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The Effect of Nanocurcumin Administration on Plasma Malondialdehyde (MDA) Levels in Pregnant Wistar Rats (*Rattus norvegicus*) as a Preeclampsia Model

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ABSTRACT

Preeclampsia is a pregnancy complication associated with oxidative stress and increased levels of malondialdehyde (MDA), leading to endothelial dysfunction and impaired placental perfusion. Nanocurcumin possesses antioxidant properties that can mitigate oxidative stress; however, its effectiveness in reducing MDA levels in preeclampsia requires further investigation. This study aims to evaluate the effect of nanocurcumin administration on plasma MDA levels in pregnant Rattus norvegicus models of preeclampsia induced using Nω-Nitro-L-Arginine Methyl Ester (L-NAME). A total of 24 pregnant Wistar rats were divided into six groups: negative control (K-), positive control (K+), and four treatment groups receiving nanocurcumin at doses of 25 mg/KgBW (P1), 50 mg/KgBW (P2), 100 mg/KgBW (P3), and 200 mg/KgBW (P4). Preeclampsia was induced by administering L-NAME (125 mg/KgBW) for six consecutive days, followed by nanocurcumin treatment. Plasma MDA levels were measured using the Thiobarbituric Acid (TBA) assay and analyzed using the Kruskal-Wallis test and post-hoc Mann-Whitney test ($p < 0.05$). Nanocurcumin administration at 25 mg/KgBW and 50 mg/KgBW significantly reduced MDA levels compared to the preeclampsia group without treatment ($p = 0.042$, $p < 0.05$). However, a high dose of 200 mg/KgBW increased MDA levels, indicating a potential pro-oxidant effect. Low to moderate doses of nanocurcumin effectively reduced MDA levels in the preeclampsia model, but further studies are necessary to determine the optimal dosage and its safety in humans.

Kata kunci:

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ABSTRAK

Preeklamsia merupakan komplikasi kehamilan yang berhubungan dengan stres oksidatif dan peningkatan kadar malondialdehyde (MDA), yang menyebabkan disfungsi endotel dan gangguan perfusi plasenta. Nanokurkumin memiliki sifat antioksidan yang dapat mengurangi stres oksidatif, tetapi efektivitasnya dalam menurunkan kadar MDA pada preeklamsia masih perlu dikaji lebih lanjut. Penelitian ini bertujuan untuk mengevaluasi pengaruh pemberian nanokurkumin terhadap kadar MDA plasma pada tikus putih (Rattus norvegicus) bunting model preeklamsia yang diinduksi menggunakan Nω-Nitro-L-Arginine Methyl Ester (L-NAME). Sebanyak 24 ekor tikus Wistar bunting dibagi menjadi enam kelompok: kontrol negatif (K-), kontrol positif (K+), serta empat kelompok perlakuan yang menerima nanokurkumin dengan dosis 25 mg/KgBW (P1), 50 mg/KgBW (P2), 100 mg/KgBW (P3), dan 200 mg/KgBW (P4). Induksi preeklamsia dilakukan dengan pemberian L-NAME (125 mg/KgBW) selama enam hari, diikuti pemberian nanokurkumin. Kadar MDA plasma diukur menggunakan metode Thiobarbituric Acid (TBA) assay dan dianalisis dengan uji Kruskal-Wallis dan post-hoc Mann-Whitney ($p < 0.05$). Pemberian nanokurkumin 25 mg/KgBW dan 50 mg/KgBW secara signifikan menurunkan kadar MDA dibandingkan kelompok preeklamsia tanpa terapi ($p = 0.042$, $p < 0.05$). Namun, dosis tinggi (200 mg/KgBW) justru

meningkatkan kadar MDA, menunjukkan efek pro-oksidan. Nanokurkumin dosis rendah hingga sedang efektif dalam menurunkan kadar MDA pada model preeklamsia, tetapi studi lanjutan diperlukan untuk menentukan dosis optimal dan keamanannya pada manusia.

INTRODUCTION

The maternal mortality rate (MMR) is a crucial indicator of a country's healthcare quality and maternal well-being. According to the World Health Organization (WHO), maternal deaths due to pregnancy and childbirth complications reached 295,000 cases in 2017, with the majority occurring in developing countries (WHO, 2017). In Indonesia, the MMR in 2015 was recorded at 305 per 100,000 live births, with hypertensive disorders in pregnancy, including preeclampsia, being the leading cause after hemorrhage (BPS Statistics Indonesia, 2015). Preeclampsia is a hypertensive disorder that occurs after 20 weeks of gestation, characterized by systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg, along with proteinuria (≥300 mg/24 hours) (Brown et al., 2018). If left untreated, preeclampsia can progress to eclampsia, which poses significant risks of maternal and fetal mortality (Redman & Staff, 2015).

Recent studies suggest that oxidative stress plays a pivotal role in the pathogenesis of preeclampsia (Taravati & Tohidi, 2018). Oxidative stress results from an imbalance between free radical production and the body's antioxidant defense system, leading to lipid peroxidation and endothelial dysfunction (de Lucca et al., 2016). One of the primary biomarkers of oxidative stress is malondialdehyde (MDA), an end-product of lipid peroxidation that is significantly elevated in preeclamptic patients (Ayala et al., 2014). Increased MDA levels not only reflect the severity of oxidative stress but also correlate with placental dysfunction, endothelial impairment, and systemic inflammation, which are hallmarks of preeclampsia (Rumbold et al., 2008).

To mitigate the detrimental effects of oxidative stress in preeclampsia, various antioxidant-based interventions have been developed, including the use of curcumin, a polyphenolic compound found in Curcuma longa (Perrone et al., 2015). Curcumin exhibits antioxidant, anti-inflammatory, and neuroprotective properties and is capable of suppressing free radical production by enhancing the activity of antioxidant enzymes, such as superoxide dismutase (SOD) and glutathione peroxidase (GPx) (Nelson et al., 2017). However, conventional curcumin has low bioavailability due to its hydrophobic nature and rapid metabolism in the liver and intestines, reducing its overall efficacy (Bisht et al., 2007). To overcome these limitations, nanocurcumin has been developed, enabling improved absorption, distribution, and stability in biological systems (Karthikeyan et al., 2020).

Nanocurcumin is formulated using nanoparticle technology to enhance water solubility and cellular penetration, thereby increasing its effectiveness in combating oxidative stress (Mishra et al., 2008). Studies have shown that nanocurcumin administration significantly reduces MDA levels in various oxidative stress-related disease models, including preeclampsia (Situmorang et al., 2019). However, some studies also indicate that higher doses of nanocurcumin may exhibit paradoxical effects, potentially acting as pro-oxidants and exacerbating oxidative stress under certain conditions (Esperanza et al., 2021). Therefore, determining the optimal dosage of nanocurcumin is critical to maximize its protective effects against oxidative stress while avoiding toxic side effects.

Based on this background, this study aims to evaluate the effect of nanocurcumin administration on plasma MDA levels in pregnant Wistar rats (Rattus norvegicus) as a preeclampsia model. This study is expected to provide new insights into the effectiveness of nanocurcumin in reducing oxidative stress in preeclampsia and establish a scientific foundation for developing optimal antioxidant-based therapies for pregnancy-related disorders.

METHOD

Study Design

This study employed a True Experimental Design with a Post-test Only Control Group Design approach to evaluate the effects of nanocurcumin administration on plasma malondialdehyde (MDA) levels in pregnant Wistar rats (Rattus norvegicus) as a preeclampsia model. This design was chosen to prevent learning effects or bias caused by pre-tests, ensuring that measurements were conducted only after the treatment (Kirk, 2013). The experimental animals were divided into six groups: negative control (K-), positive control (K+), and four treatment groups (P1, P2, P3, P4). The K- group received no treatment, while the K+ group was induced with preeclampsia using L-NAME at 125 mg/KgBW without nanocurcumin administration. Groups P1 to P4 received L-NAME-induced preeclampsia and nanocurcumin treatment at different doses, specifically 25 mg/KgBW (P1), 50 mg/KgBW (P2), 100 mg/KgBW (P3), and 200 mg/KgBW (P4) administered orally via a gastric tube.

Sample and Randomization

The study population consisted of female Wistar rats aged 8–12 weeks, weighing 150–200 grams, obtained from the Pharmacology Laboratory, Faculty of Medicine, Universitas Brawijaya. The sample was selected using simple random sampling, ensuring equal selection probability for each rat meeting the inclusion criteria (Flecknell, 2015). Inclusion criteria comprised healthy female rats without anatomical or physiological abnormalities, within the specified weight range, and exhibiting pregnancy signs after mating. Exclusion criteria included rats that failed to conceive after mating, experienced miscarriage before completing treatment, developed infections or deteriorating health, or died before the study ended. Out of 35 initial rats, six were excluded due to mortality or declining health, while five were excluded from analysis due to premature delivery before treatment completion. Thus, the final sample consisted of 24 rats, evenly distributed among six experimental groups.

Preeclampsia Model Induction

The preeclampsia model was induced by intraperitoneal administration of L-NAME at 125 mg/KgBW for six

consecutive days, starting from gestation day 13 to day 18. L-NAME is a nitric oxide synthase (NOS) inhibitor, which induces vascular endothelial dysfunction, hypertension, and increased oxidative stress, characteristics of preeclampsia (de Alwis et al., 2022; Mert et al., 2012). On gestation day 19, the success of preeclampsia induction was confirmed by measuring blood pressure using the tail-cuff method, with systolic ≥140 mmHg and diastolic ≥90 mmHg used as preeclampsia cut-off values (Kanasaki et al., 2008). Additionally, proteinuria was assessed using a 24-hour urine dipstick test, where results of +1 to +3 indicated preeclamptic conditions.

Nanocurcumin Administration

Nanocurcumin was administered orally via a gastric tube, dissolved in 0.9% physiological NaCl solution to enhance its stability. Treatment lasted for six consecutive days (gestation day 13 to day 18) following confirmation of successful preeclampsia induction. The selected dosages were based on previous studies demonstrating that nanocurcumin exhibits protective effects against oxidative stress by reducing MDA levels in various disease models (Ganugula et al., 2017). Administration was conducted at the same time each day to ensure consistent absorption and pharmacological effects.

MDA Level Measurement

Plasma MDA levels were measured on gestation day 19, after all treatments were completed. Blood samples were collected via the orbital sinus using heparinized capillary tubes and centrifuged at 3,000 rpm for 10 minutes to separate plasma from blood cells. MDA levels were determined using the Colorimetric Thiobarbituric Acid (TBA) assay, using kit serial number E-BC-K025-S, known for its high sensitivity in lipid peroxidation detection (Yagi, 1998). Absorbance was measured using a UV-Vis spectrophotometer at 532 nm, following standard protocols for plasma MDA measurement (Alizadeh & Kheirouri, 2019).

Statistical Analysis

Data analysis was performed using SPSS version 25.0, with a series of predetermined statistical tests to ensure the validity of the study results. First, the Shapiro-Wilk test was used to assess the normality of the data distribution. If the data were not normally distributed, the Kruskal-Wallis test was conducted as an alternative to one-way ANOVA to compare MDA levels among groups. If significant differences were found in the Kruskal-Wallis test, a post-hoc analysis using the Mann-Whitney test was performed to determine which groups exhibited significant differences. Additionally, Levene's test for homogeneity of variances was conducted to ensure equal variance across treatment groups. Statistical significance was set at $p < 0.05$, meaning that results with p-values less than 0.05 were considered statistically significant.

Ethical Considerations

This study received ethical approval from the Animal Research Ethics Committee, Faculty of Medicine, Universitas Brawijaya, with approval number 226/EC/KEPK/10/2022. All experimental procedures were conducted following the International Guidelines for the Use and Care of Laboratory Animals as published by the National Research Council (NRC, 2011) and adhered to the 3R principles (Replacement, Reduction, and Refinement) in animal research (Russell & Burch, 1959).

During the study, the animals were treated under strict animal welfare standards. The Wistar rats were housed in a controlled environment with a temperature of 22–25°C, humidity of 50–70%, and a 12-hour light/dark cycle. Standard feed and ad libitum access to drinking water were provided throughout the experiment to maintain optimal nutritional balance.

Preeclampsia was induced using L-NAME, and nanocurcumin administration was conducted while minimizing stress and discomfort to the animals. During blood sampling via the orbital sinus, ketamine (50 mg/KgBW) and xylazine (5 mg/KgBW) anesthesia was administered to reduce pain and distress in the rats (Flecknell, 2015). At the end of the study, all animals that had undergone experimental procedures were humanely euthanized using an intraperitoneal overdose of sodium pentobarbital (≥150 mg/KgBW), in accordance with American Veterinary Medical Association (AVMA, 2020) recommendations.

Furthermore, this study ensured that the minimum number of animals was used while maintaining statistical validity, aligning with the Reduction principle in animal research ethics. All procedures involving animal handling were conducted by trained researchers in laboratory animal anesthesia and handling to minimize bias and enhance the reliability of the study data.

RESULTS OF STUDY

This study involved 35 female Wistar rats (Rattus norvegicus) selected based on predetermined inclusion and exclusion criteria. Following the adaptation and mating process, 24 rats met the eligibility criteria as study subjects, while 11 rats were excluded for failing to meet the inclusion criteria. Among the excluded rats, six dropped out due to mortality before completing the treatment or due to deteriorating health conditions, while five were excluded because they gave birth before the treatment was completed.

Preeclampsia induction using L-NAME (125 mg/KgBW) for six consecutive days (gestation days 13–18) successfully induced preeclampsia, as confirmed by increased blood pressure and proteinuria. Blood pressure measurements three days after L-NAME induction showed that the preeclampsia group exhibited systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg. Additionally, 24-hour urine dipstick tests indicated positive proteinuria results (+1 to +3), confirming kidney dysfunction due to preeclampsia.

On gestation day 19, plasma MDA levels were measured using the Colorimetric Thiobarbituric Acid (TBA) assay to assess oxidative stress levels. The findings revealed that the negative control group (K-) had the lowest plasma MDA levels, whereas the treatment group receiving 25 mg/KgBW nanocurcumin (P1) showed the most significant reduction in MDA levels compared to the preeclampsia group without therapy (K+). Conversely, the P4 group (200 mg/KgBW) exhibited a higher increase in MDA levels than the preeclampsia group without therapy, suggesting a potential pro-oxidant effect at high doses.

The plasma MDA levels for each group are presented in Figure 1. The preeclampsia group without therapy (K+) displayed significantly higher plasma MDA levels than the normal control group (K-), confirming that preeclampsia induces oxidative stress. Administration of 25 mg/KgBW nanocurcumin (P1) significantly reduced plasma MDA levels compared to the preeclampsia group without therapy ($p = 0.020$, $p < 0.05$). However, the 200 mg/KgBW dose (P4) increased plasma MDA levels compared to the untreated preeclampsia group (K+), indicating a potential pro-oxidant effect.

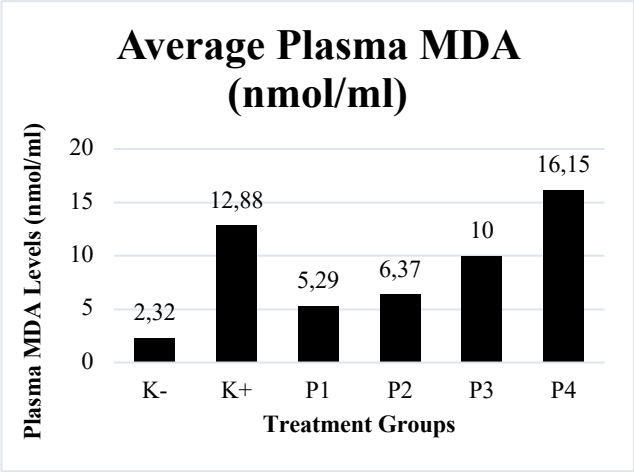

Figure 1. Graph of Average Plasma MDA Levels

To ensure the validity of the study results, a series of statistical tests were performed. The results of the data distribution, variance homogeneity, and group comparisons are presented in Table 1. The Shapiro-Wilk normality test confirmed that the data were normally distributed ($p > 0.05$). However, the Levene's test for homogeneity of variances indicated that the data were not homogeneous ($p < 0.05$), making it unsuitable for One-Way ANOVA analysis. Instead, the Kruskal-Wallis test was conducted, revealing significant differences between groups ($p = 0.003$, $p < 0.05$).

Table 1. Results of Analysis Tests

Test	Independent Variable	p-value	Interpretation
Normality (Shapiro-Wilk)	Plasma MDA Levels	> 0,05	Data is normal
Homogeneity of Variance (Levene's Test)	Plasma MDA Levels	< 0,05	Data is not homogeneous
Kruskal-Wallis	Plasma MDA Levels	0,003	Significant difference

The Mann-Whitney post-hoc test results, presented in Table 2, demonstrated significant differences in MDA levels between groups K- and K+ ($p = 0.020$, $p < 0.05$), confirming that preeclampsia increases plasma MDA levels. Significant differences were also found between K+ and P1 ($p = 0.020$, $p < 0.05$), as well as between K+ and P2 ($p = 0.042$, $p < 0.05$), indicating that 25 mg/KgBW and 50 mg/KgBW nanocurcumin effectively reduced MDA levels in the preeclampsia model. However, no significant differences were observed between K+ and P3 ($p = 0.245$) or between K+ and P4 ($p = 0.772$), suggesting that nanocurcumin at 100 mg/KgBW and 200 mg/KgBW did not provide a significant protective effect.

Table 2. Results of the Mann-Whitney Test

P-value	K-	K+	P1	P2	P3	P4
K-		0,020*	0,021*	0,021*	0,021*	0,021*
K+			0,020*	0,042*	0,245	0,772
P1				0,386	0,021*	0,021*
P2					0,083	0,043*
P3						0,564

Based on the 95% Confidence Interval (CI), it was observed that group K- had significantly lower MDA levels than the preeclampsia group (K+), whereas P1 and P2 had CI ranges closer to the K- group, indicating that lower doses of nanocurcumin (25 mg/KgBW and 50 mg/KgBW) were more effective than higher doses.

Table 3. Confidence Interval (CI 95%) Analysis for Plasma MDA Levels in Each Group

Group	Mean ± SD	95% CI
K-	2.32 ± 0.79	(1.89 - 2.75)
K+	12.88 ± 3.91	(10.32 - 15.44)
P1	5.29 ± 0.74	(4.89 - 5.69)
P2	6.37 ± 2.20	(5.10 - 7.64)
P3	10.00 ± 1.88	(8.90 - 11.10)
P4	16.15 ± 9.93	(10.47 - 21.83)

DISCUSSIONS

The findings of this study demonstrate that administration of L-NAME at a dose of 125 mg/KgBW for six days successfully induced preeclampsia in pregnant Wistar rats, as evidenced by increased blood pressure and proteinuria. This condition is closely related to oxidative stress mechanisms, which play a central role in the pathogenesis of preeclampsia (Mert et al., 2012). Oxidative stress in preeclampsia results from an imbalance between free radical production and the body's antioxidant system, leading to vascular endothelial dysfunction, inflammation, and impaired placental perfusion (Burton & Jauniaux, 2011; Kanasaki et al., 2008).

One of the primary biomarkers of oxidative stress is malondialdehyde (MDA), a final product of lipid peroxidation due to increased reactive oxygen species (ROS) in the body (Ayala et al., 2014). Elevated MDA levels in the blood are frequently used as an indicator of oxidative damage to cell membranes, contributing to placental dysfunction and vascular endothelial impairment in pregnant women with preeclampsia (Sánchez-Aranguren et al., 2014; Myatt, 2010).

In this study, the preeclampsia group without therapy (K+) exhibited significantly higher MDA levels compared to the negative control group (K-), confirming that endothelial dysfunction and oxidative stress due to preeclampsia lead to increased lipid peroxidation (Nelson et al., 2017). Elevated MDA levels were also associated with increased expression of NADPH oxidase enzymes, which play a role in the production of superoxide (O_2^-) and hydrogen peroxide (H_2O_2) within the maternal vascular system in preeclampsia (Rana et al., 2019). Additionally, previous studies have reported that high MDA levels in preeclampsia correlate with placental dysfunction and systemic inflammation, contributing to placental tissue hypoxia and reduced nitric oxide (NO) production, which is essential for placental blood vessel vasodilation (Rumbold et al., 2008; Redman et al., 2021).

Administration of nanocurcumin at doses of 25 mg/KgBW (P1) and 50 mg/KgBW (P2) significantly reduced MDA levels compared to the preeclampsia group without therapy (K+). This effect is likely due to the strong antioxidant properties of curcumin, which function by suppressing ROS production, inhibiting lipid peroxidation, and enhancing the activity of antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT) (Ganugula et al., 2017; Perrone et al., 2015). Furthermore, nanocurcumin exhibits higher bioavailability than conventional curcumin,

making its protective effects against oxidative stress more effective (Nelson et al., 2017; Prasad et al., 2014).

Previous studies have demonstrated that nano-formulated curcumin is more effective in enhancing total antioxidant capacity and improving vascular endothelial function, which is critical for preeclampsia management (Aggarwal & Sung, 2009; Youshia et al., 2023). Additionally, a study by Gong et al. (2016) found that nanocurcumin can suppress the production of pro-inflammatory cytokines such as TNF-α and IL-6, which are frequently elevated in preeclampsia and contribute to systemic inflammation and placental dysfunction. Thus, the results of this study further support the potential of nanocurcumin as an adjuvant therapeutic agent for mitigating oxidative stress in preeclampsia.

This study revealed that the group receiving high-dose nanocurcumin (200 mg/KgBW) exhibited higher MDA levels than the preeclampsia group without therapy, reinforcing the notion that high-dose antioxidants may exhibit pro-oxidant effects under certain conditions, as reported in previous studies (Nelson et al., 2017; Mishra et al., 2008; Yang et al., 2018). The pro-oxidant effects of high-dose nanocurcumin can be explained through the redox cycling theory, in which excessive curcumin undergoes auto-oxidation, forming semiquinone radicals that paradoxically increase free radical production (Mishra et al., 2008). Furthermore, in hypoxic conditions such as preeclampsia, excessive antioxidant activity can lead to cellular redox system imbalance, accelerating placental cell apoptosis and necrosis (Bisht et al., 2007; Sarkar et al., 2016).

Additionally, high-dose nanocurcumin affects mitochondrial function by disrupting electron transport, leading to increased ROS production and toxic effects on endothelial cells (Calsolaro & Edison, 2016; Wang et al., 2009). Research by Jara et al. (2025) demonstrated that high-dose curcumin can alter mitochondrial protein expression involved in redox balance, thereby contributing to increased oxidative stress in tissues. This effect can be exacerbated in preeclampsia, where pre-existing mitochondrial dysfunction in trophoblasts is already present due to chronic placental hypoxia (Cindrova-Davies et al., 2018).

In another study, high-dose curcumin was also reported to induce apoptosis pathways by activating caspase-3 and caspase-9, leading to decreased placental cell viability and worsening hypoxia (Nurseta et al., 2018). Therefore, these findings support the notion that determining the optimal nanocurcumin dosage is crucial to ensuring protective effects without toxic risks, particularly in pregnancy-related disorders that are highly sensitive to oxidative stress, such as preeclampsia.

The findings of this study align with research by Ganugula et al. (2017), which reported that low to moderate doses of nanocurcumin (25-50 mg/KgBW) effectively reduce MDA levels in oxidative stress animal models. This study also supports previous research showing that low-dose nanocurcumin enhances glutathione (GSH) levels and antioxidant enzymes in endothelial cells, thereby improving vascular function in preeclampsia (Singh et al., 2019).

Additionally, research by Perrone et al. (2015) demonstrated that curcumin enhances antioxidant enzyme expression and suppresses placental inflammation, contributing to its protective effects in preeclampsia. However, this study also confirms that high-dose curcumin may have cytotoxic effects, particularly in pathological conditions like preeclampsia (Aouache et al., 2018).

In a clinical context, the results of this study suggest that nanocurcumin holds potential as an adjuvant therapy for preeclampsia management. Nanocurcumin could be developed as an antioxidant supplement for pregnant women at risk of preeclampsia to reduce oxidative stress and improve vascular endothelial function. However, this study also emphasizes that nanocurcumin dosage should be carefully determined, as high doses may have pro-oxidant effects that could exacerbate preeclampsia symptoms (Karthikeyan et al., 2020). Further clinical studies are required to assess the safety, bioavailability, and efficacy of nanocurcumin in human populations.

This study has several limitations that must be acknowledged. First, the preeclampsia model used is an animal model, so the findings must be validated through clinical trials in humans. Second, this study only evaluated MDA levels as an oxidative stress biomarker; thus, further research is needed to assess other antioxidant enzyme activities, such as SOD, GPx, and CAT, to better understand nanocurcumin's mechanisms of action. Furthermore, this study did not evaluate nanocurcumin's pharmacokinetics, including absorption, distribution, metabolism, and excretion (ADME) in rats. Therefore, future studies should analyze nanocurcumin's pharmacokinetics and measure its bioavailability in placental tissues. Additionally, further research is necessary to explore the effects of combining nanocurcumin with conventional therapies for preeclampsia management.

CONCLUSIONS

The results of this study indicate that preeclampsia induced by Nω-Nitro-L-Arginine Methyl Ester (L-NAME) significantly increases plasma malondialdehyde (MDA) levels compared to the negative control group, thereby confirming the central role of oxidative stress in the pathogenesis of preeclampsia. This increase in MDA levels reflects the high degree of lipid peroxidation resulting from an imbalance between free radical production and the body's antioxidant defense systems. Administration of nanocurcumin at doses of 25 mg/KgBW and 50 mg/KgBW significantly reduced plasma MDA levels compared to the preeclampsia group without treatment, demonstrating the protective antioxidant effect of nanocurcumin in inhibiting lipid peroxidation. However, treatment with a high dose of nanocurcumin (200 mg/KgBW) actually increased MDA levels, suggesting a potential pro-oxidant effect at excessive doses. These findings indicate that nanocurcumin has the potential to be developed as an antioxidant therapeutic agent for managing preeclampsia, but the determination of an optimal dosage is critical to avoid undesirable toxic effects.

Based on these findings, several recommendations for future research emerge. First, further development of nanocurcumin therapy as an adjunct treatment for preeclampsia is warranted, particularly for reducing oxidative stress that contributes to the disease's pathogenesis; however, additional studies are needed to determine the effective and safe therapeutic dosage before clinical application. Second, human clinical trials are essential to evaluate the efficacy and safety of nanocurcumin under human biological conditions, especially in pregnant women at risk for preeclampsia. Third, pharmacokinetic studies should be conducted, as nanocurcumin exhibits higher bioavailability than conventional curcumin; further research is required to understand its distribution, metabolism, and excretion in pregnant women to ensure its long-term effects in preeclamptic conditions. Additionally, long-term studies are

needed to evaluate the impact of nanocurcumin on fetal development and other pregnancy complications. Future research should also explore the potential synergistic effects of combining nanocurcumin with conventional therapies, such as low-dose aspirin or antihypertensives, to reduce the risk of preeclampsia complications.

DECLARATION

Consent for publication:
All participants were informed of the objectives and procedures of the study and subsequent publication of the results.

Availability of Data and Material (ADM):
The data supporting the findings of this study are available upon reasonable request from the corresponding author.

Competing interests:
Authors declare no conflict of interest

Funding:
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Authors' contributions:
The authors confirm responsibility for the following - study conception and design, data collection, analysis and interpretation of results, and manuscript preparation.

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