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Effect of nanocurcumin administration on superoxide dismutase and progesterone level exposure to noise stress during pregnancy in mice

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ABSTRACT

Background: Continuous noise with high decibels (dB) intensity continuously can cause psychological stress in a person. Stress during pregnancy can have a negative impact on fetal development; this is due to the narrowing of the placental artery and ends in the obstruction of the flow of nutrients and oxygen to the fetus. Increased cortisol levels during pregnancy stress will signal the placenta to reduce the production of progesterone and estradiol and stimulate the secretion of prostaglandins that activate contractions.

Aim: This study aims to determine the effect of nanocurcumin administration on pregnant mice under the stress of 135 dB disturbance for 40 minutes with a continuous pattern.

Methods: This experimental study used 25 female mice in five groups: K(−) with no treatment, K(+) with 135 dB disturbance induction for 40 minutes with a continuous pattern, P1 given disturbance and nanocurcumin dose 14 mg/kgBW, P2 given disturbance and nanocurcumin dose 21 mg/kgBW, and P3 given disturbance and nanocurcumin 24.5 mg/kgBW. SOD and progesterone were tested using ELISA.

Result: Data analysis using one-way ANOVA followed by the least significant difference. The result of this study conducted nanocurcumin dose of 24.5 mg/kgBW gave the most significant effect ($P < 0.05$) in reducing SOD levels and restoring progesterone levels in mice that had disorders during pregnancy compared with doses of 14 and 21 mg/kgBW, respectively.

Conclusion: The conclusion of this study, an administration of nanocurcumin at a dose of 24.5 mg/kgBW, was effective in reducing oxidative stress and increasing progesterone levels in mice that experienced stress due to disorders during pregnancy.

Keywords: Mice, Nanocurcumin, Noise stress, SOD, Progesterone.

Introduction

Noise is an unwanted sound that is either intermittent or continuous. Measurement of sound intensity can use decibels (dB). The impact of noise on an individual's behavior depends not only on dB, frequency (Hz), duration, and pattern but also on the hearing ability of the species, race, age, and physiological condition (Broucek, 2014). Normal noise exposure by the Occupational Safety and Health Administration is 85 dB, while noise intensity of more than 115 dB can cause direct mechanical trauma to ear cells and tissues (Jongkamonwiwat *et al*., 2020). Continuous noise with high dB intensity can cause psychological stress in an individual. Psychological stress can increase lipid peroxidation and cell damage. This occurs because of high oxygen consumption and relatively weak antioxidant defenses against excessive free radicals (Rasmus and Kozlowska, 2023). Some antioxidants produced in the body or endogenous antioxidants include superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX) (Wirawan *et al*., 2019).

Antioxidant activities that are often used to assess oxidative stress are SOD and GPX (Ngestiningsih *et al*., 2019). SOD is one of the antioxidant enzymes that catalyzes the dismutase reaction or disproportionation of superoxide into oxygen molecules (O_2) and hydrogen peroxide (H_2O_2) so that hydroxyl radicals are not formed (Ghareghomi *et al*., 2021). In addition, SOD is an important enzyme for removing superoxide in the cell cytosol, mitochondria, and endoplasmic reticulum and can function to detoxify peroxynitrite nitration ($ONOO^-$), produced by the reaction of superoxide anion with nitric oxide (Jafari *et al*., 2017).

In addition, stress caused by noise can cause the release of stress hormones such as catecholamines and

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glucocorticoids. Stress that occurs during pregnancy can have a negative impact on fetal development, this is due to the narrowing of the placental arteries and resulting in obstruction of the flow of nutrients and O_2 to the fetus (Trifu *et al.*, 2019). Increased cortisol levels during pregnancy stress will signal the placenta to reduce the production of progesterone and estradiol and stimulate the secretion of prostaglandins that act on contractions (Wu *et al*., 2021). Progesterone functions to prepare the endometrium and provide an adequate environment for pregnancy. Low progesterone levels can cause miscarriage (Yuliani *et al*., 2019).

Nanocurcumin is a powerful antioxidant that can reduce oxidative stress. Nanocurcumin can stimulate antioxidant enzymes such as SOD, GPX, and CAT, thereby causing reactive oxygen species (ROS) detoxification (Ranjbar *et al*., 2020). In addition, nanocurcumin has an anti-inflammatory effect by inhibiting the activation of NF-κB which is the main pathway involved in the production of pro-inflammatory cytokines (Tossetta *et al*., 2021).

Materials and Methods

Study period and location

This experimental study was conducted in June–December 2024. The acclimatization process, research treatment, and sampling were carried out at the Embryology Laboratory of the Faculty of Veterinary Medicine, Airlangga University. Examination of SOD and progesterone levels was carried out by the Animal Disease Diagnostic (ADD-Lab) using an ELISA test carried on Brawijaya University.

Medium preparation

The materials used in this study were 5-month-old male mice, 3 months old female mice, pregnant mare serum gonadotropin, human chorionic gonadotropin, SOD and progesterone ELISA kit, and sound source with a size of 135 dB which is placed in a soundproof box.

Serum ELISA test

Mice serum was obtained from blood collection via intracardiac then collected vacutainer tube and centrifuged for 10 minutes at 6,000 rpm at a temperature of 40°C. After the serum was formed, serum was collected in a 1.5 ml eppendorf tube and stored for SOD (Afrazeh *et al*., 2015), and progesterone was examined using the ELISA method with CV<10% (Ighadaro and Akinloye, 2018).

Data analysis

The research data were analyzed using ANOVA and continued using the Least Significant Difference (LSD) test via Statistical Package for the Social Science.

Ethical approval

We carried out this research under ethical clearance designation from Brawijaya University, No 029-KEP-UB-2024.

Results

Statistical analysis showed a significant relationship between organophosphate exposure and nanocurcumin administration on SOD levels in each group. Based on the statistical results, the data from the concentration examination showed that SOD was normally distributed ($P > 0.05$) and heterogeneous ($P < 0.05$) so that the data from the five groups varied. The results of the ANOVA examination showed that the average in each group was different ($P < 0.05$), it can be concluded that it was significantly different (Table 1).

The results of the analysis showed that the administration of nanocurcumin at a dose of 24.5 mg/kgBW had a significant effect on the tested groups. Specifically, the group receiving a dose of nanocurcumin at a dose of 24.5 mg/kgBW showed significant changes compared to the control group.

The results of Figure 1 are analysis of the ELISA test showing that nanocurcumin has a significant effect on increasing the SOD activity of pregnant mice exposed to 135dB stress. The most significant increase was seen at the P3 dose, which shows its effectiveness in increasing the body's antioxidant activity. These findings indicate that nanocurcumin can play an important role in increasing the body's defense mechanism against oxidative stress by increasing SOD activity.

Mice exposed to noise stress showed a significant decrease in progesterone levels to 16.464 ng/m. In the group exposed to a combination of noise stress and nanocurcumin, progesterone levels increased by 14 mg/kg BW; 21 mg/kg BW; and 24.5 mg/kg BW to 27.915 ng/mL; 15.949 ng/mL; and 16.284 ng/mL.

Discussion

Stress has a significant impact on various physiological processes in the body, including the levels of antioxidant enzymes such as SOD. In pregnant female mice, stress can result in decreased blood levels of SOD, which serves as an important defense against free radicals. When mice experience stress, their bodies respond by releasing stress hormones such as corticosterone. These hormones, although useful in short-term emergency situations, can have detrimental effects if released excessively or for a prolonged period. One of the negative impacts is the increased production of free radicals or ROS (Tang *et al*., 2023). Free radicals are highly reactive molecules that can damage body cells, including DNA, proteins, and cell membrane lipids. To combat these free radicals, the body has an antioxidant

Table 1. Progesterone levels of each treatment group.

SAMPLE	MEAN±SD	ANOVA
K+	16.464 ± 1.11	
K-	32.248 ± 1.41	
P1	27.915 ± 3.26	*P value* = 0.000
P2	15.949 ± 1.53	
P3	16.284 ± 2.17	

**P value* conducted ANOVA followed LSD test.

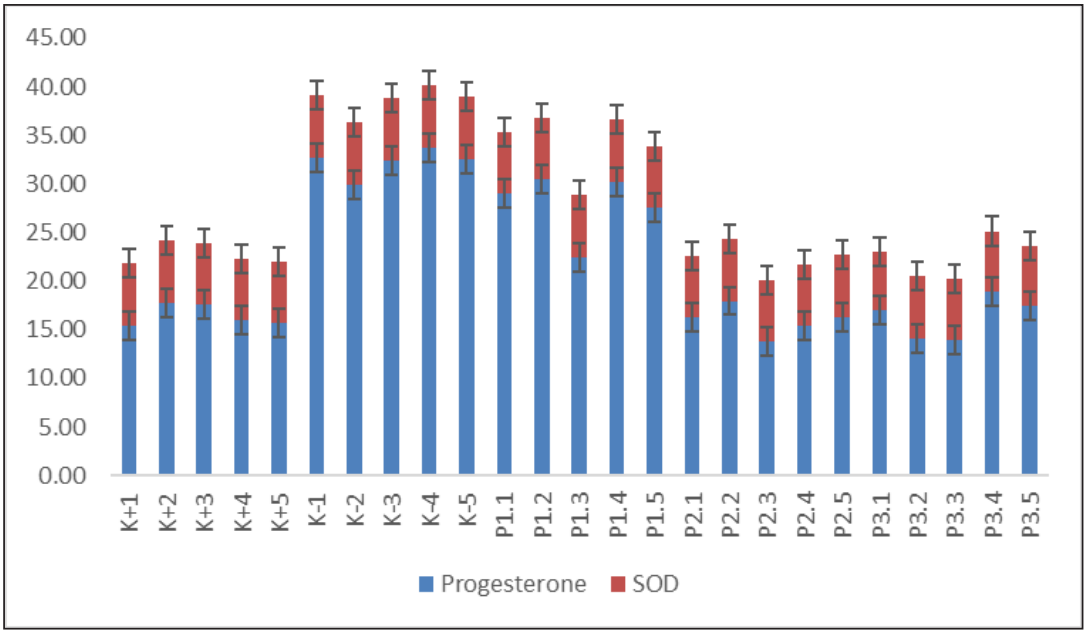

Fig. 1. Progesterone and SOD levels in each treatment group.

system, including the enzyme SOD which catalyzes the conversion of superoxide (one type of free radical) to O_2 and H_2O_2, which can then be further degraded by other enzymes such as CAT and GPX. However, when pregnant female mice experience chronic stress, the body's capacity to produce and maintain antioxidant enzymes such as SOD can be reduced. This decrease in SOD levels leads to uncontrolled accumulation of free radicals, which can ultimately cause oxidative damage to body tissues, including the developing fetus (Duan *et al*., 2021).

The decrease in SOD levels due to 135 dB noise stress in pregnant female mice indicates that their bodies become less effective in neutralizing free radicals. As a result, there is an accumulation of free radicals that can cause oxidative damage to body tissues, including the developing fetus. This oxidative damage can have negative impacts on maternal health and fetal development, increasing the risk of pregnancy complications and impaired fetal development (Jafari *et al*., 2019). Nanocurcumin is a form of curcumin that has been optimized through nanotechnology to increase its bioavailability and effectiveness. Curcumin itself is the main active compound found in turmeric (*Curcuma longa*) and is known to have various health benefits, including antioxidant and anti-inflammatory properties. Research shows that nanocurcumin can increase SOD levels in mice, which is an important enzyme in the body's defense system against free radicals (Amir and Fessler, 2013). The use of nanocurcumin has several advantages compared to regular curcumin. Due to its smaller particle size, nanocurcumin has better absorption in the body, so it can reach higher concentrations in the blood and tissues (Jakubczyk, 2020). This allows nanocurcumin to more effectively increase SOD levels in the body. Studies in mice have shown that supplementation with nanocurcumin can increase SOD activity. This may be due to several mechanisms, including increased absorption of curcumin in cells and increased stability of curcumin in the body.

Progesterone is a steroid hormone produced by the ovaries, specifically by the corpus luteum after ovulation, and by the placenta during mouse pregnancy. This hormone plays an important role in the female reproductive cycle and in maintaining pregnancy. Some of the main functions of progesterone include preparing the lining of the uterus (endometrium) to receive and support the implantation of a fertilized egg. If pregnancy occurs, progesterone helps maintain the endometrium so that the fetus can develop properly. During pregnancy, progesterone helps prevent uterine muscle contractions, thereby reducing the risk of miscarriage. Progesterone also has effects on the immune system, helping the body not to reject the fetus as a foreign object during pregnancy (Nelson *et al*., 2001). Noise stress can affect placental function, which can reduce progesterone production and lower blood levels of this hormone. Decreased progesterone levels in pregnant mice due to noise stress can have negative effects on pregnancy, including the risk of miscarriage, fetal growth retardation, and other complications. Noise stress can alter the balance of neurotransmitters in the brain, such as dopamine, serotonin, and norepinephrine, all of which can affect the secretion of reproductive hormones. Granulosa and luteal cells are

the main producers of progesterone; damage to these cells will reduce hormone production. Noise stress can cause vasoconstriction, which reduces blood flow to the ovaries and placenta. Decreased blood flow can reduce the supply of nutrients and O_2 to these tissues, impairing progesterone production. Corticosterone can inhibit the activity of enzymes involved in progesterone synthesis, such as 3β-hydroxysteroid dehydrogenase. Corticosterone can affect the expression and sensitivity of receptors that are important for progesterone production and release (Lechat *et al*., 2022).

Nanocurcumin, a nano form of curcumin derived from turmeric, has shown potential in various studies as an anti-inflammatory and antioxidant agent. In the context of noise-stressed pregnant mice, the mechanism of nanocurcumin may play a role in reducing progesterone levels through several pathways related to stress response and hormonal regulation (Salimi *et al*., 2022). Nanocurcumin has potent anti-inflammatory properties. Noise stress can cause systemic or local inflammation that can affect the function of the ovaries or placenta, where progesterone is produced. By reducing inflammation, nanocurcumin may help maintain the function of these organs and affect progesterone levels (Tossetta *et al*., 2021).

Conclusions

Based on the results of the study, the nanocurcumin dose of 24.5 mg/kgBW in the P3 group was the best dose that provided the most significant effect in reducing SOD levels and restoring progesterone levels close to the normal range in pregnant mice exposed to noise. This dose showed the highest effectiveness in reducing oxidative stress and mitigating the negative impact of noise on hormonal status.

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Conflict of interest

The authors declare no conflict of interest.

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Author's contribution

VFH: Writing original draft, Visualization, Validation, Methodology, Investigation, Conceptualization. DM: Writing review & editing, Supervision, Methodology, Investigation, Conceptualization. IFONAI: Writing review & editing, Investigation.

Data availability

All data are provided in the manuscript.

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