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Original Article

Effects of Tamarillo (*Solanum betaceum*) Extract on Glutathione Peroxidase Expression and Inflammatory Reactions in Lead Acetate-Induced Lung Tissue of Mice

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Abstract

Background: Lead acetate exposure through oral route has a significant impact on lung tissue as lead can induces the formation of reactive oxygen species (ROS), resulting in decreased glutathione peroxidase (GPx) and triggering inflammatory responses. The induction of exogenous antioxidants may prevent this mechanism. This study aimed to evaluate the protective effect of Tamarillo ethanol extract on GPx expression and inflammatory reactions in the lung tissue of mice induced with lead acetate.

Methods: This true experimental laboratory study utilized stored formalin-fixed-paraffin-embedded (FFPE) lung tissue from 30 male mice (*Mus musculus)*. The samples were divided into five intervention groups, each consisting of six mice. Immunohistochemistry and histopathology assessments were performed at 100x and 400x magnification to evaluate the GPx expression using the H-score and to assess inflammatory reactions based on five scoring parameters, which were summed to obtain the total lung injury score.

Results: Lead exposure significantly increased inflammatory reactions, particularly in the hemorrhage parameters (p=0.041). A significant increase in GPx expression was observed following lead acetate administration (p=0.027). Administration of Tamarillo ethanol extract at a dose of 400 mg/kg body weight (BW) increased GPx expression compared with the positive control group (p=0.027).

Conclusions: Tamarillo ethanol extract, especially at a dose of 400 mg/kgBW, significantly increases GPx expression in lead acetate-induced lung tissue of mice. This finding highlights the potential role of Tamarillo extract as an antioxidant source to reduce lead-induced lung injury, supporting broader efforts to promote healthy lifestyle practices that protect against environmental toxin exposure.

Keywords: Glutathione peroxidase, inflammation, lead-induced, lung tissue, Tamarillo

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Introduction

Lead (Pb) is a chemical element commonly found in daily life and is recognized as a toxic heavy metal capable of causing severe and permanent health effects. Lead exposure occur primarily through two main routes, which are oral ingestion and inhalation.[1] When lead enters the body through oral route, it passes through the gastrointestinal tract and is systemically absorbed, causing symptoms in several visceral organs, including the lungs. In the respiratory tract, lead exposure may manifest as productive cough and reduction in pulmonary function test (PFT) values.[2] These symptoms highlight the urgency of addressing the harmful effects of lead on lung health, as long-term exposure can increase the

risk of chronic obstructive pulmonary disease (COPD), which currently affects approximately 209 million people and causes 3.2 million deaths globally.[3]

The harmful impact of lead on respiratory health is supported by a study conducted in Denpasar City in 2021, which reported increased blood lead levels among exposed workers, with a rise of 2.61% in males and 5.14% in females.[4] Individuals exposed to lead through the oral route in the occupational settings are at risk of experiencing elevated blood Pb concentrations due to its distribution into soft tissue, potentially leading to respiratory dysfunction or failure.[5] Lead at concentrations up to 10 µg/dl can be absorbed by the body and is considered an acceptable threshold. When the concentration exceeds this limit, lead can exert harmful effects.[6]

Elevated lead levels increase the production of reactive oxygen species (ROS), causing oxidative stress in lung tissue. Under physiological conditions, endogenous antioxidants such as glutathione peroxidase (GPx) function to neutralize oxidants. The GPx also has chemopreventive properties. However, this mechanism become impaired due to decreased antioxidant levels caused by excessive ROS expression.[7] This condition can trigger inflammatory responses in the human body.[8]

Tamarillo (*Solanum betaceum*) is widely recognized as a medicinal plant in Indonesia. Its fruit pulp contains antioxidant compounds such as alkaloids, flavonoids, and anthocyanins that can counteract toxic damage.[9] A previous study has shown that tamarillo extract administered orally significantly increased sperm motility in mice exposed to lead, suggesting a protective antioxidant effect against lead toxicity in reproductive tissue.[10] Given these findings, this study aimed to analyze the effect of tamarillo (*Solanum betaceum*) ethanol extract on lung morphology and GPx expression in mice exposed to lead acetate. The study focused on the ability of tamarillo extract to counteract ROS-induced oxidative stress and associated inflammatory response in lung tissue.

Methods

This study employed a completely randomized design (posttest-only control group design) using stored formalin-fixed-paraffin-embedded (FFPE) lung tissue obtained from 30 healthy male mice (*Mus musculus*) weighing 25–30 grams and aged 8 to 12 weeks. The mice were divided into five treatment groups, each consisting of six male mice. All interventions were administered orally using a feeding tube.

Group K0 served as the negative control and received distilled water (aquadest). Group K1 served as the positive control and was given lead acetate at a dose of 0.075 g/kg body weight (BW). Groups P1, P2, and P3 were exposed to lead acetate and concurrently administered ethanol extract of tamarillo (*Solanum betaceum*) at doses of 100 mg/kg, 200 mg/kgBW, and 400 mg/kgBW, respectively, for 35 consecutive days. Starting on day 4, lead acetate was administered daily to groups K1, P1, P2, and P3 until day 35.

The study was conducted at the Biomedical Science Laboratory and the Anatomical Pathology Laboratory, Faculty of Medicine, Universitas Airlangga, Indonesia from June 2024 to March 2025. Ethical approval was obtained from the Health Research Ethics Committee of Universitas Airlangga School of Medicine, Surabaya, Indonesia (Approval No: 39/EC/KEPK/FKUA/2024).

Preparation of GPx immunohistochemistry slides consisted of staining, counterstaining, and mounting.[11,12] Tissue slides were first dried, immersed in hydrogen peroxide, and washed twice with phosphate-buffered saline (PBS) for 4 minutes each. Slides were then incubated in 0.025% trypsin solution for 15 minutes at 37°C, followed by two washes with PBS.

Ultra V Block was applied for 5 minutes and rinsed off. Subsequently, the slides were incubated with GPx-1/2 primary antibody ((B-6): sc-133160, Santa Cruz, USA) for 60 minutes, washed twice with PBS, and treated with the secondary IgG Biotinylated Link Drops (yellow) for 30 minutes. After washing, slides were then incubated with DAB (3,3'-diaminobenzidine) chromogen diluted with 2% diluent for 6–10 minutes and rinsed twice with PBS and distilled water.[12] Counterstaining was performed using Mayer's Hematoxylin for 3–10 minutes, rinsed under running water for 5 minutes, dipped in ammonium hydroxide solution for 3 minutes, and rinsed again in distilled water for 3–5 minutes. Mounting was completed according to standard procedures.

Observations were conducted under a light microscope at 100x and 400x magnification by two independent examiners. Each tissue sample was evaluated across all field of view, and scores were averaged for comparison between groups.

The GPx expression was calculated based

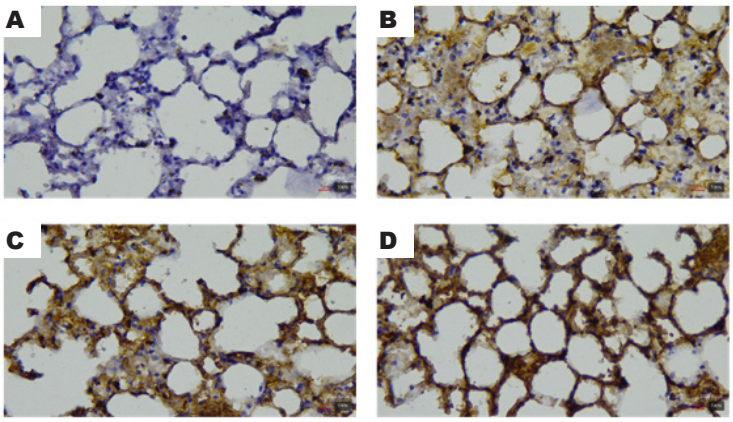

Figure 1 Representative GPx Immunohistochemical staining Intensities (400x) Illustrating the Criteria Used for H-score Determination

Note: A= negative intensity (K0), B= weak intensity (K1), C= moderate intensity (P1), D= strong intensity (P3).

on the percentage of positive cells (score A), indicated by the presence of brown staining in the cytoplasm of alveolar macrophages and pneumocytes, exhibiting specificity to the primary antibody (anti-GPx), and the staining intensity (score B). These scores were incorporated into the H-score formula (1 x % of weak staining +2 x % of moderate staining + 3 x % of strong staining).[13,14]

Data were analyzed using SPSS version 23. Normality was assessed with the Shapiro-Wilk test. For normally distributed but nonhomogeneus data, Welch's ANOVA was applied, followed by independent samples t-test for post hoc analysis ($p<0.05$).

Histopathological examination began with

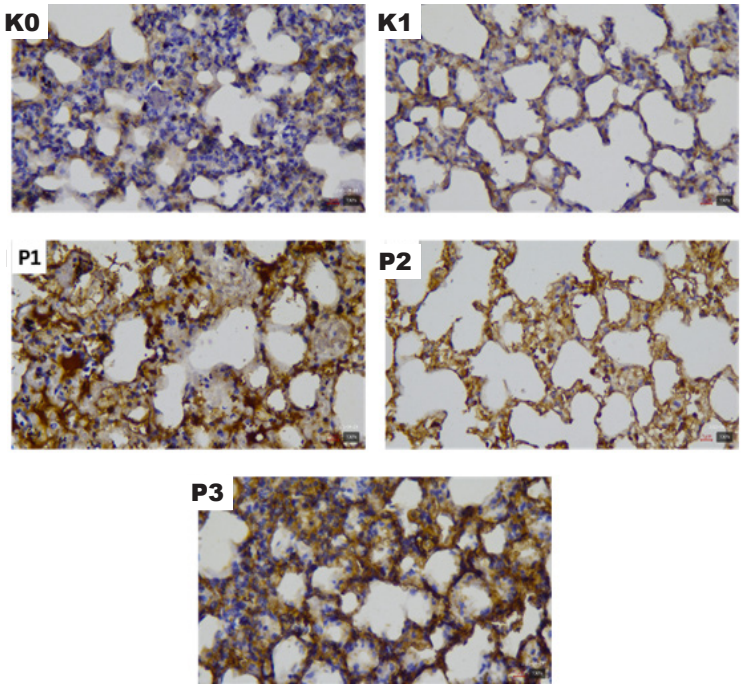

Figure 2 GPx Immunohistochemical staining from the Five Treatment Groups

Note: Increased brown cytoplasmic staining indicates higher GPx expression. K0 (Negative control); K1 (Lead acetate 0.075 g/kg body weight); P1 (Ethanol extract of tamarillo 100 mg/kg body weight combined with lead acetate 0.075 g/kg body weight); P2 (Ethanol extract of tamarillo 200 mg/kg body weight combined with lead acetate 0.075 g/kg body weight); P3 (Ethanol extract of tamarillo 400 mg/kg body weight combined with lead acetate 0.075 g/kg body weight).

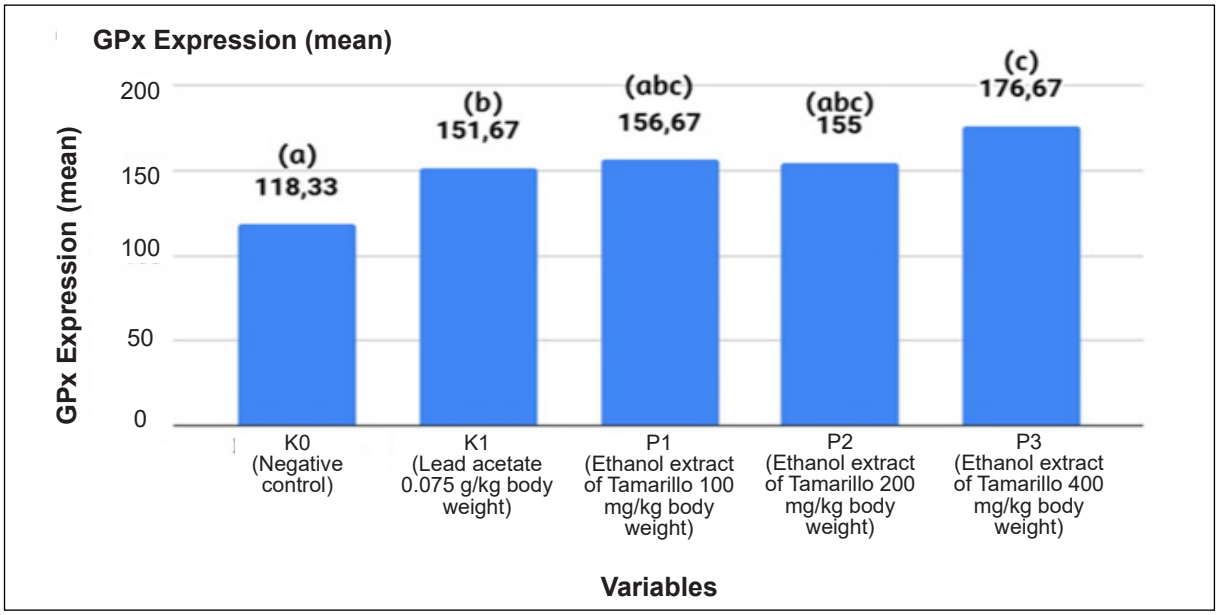

Figure 3 Effect of Tamarillo Extract on GPx Expression based on H-score Analysis

Note: Groups labeled with different letters indicate a statistically significant difference ($p<0.05$)

sequential dehydration of tissue sections in xylene I–II, absolute alcohol I–II, and graded alcohols (96%, 90%, 80%, 70%), followed by distilled water for 1 minute each. Slides were stained with hematoxylin-eosin (HE) for 5–10 minutes, rinsed in tap water, dipped in ammonia solution, and washed in distilled water. Tissues were then dehydrated again through graded alcohols and cleared in xylene.[11,12]

Inflammatory reactions were evaluated based on five parameters: inflammatory cell infiltration, alveolar septal thickening, hemorrhage, intra-alveolar edema, and pulmonary congestion. Observations were conducted at 100x and 400x magnification by two independent examiners. Each parameter was scored from 0 to 4, where 0=negative, 1=mild, 2=moderate, 3=severe, and 4=very severe. The sum of all parameter scores constitued the total lung injury score.[15] Analysis of inflammatory reaction data was performed using nonparametric tests (Kruskal-Wallis and Mann-Whitney) with SPSS version 23.

Results

A total of 30 FFPE lung tissue samples were analyzed for GPx expression and inflammatory responses. Immunohistochemical assessment demonstrated clear differences in staining intensity among group.

The negative control group (K0) showed minimal GPx staining, whereas lead acetate exposure (K1) resulted in weak staining. In contrast, tamarillo extract administration (P1, P2, P3) increased staining intensity in a dose-dependent manner (Figure 1).

Quantitative H-score analysis confirmed that lead acetate significantly reduced GPx expression compared with the negative control. Treatment with tamarillo extract increased GPx expression across all doses, with the 400 mg/kg body weight producing the highest H-score and showing a statistically significant improvement over the positive control ($p=0.027$). The dose of 100 mg/kg and 200 mg/kg doses also increased GPx expression, although the effects were less pronounced compared with P3 (Figure 2 and Figure 3).

Inflammatory reaction was evaluated based on five parameters, which were inflammatory cell infiltration, alveolar septal thickening, hemorrhage, intra-alveolar edema, and congestion. Lead acetate exposure (K1) produced marked inflammatory changes as shown in Figure 4. Hemorrhage was significantly increased in the K1 group than the negative control ($p=0.041$), demonstrated by ruptured blood vessel on histopathology (Figure 4B). Administration of tamarillo extract (P1, P2, P3) reduced the severity of inflammation across all parameters, with the P2 and P3 groups exhibiting tissue morphology most closely resembling the negative control

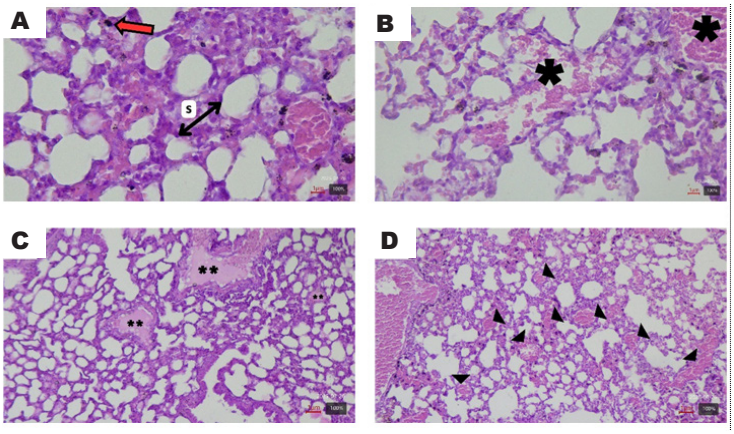

Figure 4 Histopathological Changes in Lead-Exposed Lung Tissue (Hematoxylin-Eosin staining, magnifications 100x and 400x

Note: A= inflammatory cell infiltration (red arrow) and alveolar septal thickening (S), B= hemorrhage (*) , C= intra-alveolar edema (**), and D= congestion (arrowheads)

(Figure 5).

Descriptive analysis of total lung injury score demonstrated that tamarillo extract reduced overall lung inflammation compared with the positive control group. Although differences between group did not reach statistical significance (p=0.171), the P2 group showed the lowest injury score among the treatment groups, indicating a potential protective effect (Figure 6).

Discussion

Lead acetate exposure in mice has been shown

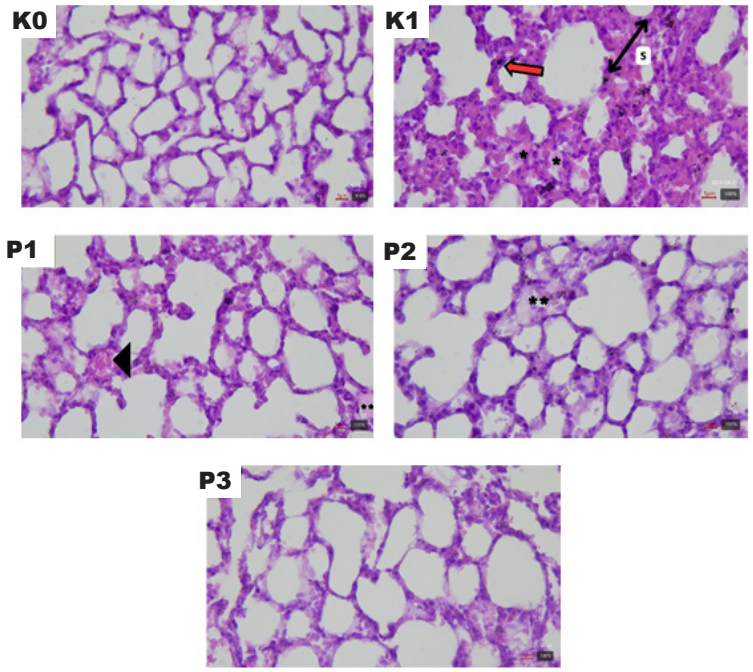

Figure 5 Histopathology of Lung Tissue from All Treatment Groups Illustrating in Inflammatory Cell Infiltration (Red Arrow), Alveolar Septal Thickening (S), Hemorrhage (*), Intra-Alveolar Edema (**), and Congestion (arrowheads).

Note: K0 (Negative control); K1 (Lead acetate 0.075 g/kg body weight); P1 (Ethanol extract of tamarillo 100 mg/kg body weight combined with lead acetate 0.075 g/kg body weight); P2 (Ethanol extract of tamarillo 200 mg/kg body weight combined with lead acetate 0.075 g/kg body weight); P3 (Ethanol extract of tamarillo 400 mg/kg body weight combined with lead acetate 0.075 g/kg body weight).

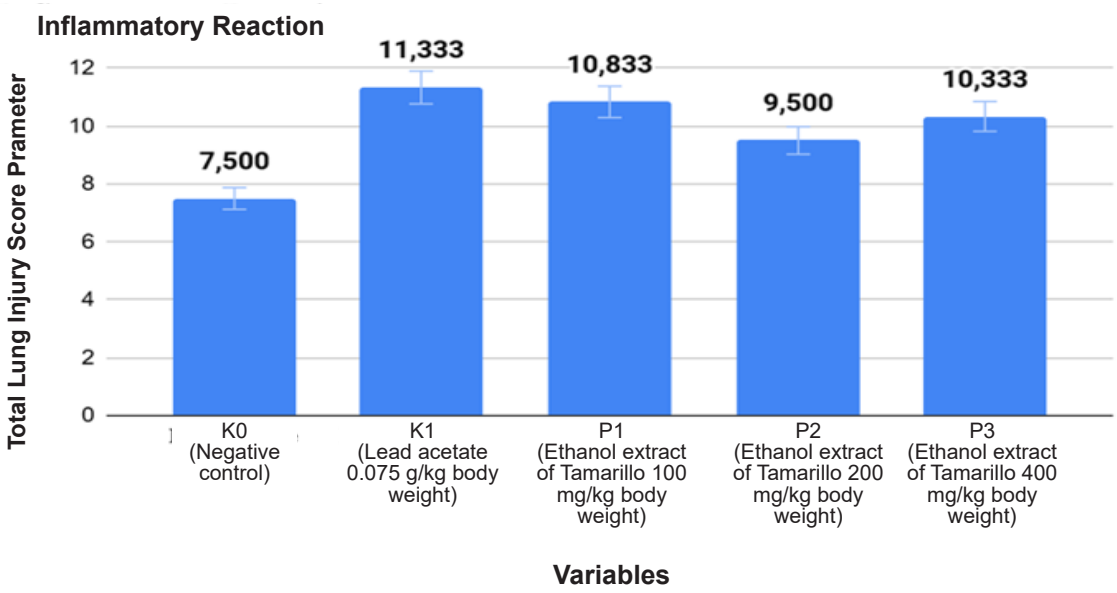

Figure 6 Comparison of the Five groups (K0, K1, P1, P2, and P3) in Total Lung Injury Scores

Note: Data were expressed as mean values. sum of 5 parameters: inflammatory cell infiltration, alveolar septal thickening, hemorrhage, intra-alveolar oedema, and pulmonary congestion) representing inflammatory response

to cause damage to various tissues, including the lung. This occurs through the induction of oxidative stress, lipid peroxidation, and inflammatory processes.[16] The body's compensatory response, to counteract lead-induced free radicals involves the GPx expression. As an endogenous antioxidant, GPx plays an essential role in protecting cells from oxidative stress. This mechanism is characterized by the synergistic action of superoxide dismutase (SOD) and catalase enzymes to form a system that reduces ROS. Its primary mode of action involves metabolizing hydrogen peroxide (H_2O_2).[17,18] Hydrogen peroxide (H_2O_2) plays a role in stimulating GPx gene expression,[19] and the increase in GPx levels after lead exposure reflects cellular efforts to counteract oxidative injury. Exposure of mice lung tissue to lead acetate stimulates endogenous antioxidant defense mechanisms. This mechanism is consistent with findings reporting a 57% increase in GPx expression in lungs of Wistar rats following lead exposure. This occurs because lead can enhance cellular stress responses, which increases GPx expression.[19]

The histopathological findings in this study also support the toxic effects of lead acetate. Hemorrhage is a primary marker of tissue injury, accompanied by inflammatory cell infiltration, septal thickening, intra-alveolar edema, and congestion. These findings align with previous studies demonstrating that the lungs are a primary target for lead accumulation due to their extensive soft tissue structure and high vascularization, making them susceptible to inflammatory and hemorrhage damage.[8,20]

Tamarillo (*Solanum betaceum*) contains potent antioxidant compounds, particularly flavonoids and anthocyanins that enhance endogenous antioxidants enzyme activity. In this study, tamarillo (*Solanum betaceum*) ethanol increases GPx expression in a dose-dependent manner, with the 400 mg/kg dose showing the strongest effect. High antioxidant activity of tamarillo (*Solanum betaceum*) fruit has been previously documented,[21] and the abundant anthocyanin content within the fruit has been shown to function as a direct substrate in neutralizing hydrogen peroxide.[22] This mechanism can explain the elevated GPx expression observed in treated groups and supports the protective effect of tamarillo (*Solanum betaceum*) extract against oxidative stress.

Tamarillo (*Solanum betaceum*) ethanol extract also reduces inflammatory responses descriptively, as indicated by lower total lung injury scores across treatment groups. The greatest reduction in total lung injury scores was found at the of 200 mg/kg dose, followed by 400 mg/kg and 100 mg/kg. However, these findings cannot confirm that either dose is truly effective. This may be due

to high doses of exogenous antioxidants can disrupt the balance between free radicals and endogenous antioxidant mechanisms, as well as physiological adaptive responses, thereby allowing inflammatory processes to occur in lung tissue.[23,24] Similar findings have been reported in studies where tamarillo (*Solanum betaceum*) ethanol extract did not produce significant changes in inflammatory cytokines such as IL-6, indicating incomplete suppression in inflammatory pathways.[25,26] This suggest that while tamarillo (*Solanum betaceum*) extract may partially reduces free radicals, pro-inflammatory cytokines may continue to induce changes in lung tissue, as reflected in the five parameters of inflammatory markers.[25,27] In future studies, the dosage used in this research will be further evaluated and converted to human-equivalent doses. This process requires additional investigations and systematic pharmacological and therapeutic conversion studies before proceeding to clinical trials.

Limitations of this study include the lack of further testing of anthocyanins for their anti-inflammatory and antioxidant effects in the lungs, leading to a primary focus on determining the appropriate dosage of tamarillo (*Solanum betaceum*). Furthermore, interaction mechanism between GPx and the inflammatory response was not evaluated, an area of the study that would benefit from including additional variables in future studies.

In conclusion, administration of tamarillo (*Solanum betaceum*) ethanol extract at a dose of 400 mg/kgBW significantly increases GPx expression in the lungs of mice exposed to lead acetate, although it did not significantly reduce overall inflammatory responses. A trend toward reduced inflammation was observed, particularly at the 200 mg/kg dose, suggesting potential protective effect requiring further investigation.

These findings underscore the potential value of tamarillo (*Solanum betaceum*) extract as a natural antioxidant source that may support lung health and reduce risk associated with environmental lead exposure. Incorporating nutrient-dense, antioxidant-rich foods such as tamarillo (*Solanum betaceum*) into dietary practices may provide a practical, plant-based strategy to enhance wellness and prevent toxin-related diseases. With further development into functional food products or supplements, tamarillo (*Solanum betaceum*) could serve as a valuable preventive intervention, particularly for vulnerable populations such as children, older adults, and individuals living in high exposure environments.

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Authors' Contributions

SH, RI, and AR contributed to the conception and construction of the research idea. The study methodology was planned by SH under the supervision of RI and AR. Overall project supervision was provided by RI, AR, and NF. Biological materials were provided by RI. Data collection was performed by SH and AR. Data management and statistical analysis were conducted by SH under the supervision of RI and AR. Data analysis and interpretation were carried out by SH. Critical review and intellectual refinement of the manuscript were performed by RI, AR, and NF.

Conflict of Interest

The authors declare no conflict of interest.

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