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The Potential of Tamarillo (*Solanum betaceum*) ethanol extract on Superoxide Dismutase (SOD) expression in the kidneys of lead acetate-exposed mice (*Mus musculus*)

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Abstract

Background: Lead is a highly toxic heavy metal that can cause harmful effects when it enters the body in large amounts. Lead that enters the body often originates from environmental contamination, posing a significant threat to public health. As an excretory organ, the kidney is one of the organs affected by lead accumulation. Accumulated lead increases the production of Reactive Oxygen Species (ROS), which can induce oxidative stress and reduce the activity of antioxidant enzymes such as superoxide dismutase (SOD). Tamarillo (*Solanum betaceum*) ethanol extract contains several antioxidants which play important roles in combating oxidative stress.

Objective: This study aimed to evaluate the potential of tamarillo (*Solanum betaceum*) ethanol extract on superoxide dismutase (SOD) expression in kidneys of male mice exposed to lead acetate.

Methods: This study was a true experimental post-test only control group using 25 archived mice kidney tissue samples. The treatment variable was divided into five groups (n=5): K0 (negative control – distilled water), K1 (positive control – lead acetate 75 mg/kgBW), P1 (lead acetate + tamarillo extract 100 mg/kgBW), P2 (lead acetate + tamarillo extract 200 mg/kgBW), and P3 (lead acetate + tamarillo extract 400 mg/kgBW). The treatments were administered for 35 days. SOD expression was assessed immunohistochemically using H-Score.

Results: The group exposed to lead acetate without any treatment showed the highest mean H-Score, suggesting compensatory upregulation. Administration of tamarillo ethanol extract reduced SOD expression, bringing it closer to the level observed under normal physiological conditions.

Conclusion: Lead acetate exposure induced compensatory upregulation response. Tamarillo ethanol extract at 100 and 200 mg/kgBW/day significantly attenuated this response, suggesting reduced oxidative stress burden in renal cells.

Keywords: *Solanum betaceum*; Superoxide dismutase (SOD); Lead (Pb) acetate; Chronic Kidney Disease (CKD); Oxidative stress

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1. Introduction

Lead exposure remains a serious problem, causing approximately 52,940 deaths worldwide in 2019.[1] Although the number of male deaths from chronic kidney disease (CKD) caused by lead exposure was higher than that of females in 1990 and 2021, the rate of increase in the disease burden among women was actually greater than that among men.[2] In addition, it is estimated that approximately 800 million children worldwide, including more than 8 million children in Indonesia, have blood lead levels of ≥5 μg/dL, which may lead to long-term health effects.[3,4]

Lead (Pb) is a soft, corrosion-resistant heavy metal, making it useful in many aspects of daily life. Although its use is now rare, lead was once found in gasoline, batteries, and even house paint and toys. Lead that enters the human body is absorbed through the digestive tract before being distributed via the bloodstream to other organs, including the kidneys.[3] The kidneys are one of the primary organs targeted by lead due to their role in the excretion process. Acute lead exposure can result in AKI, which, if the exposure persists, may progress to CKD. This is partly because lead promotes ROS accumulation, which impairs the antioxidant defense system and elevates inflammatory markers.[5] Among the antioxidant enzymes affected is superoxide dismutase (SOD), the body's first-line defense against oxidative stress, which catalyzes the conversion of superoxide anions into hydrogen peroxide and oxygen.[6,7] Excessive lead accumulation can disrupt SOD function, further compromising the cell's ability to neutralize ROS.

Tamarillo (*Solanum betaceum* Cav.), also known as tree tomato, is a plant of the Solanaceae family rich in bioactive compounds with antioxidant potential, including flavonoids, phenolic acids, anthocyanins, carotenoids, and vitamin C.[8] These compounds play a role in scavenging free radicals and maintaining the balance of the body's antioxidant system. Several studies have reported that tamarillo extract possesses antioxidant activity capable of reducing oxidative stress.

Based on the above background, this study aimed to determine the effect of tamarillo (*Solanum betaceum*) ethanolic extract on superoxide dismutase (SOD) expression using immunohistochemical analysis and kidney histopathology in mice exposed to lead acetate. Three doses of tamarillo were tested in this study.

2. Materials and methods

The study employed a true experimental design, using stored raw material from the kidneys of male mice (*Mus musculus*) in the form of paraffin blocks. The study design utilized a completely randomized design (post-test only control group design) on the kidneys of male mice. The sample size was determined using Federer's formula, requiring a total of 25 paraffin blocks, with 5 blocks per group across 5 groups. The five groups were: K0 (negative control – distilled water), K1 (positive control – lead acetate 75 mg/kgBW), P1 (lead acetate + tamarillo extract 100 mg/kgBW), P2 (lead acetate + tamarillo extract 200 mg/kgBW), and P3 (lead acetate + tamarillo extract 400 mg/kgBW). The extracts were administered for 35 days, while lead acetate was administered from day 4 through day 35. All groups received distilled water as a vehicle.

Observations were conducted using a light microscope at 100–400x magnification. SOD expression was then assessed based on a positive reaction to the SOD antibody. A reaction was considered positive (+) if a brown color appeared in the cell regions specific to the primary antibody used. A negative (–) reaction was indicated by a blue color in the cell nucleus. Scoring was performed using the H-Score on a scale of 0–3, ranging from no staining to the strongest staining intensity. The H-Score was calculated using the formula: H-Score = (0 × % intensity 0) + (1 × % intensity 1) + (2 × % intensity 2) + (3 × % intensity 3), with a range of 0-300.

Data analysis began with a descriptive analysis, followed by a normality test using the Shapiro-Wilk test and a homogeneity test using the Levene test. If both data sets were normally distributed and homogeneous, the analysis proceeded with a one-way ANOVA and Tukey's post hoc test. If either condition was not met, the analysis proceeded with the nonparametric Kruskal-Wallis test. If significant differences were found, the analysis continued with the Mann-Whitney test to compare between groups.

Ethical considerations were fulfilled through approval from the Health Research Ethics Committee of the Faculty of Medicine, Universitas Airlangga, with certificate number 90/EC/KEPK/FKUA/2026. This ethical exemption is valid from April 27, 2026, through April 27, 2027.

3. Results and discussion

3.1. Immunohistochemistry of SOD Expression in Mice Kidneys

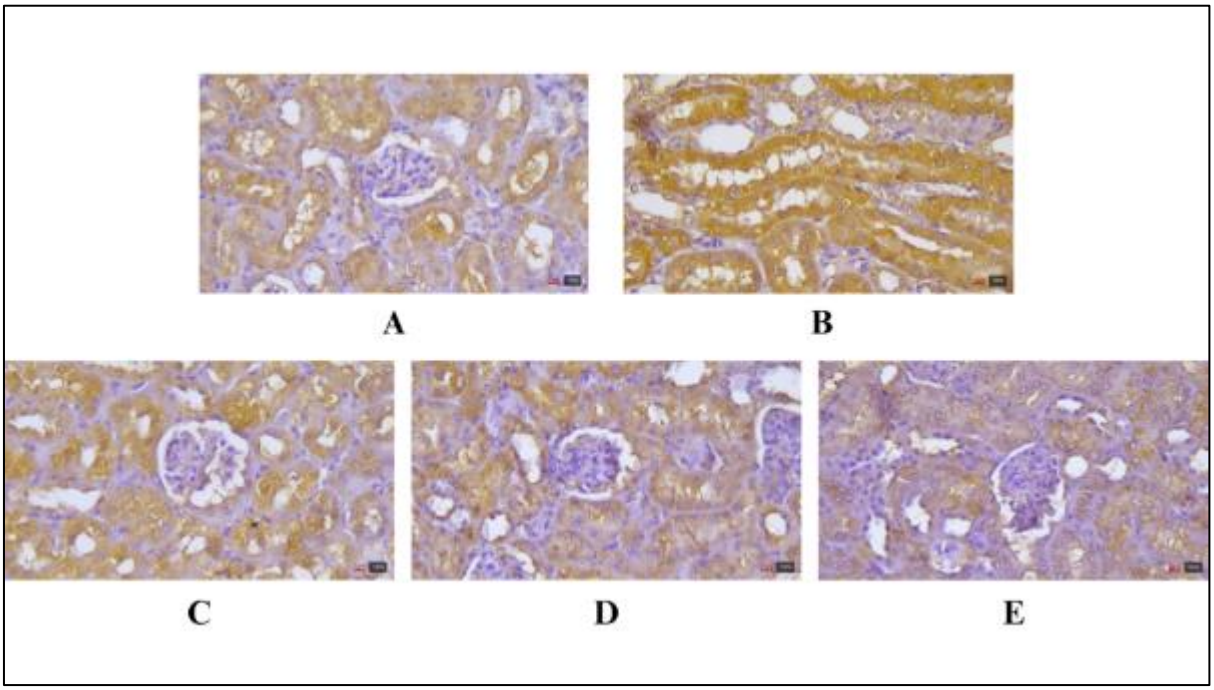

Figure 1 Immunohistochemistry Expression of SOD in Mice Kidney (100x)

Figure 1. Immunohistochemistry of the SOD marker. (A) K0, shows a predominance of moderate intensity staining with minimal strong intensity staining. (B) K1, shows a predominantly strong intensity of brown staining, indicating high SOD expression. (D) P2, shows lower strong intensity staining compared to (C) which was taken from P1. (E) P3, shows a greater number of strong intensity brown stains compared to the other treatment groups.

3.2. Descriptive Analysis and Normality Test

The expression of superoxide dismutase (SOD) in kidney tissue of *Mus musculus* exposed to lead acetate and given an ethanol extract of *Solanum betaceum* was analyzed descriptively and statistically.

Table 1 Descriptive Analysis and Normality Test

Group	Mean	Std. Deviation	Minimum	Maximum	Normality Test (Shapiro-Wilk Test)	Kruskal-Wallis Test
K0	148	18,90767	115	160	**0,019**	**0,052**
K1	184	18,50676	160	205	0,687	
P1	141	29,66479	90	160	**0,029**	
P2	133	27,29469	110	165	0,071	
P3	153	37,01351	100	190	0,477	

Descriptive analysis showed an increase in SOD expression in K1 compared to K0. Contrary to expectations, SOD expression decreased in the treatment groups (P1, P2, P3) compared to K1. A normality test using the Shapiro-Wilk test showed that the two groups (K0 and P1) were not normally distributed. Therefore, a homogeneity test was not performed, and the assumptions for a one-way ANOVA were not met. Consequently, nonparametric tests were used for comparisons.

The increase in SOD expression in the lead-exposed group and the subsequent decrease following tamarillo administration in this study suggest the possibility of compensatory upregulation by the body's cells in response to oxidative stress. The increase in ROS due to lead exposure activates cellular defense mechanisms to increase the expression of antioxidant enzymes, including SOD.[9] These findings are consistent with a previous study, which reported increased activity of Cu,Zn-SOD and catalase (CAT) in the kidneys of lead-exposed rats as a compensatory response to oxidative stress.[10] Another study also demonstrated increased activity of SOD, CAT, and glutathione S-transferase (GST) in rat kidneys following lead acetate exposure, although glutathione peroxidase (GPx) activity decreased.[11] The SOD response to lead exposure may also vary depending on the biological condition of the test animals. In female rats, the increase in SOD activity was more pronounced in the post-pubertal group (65 days old) compared to the pre-pubertal group. A significant increase in total sulfhydryl group (-SH) levels was also observed in the post-pubertal group.[12]

The Kruskal-Wallis test results showed a p-value of $p > 0.05$, which indicates that there was no significant difference in SOD expression among the treatment groups. However, the p-value, which was very close to the significance threshold, suggests the possibility of a trend toward a difference that has not yet been statistically confirmed. Therefore, even though the test results did not show a significant difference, the Mann-Whitney test was still conducted to examine specific differences between the groups.

3.3. Mann-Whitney Test

Table 2 Mann-Whitney Test

	K0	**K1**	**P1**	**P2**
K1	**0.015**			
P1	0.829	**0.015**		
P2	0.596	**0.021**	0.916	
P3	0.463	0.142	0.346	0.249

The test results showed that there were significant differences between group K1 and K0, K1 and P1, and K1 and P2, but no significant difference between K1 and P3. Furthermore, there were no significant differences among the three treatment groups (P1, P2, P3) or between these three treatment groups and the negative control group (K0).

3.4. Tamarillo Effects on SOD Expression

Table 2 shows that the mean H-scores of the three treatment groups—P2 (133.0) < P1 (141.0) < P3 (153.0)—were all lower than that of K1 (184.0). Within the framework of compensatory upregulation, this can be interpreted to mean that administration of tamarillo ethanol extract reduces the oxidative stress burden on kidney cells, so that the cells do not need to excessively increase SOD production as an emergency response. Thus, SOD expression in the treatment groups resembles the normal physiological conditions shown by the negative control group (K0).

Lead is a nephrotoxic heavy metal that can accumulate in the kidneys, as this organ plays a key role in the filtration and excretion of foreign substances from the body. Acute exposure to large amounts of lead can damage proximal tubular cells, which may manifest as glycosuria and aminoaciduria, and can lead to acute kidney injury (AKI).[5] Prolonged lead exposure, even at low levels, can progress to tubulointerstitial nephritis, fibrosis, hyperuricemia, hypertension, and ultimately chronic kidney disease (CKD). Elevated lead levels promote ROS accumulation beyond the endogenous antioxidant capacity, resulting in oxidative stress characterized by damage to membrane lipids, proteins, and DNA, as well as a decline in renal function. Damaged mitochondria further exacerbate this process by generating excessive ROS, worsening renal cell injury. The elevated ROS levels also activate inflammatory signaling pathways, including NF-κB, and increase the production of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α. Simultaneously, apoptosis is triggered through alterations in the expression of regulatory proteins, including upregulation of Bax and caspase-3 and downregulation of Bcl-2. The activation of these pathways collectively leads to chronic inflammation, tubular cell death, fibrosis, and progressive loss of renal function.[5]

Lead is a redox-inert metal and therefore does not generate ROS directly through Fenton reactions.[9] Lead has a high affinity for sulfhydryl (-SH) groups on proteins, leading to alterations in protein structure, impaired protein function, and decreased activity of various enzymes. Furthermore, lead can displace essential metal ions such as calcium (Ca^{2+}), zinc (Zn^{2+}), and iron (Fe^{2+}/Fe^{3+}) from the active sites of metalloenzymes, as well as deplete glutathione (GSH) levels and disrupt the cellular antioxidant system as a whole.[9,13] As a metalloenzyme, SOD activity is highly dependent on the

presence of essential metal cofactors. Therefore, lead-mediated displacement of metal ions at the active site of SOD can reduce its catalytic activity, consequently diminishing the cell's capacity to neutralize ROS.[13]

Tamarillo ethanol extract contains several bioactive compounds, including flavonoids, phenolics, anthocyanins, vitamin C, and carotenoids. Phenolic compounds and flavonoids are antioxidants that can help combat free radicals capable of damaging cells. The polyphenols and flavonoids in tamarillo are thought to provide protection against oxidative stress through two mechanisms. Flavonoids can directly donate hydrogen atoms to free radicals, thereby neutralizing ROS and helping maintain intracellular redox balance. Indirectly, flavonoids activate Nrf2 by releasing it from Keap1, which in turn promotes the transcription of endogenous antioxidant enzymes such as SOD, CAT, GPx, and GR.[14] Beyond enhancing the antioxidant system, this Nrf2-mediated pathway has also been shown to reduce inflammation and apoptosis.[15]

The dose-response patterns observed in all three groups were non-monotonic. Group P2 exhibited the lowest H-score; however, in Group P3—which received a higher dose—the H-score actually increased again, approaching that of the positive control group. This pattern is consistent with the concept of non-monotonic dose-response (NMDR), in which the relationship between dose and biological response is not always linear.[16]

4. Conclusion

In this study, it was found that SOD expression increased in kidneys exposed to lead acetate, presumably as a compensatory upregulation in response to oxidative stress. Administration of tamarillo ethanol extract at doses of 100 mg/kgBW and 200 mg/kgBW reduced SOD expression, bringing it back closer to baseline (normal physiological conditions). However, although the 400 mg/kgBW dose showed lower SOD expression compared to the group exposed only to lead, SOD expression was higher than at the other doses, indicating a dose-response pattern for NMDR.

Compliance with ethical standards

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Disclosure of conflict of interest

All authors have no conflict of interest.

Statement of ethical approval

Ethical approval for this research was obtained from the Health Research Ethics Committee of the Faculty of Medicine, Universitas Airlangga (No. 90/EC/KEPK/FKUA/2026, on April 27, 2026).

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