iNOS/NOS2), and endothelial NOS (eNOS/NOS3). These enzymes catalyze the oxidation of L-arginine to generate NO and citrulline. While nNOS and iNOS are mainly located in the cytosol, eNOS is attached to the cell membrane through palmitoylation and myristoylation, allowing it to function at the cellular interface. In preeclampsia, inducible nitric oxide synthase (iNOS) is stimulated by several inflammatory mediators, including cytokines such as IL-1 and TNF, as well as lipopolysaccharides (LPS). The NF-κB and MAPK signaling pathways play a key role in regulating iNOS protein expression, working together with transcription factors like AP-1 and STAT1, which are activated by interferon-γ (IFN-γ) (Alese et al., 2021). These combined

processes lead to excessive nitric oxide (NO) production and endothelial dysfunction (Lee et al., 2019), hallmarks of preeclampsia.

The results of this experiment showed that curcumin treatment at doses of 30, 50, and 100 mg/kg body weight (P1, P2, and P3) reduced iNOS expression in the liver tissue of rats. All three treatment groups displayed a gradual downward trend compared to the positive control group. Among them, the 100 mg/kg dose produced the strongest effect, bringing iNOS expression levels closest to those seen under normal physiological conditions. These findings suggest that curcumin has significant antioxidant and anti-inflammatory potential, effectively suppressing iNOS expression in the liver during preeclampsia. The findings of this study are consistent with those of Naemi et al., (2021), who reported that preeclamptic plasma increases the expression of pro-inflammatory cytokines in monocytes. However, curcumin intake at varying doses was shown to inhibit the expression of IL-1β, TNF-α, and IL-6. This effect is thought to be related to curcumin's ability to block NF-κB activation, a key regulator in cytokine transcription. Similarly, Khudair & Al-Gareeb, (2024) confirmed that curcumin acts as a potent antioxidant, capable of neutralizing ROS and RNS generated by methotrexate in hepatocytes. By suppressing iNOS expression, curcumin reduces the production of intracellular RNS. The observed decrease in MDA levels in curcumin-treated groups further indicates reduced lipid peroxidation caused by oxidative stress. Beyond its anti-inflammatory effects, curcumin also combats oxidative stress through activation of the Nrf2-Keap1 pathway, stimulation of antioxidant enzymes such as catalase, SOD, and GPx, and direct interaction with NADPH oxidase (Martins et al., 2023). These mechanisms highlight the synergistic antioxidant and anti-inflammatory potential of curcumin.

Curcumin is considered safe and shows promise as a treatment for a wide range of pathological conditions, including preeclampsia. It works by regulating multiple molecular processes, either through direct interaction with target molecules or indirectly by influencing transcription factors, enzyme activity, or gene expression (Hidayati et al., 2022). Curcumin has been shown to inhibit cytokines such as IL-8 and TGF-β. In addition, it acts as an immunomodulatory, immunostimulatory, and antioxidant agent, making it useful in preventing cell proliferation and fibrosis. Its combined anti-inflammatory and antioxidant properties help protect against endothelial dysfunction (Subandi et al., 2024), further highlighting its therapeutic potential .

According to Kunnumakkara et al., (2023), curcumin is effective in inducing heme oxygenase-1 and acts as a potent inhibitor of several oxygen radical–producing enzymes, including cyclooxygenase (COX), inducible nitric oxide synthase (iNOS), lipoxygenase, and

xanthine dehydrogenase/oxidase. As a powerful antioxidant, curcumin helps neutralize reactive oxygen species (ROS) and reactive nitrogen species (RNS) in hepatocytes. In addition, (Farzaei et al., 2018) reported that curcumin suppresses iNOS activity, thereby reducing the formation of intracellular RNS.

Curcumin exerts its hepatoprotective effects through multiple mechanisms, including the regulation of apoptotic pathways in liver cells. Evidence of this protective role is seen in the elevated levels of AST and ALP, accompanied by a marked reduction in lipid peroxidation, as indicated by lower MDA levels. These findings (Khudair & Al-Gareeb, 2024) suggest that curcumin helps prevent hepatocyte apoptosis and supports liver function.

Rahardjo et al., (2024) demonstrated that curcumin exerts strong anti-inflammatory effects, as reflected by increased nitric oxide (NO) levels at doses of 50 and 100 mg/kg body weight compared to the positive control group. In preeclampsia, the rise in oxidative stress and reactive nitrogen species (RNS) is largely due to an imbalance between oxidants and antioxidants, triggered by impaired spiral artery remodeling (Rahardjo et al., 2022). Curcumin helps counter this imbalance by inhibiting pro-inflammatory enzymes such as xanthine oxidase, cyclooxygenase, and lipoxygenase. In addition, curcumin enhances vascular performance (Subandi et al., 2025) by supporting the activity of antioxidant enzymes including SOD, POD, catalase, and glutathione, which collectively reduce ROS levels.

CONCLUSION

Curcumin shows promise as a potential alternative preventive approach for preeclampsia, particularly in reducing hepatic inflammation in a dose-dependent manner. Among the tested doses (30, 50, and 100 mg/kg body weight), the 100 mg/kg dose was the most effective, lowering iNOS expression in hepatic tissue to levels approaching normal physiological conditions in Wistar rats (Rattus norvegicus) with a preeclampsia model.

This study focused on a single molecular factor (iNOS); therefore, further research is recommended to correlate these findings with histopathological changes and serum biomarkers of liver function, providing a more comprehensive understanding of curcumin's effects. While rodent models are valuable for initial insights, they present inherent physiological differences compared to human pregnancy and preeclampsia. Additionally, other signaling pathways potentially influenced by curcumin were not explored here, and future studies may uncover further mechanisms underlying its biological actions.

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