

ORIGINAL ARTICLE

The Potential of Ethanol Extract Tamarillo (*Solanum betaceum*) on B-Cell Lymphoma 2 Expression in Mice (*Mus musculus*) Lungs Exposed to Lead Acetate

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ABSTRACT

Introduction: Lead acetate, a toxic heavy metal compound, induces cellular and tissue injury primarily through oxidative stress. Exposure via inhalation or ingestion enables systemic absorption and distribution to target organs, particularly the lungs. One of the key anti-apoptotic proteins involved in maintaining cell survival is B-cell lymphoma 2 (Bcl-2). The administration of exogenous antioxidants represents a preventive approach to counteract the cytotoxic effects of lead, including the use of ethanol extract of tamarillo fruit. This study investigated the potential influence of tamarillo (*Solanum betaceum*) ethanol extract, known for its antioxidant content. Specifically, it examined its effect on Bcl-2 expression in the lung tissue of male mice exposed to lead acetate.

Methods: This study used a true experimental design in a controlled laboratory setting. The specimens were divided into five groups: K0 served as the negative control, while K1 acted as the positive control and was treated with lead acetate at a dose of 0.075 g/kgBW. Group P1, P2, and P3 received lead acetate combined with ethanol extract of tamarillo at doses of 100 mg/kgBW, 200 mg/kgBW, and 400 mg/kgBW, respectively.

Results: The findings showed that tamarillo ethanol extract significantly increased lung Bcl-2 expression in lead-exposed mice ($p < 0.05$). B-cell lymphoma 2 expression increased progressively with higher extract doses compared with the positive control group.

Conclusion: Administration of the tamarillo ethanol extract at 100 mg/kgBW was the most effective and provided protective effects on lung tissue.

INTRODUCTION

A healthy environment is free of pollution and contamination from substances that harm human health and other living organisms.¹ One of the contributing factors to the increasing environmental pollution in Indonesia is lead (Pb) exposure. Lead is a bluish-grey chemical compound classified as a heavy metal and is recognized as a major environmental pollutant.² Lead mining activities release dust and fine particles into the air, polluting the atmosphere and posing significant health hazards to populations living near mining areas.³ When inhaled, lead can exert toxic effects on lung cells

by increasing the formation of free radicals and reducing antioxidant defenses in the tissue. Exposure to lead in the environment has been linked to respiratory issues such as asthma. A previous study showed that children with higher blood lead levels often have higher immunoglobulin E (IgE) and eosinophil counts, suggesting a link between lead exposure and immune responses involved in asthma.⁴ Aside from asthma, lead exposure has been associated with various respiratory problems, such as chronic bronchitis, pneumonia, and even lung cancer. Continuous contact with lead can also

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disturb the digestive system, often leading to inflammation, tissue injury, and swelling in certain digestive organs.⁵

When lead is present, it tends to accelerate chemical reactions that produce unstable oxygen compounds that can damage cells.⁶ Lead can harm the lungs in several ways, mainly by triggering oxidative stress, causing inflammation, and initiating cell death processes.⁷ When inflammation occurs, the body releases cytokines and other substances that can worsen injury to lung tissue. Oxidative stress produces free radicals that damage lung cells and induce cell death. In older adults, lead exposure has been linked to a higher risk of developing interstitial lung disease and lung cancer.⁸ Alterations in apoptotic pathways are often observed in cancerous cells. High B-cell lymphoma 2 (Bcl-2) expression in patients is generally associated with poor prognosis, including increased risk of mortality and recurrence.⁹ This suggests that Bcl-2 may serve as a useful prognostic marker in cancer. It is a key regulatory protein involved in apoptosis, promoting cell survival by inhibiting programmed cell death.¹⁰ When reactive oxygen species (ROS) accumulate in the body, they can induce oxidative stress and cellular impairment. Although the body has endogenous antioxidants to counteract ROS, exogenous antioxidants are also needed to enhance antioxidant defense mechanisms. Tamarillo (*Solanum betaceum*) is one potential source of exogenous antioxidants.

In Indonesia, tamarillo is commonly known as *terong menen* and is widely found in North Sumatra.¹¹ The flavonoids present in tamarillo peel (*S. betaceum*) act as natural antioxidants capable of inhibiting free radical formation in the body.¹² This study investigated the potential influence of tamarillo (*S. betaceum*) ethanol extract, known for its antioxidant content. Specifically, it examined its effect on Bcl-2 expression in the lung tissue of male mice exposed to lead acetate.

METHODS

This study used a true experimental, post-test-only, control-group design and was conducted at the Biomedical and Anatomical Pathology Laboratories, Faculty of Medicine, Universitas Airlangga, Surabaya, from March to October 2024.

Data Collecting and Processing

The samples consisted of 25 healthy male mice (*Mus musculus*), aged 8-12 weeks old and weighing 25-30 g. All experimental mice were randomly assigned to five groups of five animals using simple random sampling. After 35 consecutive days of treatment, all animals were euthanized, and their lung tissues were

collected as paraffin-embedded blocks for further analysis. The treatment groups were as follows, with all substances administered orally: K0 (negative control) obtained 0.1 mL distilled water; K1 (positive control) was administered lead acetate at 0.075 g/kgBW; P1 received a combination of lead acetate (0.075 g/kgBW) and ethanol extract of *S. betaceum* at 100 mg/kgBW; P2 received lead acetate (0.075 g/kgBW) and *S. betaceum* extract at 200 mg/kgBW; and P3 received lead acetate (0.075 g/kgBW) and *S. betaceum* extract at 400 mg/kgBW.

The main materials used in this study included lead acetate, ethanol extract of *S. betaceum* (obtained via maceration using 90% ethanol), the primary antibody Bcl-2 (Santa Cruz Biotechnology), secondary antibody, hematoxylin and eosin stain, and supporting materials such as 10% buffered formalin, alcohol series, xylol, and paraffin. Equipment used included a light microscope, microtome, oven, water bath, micropipettes, and a digital camera.

The expression of Bcl-2 was analyzed by immunohistochemistry. The procedure followed a standard protocol that included deparaffinization, rehydration, antigen retrieval, blocking, incubation with primary and secondary antibodies, chromogen application, and counterstaining. The expression of Bcl-2 was observed under a microscope at 400× magnification and quantified using the H-score method: $H\text{-score} = (0 \times \text{percentage of cells with intensity } 0) + (1 \times \text{percentage of cells with intensity } 1+) + (2 \times \text{percentage of cells with intensity } 2+) + (3 \times \text{percentage of cells with intensity } 3+)$. The interpretation of the H-score was categorized as follows: negative (0-49), weak positive (50-100), moderate positive (101-200), and strong positive (201-300).¹³

Data Analysis

Data analysis was conducted using the International Business Machines Corporation (IBM) Statistical Package for the Social Sciences (SPSS) version 23. Normality of the data was examined using the Shapiro-Wilk test, while variance homogeneity was determined with Levene's test. Differences among the five groups were assessed using one-way analysis of variance (ANOVA), followed by least significant difference (LSD) post hoc testing if significant differences were found. The ANOVA was chosen because the data were normally distributed and the variances were homogeneous across groups.

Ethical Approval

Ethical approval was obtained from the Health Research Ethics Committee, Faculty of Medicine,

Universitas Airlangga (No. 188/EC/KEPK/FKUA/2024) on 21 November 2024.

RESULTS

Statistical Analysis of Tamarillo (*Solanum betaceum*) Ethanol Extract Administration on B-Cell Lymphoma 2 Expression in Mouse Lungs Exposed to Lead Acetate

Normality was evaluated using the Shapiro-Wilk test ($p > 0.05$ denoted a normal distribution). After confirming data normality, Levene's test for homogeneity was performed to evaluate variance homogeneity, and $p > 0.05$ was considered homogeneous. Subsequently, to compare the treatment groups, a one-

way ANOVA was performed, with $p < 0.05$. If the ANOVA result was significant, the group differences identified by ANOVA were subsequently examined using an LSD post hoc test, which showed meaningful differences among specific treatment groups.

The effect of lead acetate exposure on Bcl-2 expression was assessed by comparing Bcl-2 expression in the lead acetate-treated group (K1) with that in the negative control group (K0), which received distilled water as the only treatment. Meanwhile, the impact of varying concentrations of tamarillo (*S. betaceum*) ethanol extract was evaluated by analyzing Bcl-2 expression across the experimental groups P1, P2, and P3.

Table 1. Descriptive data on the outcome of lead acetate on B-cell lymphoma 2 expression in mouse lung tissue

Treatment Group	Mean of Replicate Values	Standard Deviation	Minimum-Maximum	Shapiro-Wilk Test	Levene's Test
K0	250.00	7.071	240-260	.325	1.957
K1	216.00	8.216	205-225	.490	
P1	239.00	13.874	225-260	.656	
P2	245.00	7.071	235-255	.325	
P3	248.00	14.832	235-270	.391	

Shapiro-Wilk test ($p > 0.05$) and Levene's test ($p > 0.05$) indicated that the data were normally distributed and had homogeneous variances across groups

According to Table 1, the normality test indicated that the data were normally distributed ($p > 0.05$). As shown in the homogeneity test, all groups exhibited p -values exceeding 0.05 ($p > 0.05$), suggesting that the data met the criterion of variance homogeneity. The administration of different doses of tamarillo (*S. betaceum*) ethanol extract showed statistically significant differences between groups. The treatment group receiving 400 mg/kgBW exhibited the highest Bcl-2 expression compared with the 100 mg/kgBW and 200 mg/kgBW groups, as demonstrated by the mean values. The highest Bcl-2 expression was observed in K0 with a mean score of 250, followed by P3 with 248, P2 with 245, P1 with 239, and K1 showing the minimum score of 216.

Because the data met the requirements for normality and equal variance ($p > 0.05$), the analysis proceeded to compare Bcl-2 expression across groups. If the significance value was much lower than 0.05, it indicated that at least one group differed significantly from the others. The results revealed a significant association between Bcl-2 expression and the treatment groups ($p < 0.001$). Following the significant ANOVA, pairwise comparisons were analyzed using the LSD test. The purpose of this test was to conduct pairwise comparisons between groups to identify which specific groups exhibited statistically significant differences in Bcl-2 expression.

Table 2. Post-hoc analysis of B-cell lymphoma 2 expression across treatment doses using the least significant difference test

Treatment Group		Sig.
K0	K1	<.001*
	P1	.122
	P2	.471
	P3	.772
K1	K0	<.001*
	P1	.003*
	P2	<.001*
	P3	<.001*
P1	K0	.122
	K1	.003*
	P2	.389
	P3	.201
P2	K0	.471
	K1	<.001*
	P1	.389
	P3	.664
P3	K0	.772
	K1	<.001*
	P1	.201
	P2	.664

*Statistically significant differences

The findings in Table 2 ($p < 0.05$) indicated significant differences in Bcl-2 expression between the control group (K0) and the negative control group (K1), and between K1 and all treatment groups (P1, P2, and P3). Moreover, pairwise comparisons showed significant differences between P1 and K1, P2 and K1, and P3 and K1.

Immunohistochemical Profile of B-Cell Lymphoma 2 in Mouse Lung Tissue across Treatment Groups

B-cell lymphoma 2 expression was analyzed by examining stained tissue sections under a light microscope at 400× magnification. The results were presented as percentages of the intensity of cytoplasmic brown staining in alveolar cells. Evaluation of Bcl-2 immunostaining was performed by classifying staining intensity into four categories: 0 (no staining), 1 (weak), 2 (moderate), and 3 (strong). The data were then quantified using the H-score, a semi-quantitative method that integrates staining intensity and the proportion of positive cells to assess Bcl-2 expression in lung tissue.

Based on the immunohistochemical observation of Bcl-2 expression (Figure 1), image A showed a negative intensity (0), indicating undetectable Bcl-2 expression, characterized by the absence of brown staining in the cytoplasm of alveolar cells. Image B represented weak intensity (1), indicating low Bcl-2 expression, with light brown staining faintly visible in

the cytoplasm of alveolar cells. Image C showed moderate intensity (2), characterized by more prominent, evenly distributed brown staining in the cytoplasm compared with the weakly stained cytoplasm. Meanwhile, image D showed strong intensity (3), indicating high Bcl-2 expression, with dense, widespread dark brown cytoplasmic staining in alveolar cells.

B-Cell Lymphoma 2 Expression Results in Each Treatment Group

Immunohistochemical evaluation was performed to analyze Bcl-2 expression in mouse lung tissue and was quantified semi-quantitatively using the H-score system. As shown in Figure 2, the mean Bcl-2 expression values obtained from five replicates in each group were 250 in K0 (negative control), 216 in K1 (positive control), 239 in P1, 245 in P2, and 248 in P3. These average scores indicated variation among groups and might serve as a basis for evaluating the effects of the treatments on Bcl-2 levels.

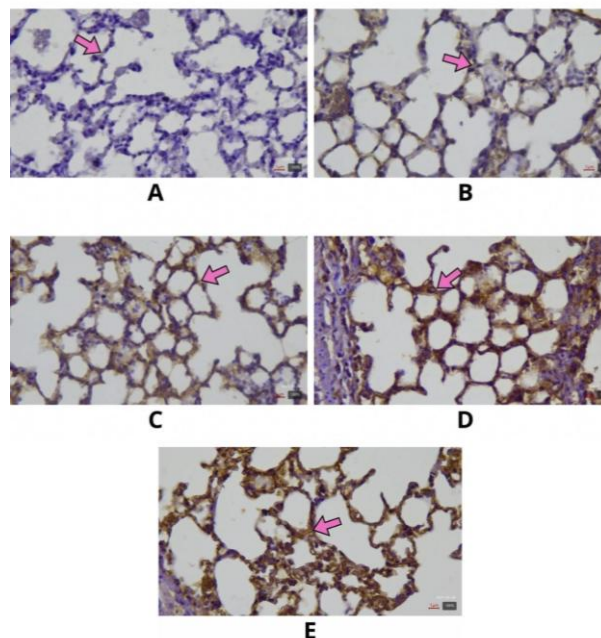


Figure 1. B-cell lymphoma 2 (Bcl-2) immunostaining was observed under a light microscope at 400× magnification. This figure illustrates the intensity categories used as references in H-score calculations. A) Negative intensity was obtained from group K1; B) weak intensity from group P1; C) moderate intensity from group P2; D) strong intensity from group K0; and E) strong intensity from group P3. Arrows indicate the cytoplasmic localization of Bcl-2 expression in the alveolar cells of mouse lung tissue. Note: K0=negative control; K1=lead acetate 0.075 g/kgBW; P1=tamarillo ethanol extract 100 mg/kgBW+lead acetate 0.075 g/kgBW; P2=tamarillo ethanol extract 200 mg/kgBW+lead acetate 0.075 g/kgBW; P3=tamarillo ethanol extract 400 mg/kgBW+lead acetate 0.075 g/kgBW

Bcl-2 expression (mean)

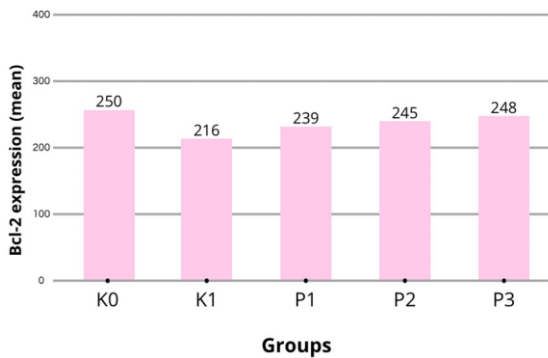


Figure 2. The effect of tamarillo (*Solanum betaceum*) ethanol extract on B-cell lymphoma 2 expression in mice exposed to lead acetate

DISCUSSION

Tamarillo (*S. betaceum*) contains anthocyanins that act as antioxidants and help protect cells from oxidative stress.¹⁴ Anthocyanins help protect cells by reducing the damage caused by reactive oxygen compounds.¹⁵ Lead acetate was applied to trigger oxidative stress in the lungs. It increases oxygen radicals by upsetting mitochondrial balance, stimulating enzyme activity, and lowering the cell's natural defense against oxidation.¹⁶ B-cell lymphoma 2 is an anti-apoptotic protein that prevents cell death by blocking activation of caspases, enzymes that break down cellular proteins during apoptosis.¹⁷ Lead exposure increases oxidative stress by elevating ROS levels and reducing Bcl-2 protein levels in cells.¹⁸ When ROS levels rise because of lead exposure, antioxidants from the body and from sources like tamarillo can help neutralize them and increase Bcl-2 levels. Table 1 shows that giving tamarillo extract led to higher Bcl-2 expression in groups P1, P2, and P3, with the average scores increasing across all treatment groups.

Comparison between the Negative Control Group (K0) and the Positive Control Group (K1)

The effect of lead acetate exposure on Bcl-2 expression was evaluated by comparing K1, which received lead acetate, with the negative control group (K0), which received distilled water. The negative control group (K0) showed the highest mean Bcl-2 expression, indicating that the pulmonary cells were in a physiologically normal state with optimal cellular conditions and the highest anti-apoptotic activity. In contrast, the positive control group (K1), exposed to lead acetate at a dose of 0.075 g/kgBW, exhibited the lowest mean Bcl-2 expression. This finding confirms that lead exposure significantly decreases Bcl-2 expression.

As shown in Figure 2, Bcl-2 expression in the negative control group (K0) averaged 250, indicating a

normal physiological condition without oxidative stress. In the K1 group, Bcl-2 expression decreased to 216, indicating the harmful effects of lead acetate exposure. This decline suggests that lead-induced oxidative stress disrupted the balance between proteins that promote and those that prevent apoptosis, thereby increasing the likelihood of cell death.

The findings from this study are consistent with and build upon results reported in previous studies. Chen, *et al.* (2023) found that lead exposure in the rat hippocampus caused lasting changes in the regulation of apoptosis-related markers, including Bcl-2, Bcl-2-associated X protein (BAX), and Caspase-3.¹⁹ These changes suggest increased cell death driven by oxidative stress. Similarly, Akaras, *et al.* (2024) observed that exposure to lead acetate could increase the rate of cell death in lung tissue.⁷ Their findings showed that rats exposed to lead acetate had higher expression of BAX, apoptotic protease-activating factor-1 (Apaf-1), and Caspase-3, genes that trigger apoptosis. In contrast, Bcl-2 expression, which normally helps prevent cell damage, was noticeably reduced. The decrease in Bcl-2 suggests that exposure to lead acetate induces lung tissue damage by promoting oxidative stress and triggering apoptosis.

Comparison between the Positive Control Group (K1) and the Treatment Groups (P1, P2, P3)

Flavonoids, anthocyanins, and phenolic acids, key natural antioxidants, contribute to cellular defense mechanisms against oxidative damage found in tamarillo (*S. betaceum*). Their effects are dose-dependent, meaning the biological response increases with higher doses administered.²⁰ The primary mechanisms of these compounds involve their ability to neutralize free radicals, reduce oxidative stress, and suppress apoptotic pathways. They enhance the expression of anti-apoptotic markers, such as Bcl-2, while suppressing pro-apoptotic markers, including BAX and Caspase-3.

As shown in Figure 2, the positive control group (K1) exposed to lead acetate at 0.075 g/kgBW showed a Bcl-2 expression level of 216. In contrast, the treatment groups that received the same dose of lead acetate along with tamarillo ethanol extract showed a progressive increase in Bcl-2 expression with increasing extract dose: P1 at 239, P2 at 245, and P3 at 248. These data demonstrate that although lead acetate reduced Bcl-2 expression in the positive control group, tamarillo ethanol extract significantly improved it, particularly at higher doses. The higher the extract dose, the greater the increase in Bcl-2 expression, demonstrating a protective role that increased proportionally with the administered dose and apoptosis in the lung tissue of lead-induced

mice.

This finding is supported by the study of Vannuchi, *et al.* (2025), who reported that ethanol extract of tamarillo (*S. betaceum*) fruit peel effectively reduced blood glucose levels in male white rats with a diabetes model, while providing cellular protection via antioxidant-mediated modulation of anti-apoptotic proteins, notably Bcl-2.²¹ It is also supported by Silva, *et al.* (2024), who found that tamarillo extract prepared with 80% ethanol contains several phenolic and flavonoid compounds that act as strong antioxidants.²² These substances can reduce the growth of cancer cells and trigger both apoptosis and cell cycle arrest. The flavonoids in the extract may affect Bcl-2 expression via the p53 pathway, helping cells withstand oxidative stress and limit damage. The mechanism is likely related to the antioxidant properties of these compounds, which help limit ROS formation and stimulate signaling pathways that promote cellular survival.²³

Comparison between the Negative Control Group (K0) and the Treatment Groups (P1, P2, P3)

As shown in Table 1, K0 exhibited a Bcl-2 expression level of 250. This value reflects the physiological expression of the anti-apoptotic gene in lung tissue under normal conditions, without oxidative stress or exposure to toxic agents, representing a healthy tissue state. In contrast, treatment groups receiving tamarillo (*S. betaceum*) ethanol extract alongside lead acetate exposure (0.075 g/kgBW) demonstrated increased Bcl-2 expression in a dose-dependent manner. According to Figure 2, group P1 (100 mg/kgBW) showed an expression level of 239, P2 (200 mg/kgBW) was 245, and P3 (400 mg/kgBW) reached 248. Although all three treatment groups showed markedly higher Bcl-2 expression than the lead-exposed positive control group, the differences among the three extract doses were not statistically significant. This suggests that 100 mg/kg BW was already effective in enhancing Bcl-2 expression, as higher doses yielded only nominal gains. Therefore, tamarillo extract showed a protective effect on lung tissue subjected to lead-induced oxidative stress, and the highest dose of 400 mg/kgBW nearly restored Bcl-2 expression to physiological levels, similar to the lowest effective dose.

Wahidah, *et al.* (2024) found that *S. betaceum* extract effectively reduced oxidative stress, as indicated by lower malondialdehyde (MDA) levels in the testes of mice treated with lead acetate.²⁴ This reduction in MDA indicates a potent antioxidant effect of the extract. Physiologically, decreased oxidative stress is associated with higher levels of anti-apoptotic markers such as Bcl-2, since lower oxidative pressure tends to preserve cell survival through anti-apoptotic pathways. In that study,

mice were assigned to five groups, three of which received graded doses of tamarillo extract: 100 mg/kgBW (P1), 200 mg/kgBW (P2), and 400 mg/kgBW (P3).²⁴ The results showed that although MDA levels decreased, indicating a likely increase in Bcl-2 expression in all treatment groups, the expression level in group P3 (400 mg/kgBW) still did not reach the level observed in the negative control group.²⁴ These results support this study, showing that tamarillo ethanol extract can help protect lung tissue from lead-induced damage. A dose of 400 mg/kg BW may be insufficient to fully restore Bcl-2 levels to normal.

Zakiah, *et al.* (2020) reported that giving male mice daily doses of tamarillo (*S. betaceum*) extract at 100, 200, and 400 mg/kgBW for 35 days showed that the 100 mg/kg BW dose was most effective in increasing sperm concentration.²⁵ These results suggest that *S. betaceum* may help protect against lead-induced damage, particularly to reproductive organs. Higher doses of 200 and 400 mg/kg BW were tested, but did not improve the results compared with the 100 mg/kg BW dose. This study lays the groundwork for future research on whether *S. betaceum* extract can protect other organs from lead-induced damage, such as the lungs, by regulating Bcl-2, a gene that plays a key role in controlling cell death.

LIMITATIONS OF THE STUDY

This study has several limitations. The inflammatory response and increased ROS due to pulmonary diseases such as chronic obstructive pulmonary disease (COPD) and pneumonia involve complex biological factors that cannot be fully controlled. In addition, the level of psychological stress that may exacerbate inflammation varies among individual subjects.

CONCLUSION

These results show that the ethanol extract of *S. betaceum* can increase Bcl-2 levels in the lung tissue of mice exposed to lead acetate. All treatment groups receiving the extract showed significantly higher Bcl-2 levels than the positive control, confirming its protective effect. Among the administered doses, 100 mg/kgBW was the most effective in promoting Bcl-2 expression, indicating its optimal mitigation of lead-induced pulmonary damage. However, the absorption of lead acetate involves a complex interplay of physiological factors that may vary among individuals or experimental animals. These factors could not be entirely isolated or controlled in this study, making direct measurement of lead absorption challenging.

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Artificial Intelligence (AI) Declaration Statement

The authors used artificial intelligence (AI)-assisted tools (e.g., language editing and grammar checking) in the preparation of this manuscript. The content and interpretations remain the sole responsibility of the authors.

Conflict of Interest

The authors declared there is no conflict of interest.

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None declared.

Authors' Contributions

Developing the concept of the study and experimental design, acquiring and assembling data, interpreting data analysis and results, drafting and revising the manuscript, conducting statistical evaluation, providing study materials, and managing administrative, technical, and logistical support: CMPI, HWS, RI, MQA. All authors contributed and approved the final version of the manuscript.

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