ORIGINAL RESEARCH

Nano-curcumin in the decrease of proteinuria in white rats (*Rattus norvegicus*) with preeclampsia

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ABSTRACT

Objective: Since preeclampsia is one of the most serious hypertensive disorders in pregnancy, as it occurs in 5-7% of all pregnancies, and causes around 70,000 maternal deaths and 500,000 fetal deaths worldwide each year, this study aimed to determine the effect of nano-curcumin on proteinuria in pregnant white rats (*Rattus norvegicus*) with preeclampsia.

Materials and Methods: In this study, 24 white rats (*Rattus norvegicus*) were randomly selected and divided into six groups. Inclusion criteria included healthy rats aged 8 weeks or older, with normal blood pressure and weight, while exclusion criteria included sick, deceased, or prematurely birthing rats, and those with high blood pressure. Treatment, administered over six days from gestational days 13-18, involved L-NAME and nano-curcumin injections. Groups included K- (no treatment) and K+, P1, P2, P3, and P4 (treated with L-NAME and varying nano-curcumin doses). Blood pressure and proteinuria were evaluated on gestation days 12, 15, and 19 to confirm the preeclampsia model and assess nano-curcumin's effect on proteinuria. Urine collected over 24 hours in metabolic cages preceded rat termination. Data analysis utilized IBM SPSS version 23, including the Shapiro-Wilk test, parametric independent sample t-tests, One-Way ANOVA tests, and LSD post-hoc tests to identify group differences.

Results: The results of this study showed that nano-curcumin had the effect of reducing proteinuria in white rats with preeclampsia. The significant results of the One-Way Anova test was p=0.001 <0.05 and the LSD post-hoc test revealed that an effective dose was 25 mg/ml. It was found that higher nano-curcumin dose had a higher average of proteinuria.

Conclusion: Nano-curcumin can affect proteinuria in preeclampsia. The most effective dose is 25 mg/ml.

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Highlights:

1. The size of curcumin was modified to nano scale in order to enhance its bioavailability and facilitate its absorption in the body.
2. As a herbal medicine, nano-curcumin has the ability to reduce proteinuria and serve as a preventive measure against preeclampsia.

INTRODUCTION

Maternal Mortality Rate (MMR) is an indicator to determine the welfare and health status of a mother. In 2017 cases of maternal death during pregnancy until the postpartum period reached 295.000 cases. Based on the result of the 2015 SUPAS MMR data, the cases was 305 per 100.000 birth.[1] Data from the Ministry of Health in 2020 showed that there was 1.110 cases of maternal death caused by several factors, including hemorrhage, infection, and hypertension.[2] Cases of hypertension in pregnancy are very high and have a risk of increasing the morbidity and mortality of pregnant women.[3]

Preeclampsia is one of the most serious hypertensive disorders. Preeclampsia causes around 70.000 maternal deaths and 500.000 fetal deaths every year worldwide.[4] Pregnant women with a preexisting history of hypertension are at a greater risk of developing preeclampsia compared to those without a history of hypertension.[5] Preeclampsia is a condition characterized by high blood pressure ($\geq$140/90 mmHg) and proteinuria (>300 mg in a 24-hour period or =+1 on the dipstick test) in pregnant women who are at least 20 weeks gestational age.[6,7]

Preeclampsia occurs because there is an imbalance between free radicals and antioxidants in the body that can result in oxidative stress. Oxidative stress can increase the production of lipid peroxidation that will cause endothelial dysfunction resulting in impaired endothelial function, namely an increase in renal endothelial permeability so that proteinuria will occur.[8–11] One way to prevent preeclampsia is by using herbal medicines as an alternative treatment. One of the herbal medicines that can be used is turmeric. Curcumin, a primary bioactive compound found in turmeric, is safe and possesses therapeutic properties for treating a range of disorders, including preeclampsia. Curcumin works by influencing various molecular targets, by physically interacting with targets, or by modulating transcription factors of enzyme activity or gene expression.[12] Experimental studies have demonstrated that turmeric has the ability to inhibit cytokines, such as IL-8 and TGF-Q. Curcumin has immunomodulatory, stimulatory, immune, and antioxidant properties, so it is effective in protecting kidney cells from proliferation and fibrosis.[13,14] Curcumin has antioxidant compounds that can prevent oxidative stress and, as an anti-inflammatory, it can prevent endothelial dysfunction.

Despite its widespread availability in Indonesia and its numerous advantages, turmeric usage as an alternative medicine, particularly for curcumin, remains uncommon. In order to enhance the absorption of curcumin into cells, it is necessary to reduce its size to the nanoscale scale, resulting in nano-curcumin. This is due to the high bioavailability and normal metabolic rate of curcumin.[15] This study aimed to determine the effect of nano-curcumin administration on the decrease of proteinuria in pregnant white rats (*Rattus norvegicus*) with preeclampsia. This study was useful for the development of science and as a clinical research on the benefits of nano-curcumin.

MATERIALS AND METHODS

This study was an experimental study with a post-only control group design. This study had received ethical clearance from the Health Research Ethics Commission, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia, No. 226/EC/KEPK/10/2022. Data were obtained from proteinuria measurement with a urine dipstick test. The population of this study were white rats (*Rattus norvegicus*) and the samples were 24 rats selected by simple random sampling and divided into six groups. Inclusion criteria in this study included healthy rats with clear eyes, active movement, hair that does not fall out, and good appetite. The rats must be at least 8 weeks old, had a systolic blood pressure of 84-134 mmHg and diastolic less than 90 mmHg, and had a minimum weight of 150 grams. The exclusion criteria in this study were rats that were sick or died before treatment, gave birth before treatment, and had high blood pressure. Furthermore, the drop out criteria included rats that were sick, died and/or gave birth during the study. Five rats were excluded from the study because they met the exclusion criteria and then six rats were excluded from the study because they met the drop-out criteria.

Data were collected for six days treatment at 13-18 days of gestation by injecting doses of L-NAME and nano-curcumin. The rats were grouped into group K- without treatment, and groups K+, P1, P2, P3, and P4 that were injected with L-NAME of 125 mg/kg body weight and nano-curcumin of 25 mg in group P1, 50 mg in group P2, 100 mg in P3, and 200 mg in P4. On gestation day 12 and 15, blood pressure and proteinuria were measured to confirm the success of the preeclampsia rat model. On gestation day 19, proteinuria was measured to determine the effect of nano-curcumin on proteinuria. Urine was collected in the metabolic cage for 24 hours, then the rats were terminated. Data were analyzed with IBM SPSS version 23 program and then the normality test was performed using the Shapiro-Wilk test. The parametric independent sample t-test and One-Way ANOVA test were performed if the data were normally distributed. Differences between groups were tested using the LSD post-hoc test.

RESULTS AND DISCUSSION

Increased blood pressure (BP) and proteinuria in rats injected with L-NAME

Injection of L-NAME has caused increase in rats' blood pressure and proteinuria (Table 1). Table 1 also shows that there is an increased blood pressure and proteinuria above normal after L-NAME administration measured at gestational age 12 and 15 days. The mean blood pressure elevation was ≥140/90 mmHg and proteinuria was ≥1 (0.3gr/L) after 24 hours of urine collection. L-NAME can change the condition of rats to pre-eclampsia. A previous study showed that L-NAME can cause preeclampsia by increasing blood pressure and damaging renal vascular endothelium, resulting in clinical symptoms of proteinuria.[16] The results of the independent simple t-test found significance level of 0.011 ($p < 0.05$), showing that in preeclampsia conditions the proteinuria was higher than in normal conditions. This was in line with a previous study that increased proteinuria continued to occur in preeclampsia pregnancies.[17,18]

The mechanism of action of L-NAME in rats entails a reduction in Nitric Oxide (NO) production due to the inhibition of Nitric Oxide Synthase (eNos). This inhibition has implications for the vasoconstriction of blood vessels, leading to elevated blood pressure in rats. Additionally, L-NAME exerts another effect by activating iNOS (inducible nitric oxide synthase), which prompts the rapid and uncontrolled production of Nitric oxide (NO). Subsequently, NO binds to superoxide, forming peroxynitrite, which oxidizes the formation of lipid peroxides. The accumulation of peroxynitrite exacerbates due to the interaction between NO and superoxide, resulting in heightened lipid peroxides or free radicals, leading to an imbalance in antioxidants and the onset of oxidative stress. Oxidative stress triggers inflammation in the vascular endothelium, culminating in vascular endothelial dysfunction. In compromised endothelium, the renal vascular endothelium's filtration capacity diminishes, leading to the inability to properly filter proteins by the glomerulus, resulting in proteinuria.[19]

Effect of nano-curcumin administration on proteinuria

Proteinuria serves as a key indicator in monitoring preeclampsia. The presence of protein in urine results partly from the physiological excretion of viscous glycoproteins by tubular cells, known as "Tamm-Horsfall protein." A pathological condition is declared when there is an excretion of protein in urine exceeding 300 mg per 24 hours. Proteinuria assessment involves immersing a dipstick test in urine collected over a 24-hour period. The onset of proteinuria stems from kidney vascular endothelial dysfunction, which impairs the glomerular filtration capacity due to oxidative stress.[19,20]

The administration of nano-curcumin was initiated for a span of 6 days between gestational ages 13-18 days, with varying doses allocated to each group: P4 received 200 mg/day, P3 received 100 mg/day, P2 received 50 mg/day, and P1 received 25 mg/day. The effect of nano-curcumin administration on proteinuria in rats was observed in the treatment groups. The effect of nano-curcumin administration in the treatment groups is presented by the average proteinuria levels recorded for each group, as detailed in Table 2. Notably, the highest average was noted in the K+ group (10 ± 3.56), whereas the lowest was observed in the K- group (0.112 ± 0.14). Across the four treatment groups, the average proteinuria levels were recorded as 0.425 ± 0.39 in P1, 5.3 ± 2.22 in P2, 6 ± 2.58 in P3, and 8 ± 2.6 in P4. The average in the K+ group surpassed that of the four groups treated with varying doses of nano-curcumin (P1=25 mg, P2=50 mg, P3=100 mg, P4=200 mg). Among the treatment groups, the highest average was observed in the P4 group (8 ± 2.6), while the lowest was noted in the P1 group (0.425 ± 0.39).

Table 1. Results of blood pressure measurements and proteinuria at 12 and 15 days' gestation

Groups	Blood Pressure (mmHg)				Proteinuria (gr/L)	
	G12		G15		G12	G15
	Sistolic	Diastolic	Sistolic	Diastolic		
K-	118.25±9.88	83±6.63	121.25±12.53	87.5±7.05	0±0.08	0.1±0.09
K+	119±5.10	86±5.94	15.15±8.70	118.75±13.67	0.2±0.09	11.8±3.95
P1	117±6.16	76.75±5.85	146.75±4.50	109.25±10.18	0.2±0.17	3.75±0.96
P2	116.25±17.78	79±13.39	147.75±31.86	115.5±23.69	0.2±0.09	6.8±3.77
P3	118.5±16.62	85.5±7.14	151.25±9.00	117.75±19.60	0.2±0.09	7.8±2.87
P4	115.25±13.07	81.75±7.89	149±17.22	125.75±15.48	0.2±0.09	10.3±.40

Proteinuria occurs due to imbalanced levels of free radicals and antioxidants, precipitating oxidative stress. The oxidative stress provokes inflammation in the vascular endothelium, ultimately leading to vascular endothelial dysfunction. Consequently, in compromised endothelium, the filtration capacity of the renal vascular endothelium diminishes, resulting in the failure to adequately filter proteins by the glomerulus, thereby manifesting as proteinuria.[21]

Table 2. Results of proteinuria measurements at 19 days' gestation

Group	Rat number-	Proteinuria (g/L)	Average (g/L)
K-	1	0	0.112±0.14
	2	0.3	
	3	0	
	4	0.15	
K+	1	7	10±3.56
	2	15	
	3	10	
	4	8	
P1	1	1	0.425±0.39
	2	0.1	
	3	0.3	
	4	0.3	
P2	1	8	5.3±2.22
	2	3	
	3	4	
	4	6	
P3	1	3	6±2.58
	2	5	
	3	7	
	4	9	
P4	1	10	8±2.16
	2	8	
	3	5	
	4	9	

Subsequently, the One-Way ANOVA test was initiated following a homogeneity test, yielding a significance level of 0.056 (p >0.05). The outcomes of the One-Way ANOVA test for proteinuria demonstrated significance with p = 0.001 <0.05, indicating significant difference among the sample groups. This substantiates the effect of nano-curcumin administration on proteinuria in white rats with preeclampsia. Previous studies have shown that oxidative stress within the body can be ameliorated through exogenous antioxidants, with curcumin being one of the sources. Curcumin exhibits the capacity to permeate target cells, effectively mitigating free radicals such as Reactive Nitrogen Species (RNS) or Reactive Oxygen Species (ROS) by harmonizing antioxidant and free radical levels within the body through the inhibition of enzymes responsible for augmenting free radical production. Consequently, this impedes the onset of oxidative stress, thereby averting inflammation in the vascular endothelium of the kidney and enhancing the glomerular filtration function.[22,23] Nano-formulated curcumin emerges as a viable therapeutic option due to its high bioavailability, enabling faster and more effective curcumin action on the targeted disease or organ.[24]

The LSD post-hoc analysis was conducted to identify differences among groups, with a significance level set at p <0.05. Table 3 summarizes the test outcomes, revealing a significant difference between the K- group and others. The p-values in the K+ group were 0.000, in P2 0.004, in P3 0.001, and in P4 0.000, showing significant differences. Moreover, the p-value in the K+ group significantly differed from those in K- (p=0.000), P1 (p=0.000), P2 (p=0.007), and P3 (p=0.019). The p-value in the P1 group was significantly difference from those in K+ (p=0.000), P2 (p=0.006), P3 (p=0.002), and P4 (p=0.000). In P2 group, the value was significantly different from those in K- (p=0.004), K+ (p=0.007), and P1 (p=0.006), while insignificantly different from those in P3 (p=0.636) and P4 (p=0.094). Group P3 exhibited significant differences from K- (p=0.001), K+ (p=0.019), and P1 (p=0.012), but not from P2 (p=0.636) and P4 (p=0.215). The p-value in group P4 was significantly different from those in K- (p=0.000) and P1 (p=0.000), but not significantly from those in K+ (p=0.215), P2 (p=0.094), and P3 (p=0.215). Consequently, the dose in P1 group (25 mg) exhibited the most signficant changes compared to other groups' doses.

The highest average proteinuria was observed in group P4, reaching 8 ± 2.16, close to the average of the positive control (K+) group at 10 ± 3.56. Group P4 received a combination of L-NAME and nano-curcumin at a dose of 200 mg/day, while the positive control group only received L-NAME. This suggests that higher doses of curcumin may potentially increase proteinuria levels. Notably, nano-curcumin exhibits an LD50 of 5000 mg/kg body weight. Experiments conducted on normal male and female subjects using doses of 50 mg, 100 mg, and 200 mg resulted in an increase in albumin, BUN, and creatinine levels, which was 0.1 in each group. Despite its LD50 of 5000 mg/kg body weight, nano-curcumin administration to normal rats can augment albumin levels.[25] Various studies elucidate that repeated administration of antioxidants in high doses can transform antioxidants into pro-oxidants, thereby amplifying free radicals and potentially damaging body cells. Additionally, nanoparticles have the capability to permeate blood vessel walls or infiltrate body cells, particularly those with sizes ranging from 20-50 nm, thereby exerting direct effects on target cells. Nano-curcumin, owing to its hydrophilic properties, readily dissolves and penetrates the bloodstream.[26,27]

Table 3. Results of post-hoc comparison test (LSD)

Groups	K-	K+	P1	P2	P3	P4
K-		0.000*	0.843	0.004*	0.001*	0.000*
K+	0.000*		0.000*	0.007*	0.019*	0.215
P1	0.843	0.000*		0.006*	0.002*	0.000*
P2	0.004*	0.007*	0.006*		0.636	0.094
P3	0.001*	0.019*	0.002*	0.636		0.215
P4	0.000*	0.215	0.000*	0.094	0.215	

The strength and limitations of the study

This study demonstrated the efficacy of curcumin as an alternative for reducing proteinuria, offering a clear and standardized measurement methodology aligned with established guidelines. The research effectively met its objectives, yielding valuable outcomes. Nonetheless, limitations were observed, particularly regarding the ultrasound tool utilized for the rats. Additionally, dropout rates were notable due to factors such as mortality, birthing, and illness among the rat subjects, potentially influenced by undisclosed external variables.

CONCLUSION

Nano-curcumin has an effect on decreasing proteinuria in white rats (*Rattus norvegicus*) with preeclampsia. The most effective dose in reducing proteinuria was 25 mg. Future research is expected to be able to analyze the effect of nano-curcumin at doses below 25 mg on proteinuria and to examine the right dose for humans.

DISCLOSURES

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Conflict of interest

There is no conflict of interest

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Author contribution

S: Supervised result, discussion, and funded this research. AIS: Collected data, designed the study, collected literature, analyzed the data, drafted this manuscript. N: Supervised and discussion. This manuscript has been reviewed and approved by all authors.

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