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Original Research Article

Dose-Response Evaluation of *Blumea balsamifera* Leaf Ethanol Extract in Acute and Subchronic Toxicity Models in Mice for Sustainable Application

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ABSTRACT

Blumea balsamifera is widely used in traditional medicine, yet its safety profile remains inadequately characterized. This study aimed to assess the dose-dependent toxicity of *Blumea balsamifera* leaf ethanol extract (BBEE) through acute (14 days) and subchronic (90 days) oral exposure in Swiss albino mice at doses ranging from 100 to 5000 mg/kg, including recovery groups to evaluate reversibility. Toxicological endpoints included body weight, food intake, organ weights, hematological indices, serum biochemistry, and urinalysis. High BBEE doses significantly reduced body weight gain ($5.3 \pm 1.6\%$ vs. $40.5 \pm 2.2\%$, $p = 0.007$) and food intake ($R^2 = 0.9966$), and increased relative liver ($r = 0.991$) and kidney ($r = 0.985$) weights ($p < 0.01$). Notable elevations were observed in RBC ($8.55 \pm 0.13 \times 10^6$/mm³, $p = 0.012$), creatinine ($r = 0.846$, $p = 0.014$), BUN ($r = 0.926$, $p = 0.009$), and urinary pH ($r = 0.973$, $p = 0.007$). However, all alterations were dose-dependent and fully normalized in satellite groups ($p > 0.05$). Overall, BBEE induced reversible physiological and biochemical changes at high doses, while lower doses were well tolerated. These findings support the safe use of BBEE at moderate levels and its potential for further development as a sustainable natural product.

Key words: *Blumea Balsamifera*, Dose-Response Relationship, Acute Toxicity, Subchronic Toxicity, Ethanol Extract, Murine Model, Safety Evaluation

Introduction

Medicinal plants have garnered increasing attention as sources of bioactive compounds with therapeutic potential and lower adverse effects compared to synthetic drugs[1]. *Blumea balsamifera* (L.) DC., a member of the Asteraceae family, is widely used in Southeast Asian traditional medicine for its reported antioxidant, anti-inflammatory, and antimicrobial activities[2]. Ethanol extracts of *B. balsamifera* leaves have been shown to contain flavonoids, terpenoids, and essential oils that contribute to its pharmacological effects[3]. Despite its ethnobotanical significance and increasing commercial use in herbal formulations, the safety profile of *B. balsamifera*, particularly in standardized extract form, remains underexplored. Establishing the dose-dependent toxicity thresholds is essential to ensure their safe application in health-related products. While previous studies have demonstrated the therapeutic efficacy of *B. balsamifera*[4], data on its systemic effects under acute and subchronic exposure conditions remain limited. This study was therefore designed to evaluate the toxicity profile of *B. balsamifera* leaf ethanol extract (BBEE) in mice using standardized acute and subchronic models, including recovery (satellite) groups. The study focused on physiological, hematological, biochemical, and urinary parameters and applied dose-response analysis to determine the correlation between BBEE exposure and systemic alterations, thereby providing a scientific basis for its sustainable medicinal application.

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Materials and methods

Plant material and extract preparation

Fresh leaves of Blumea balsamifera L. (DC) were collected in November 2024 from Cam Thuy district, Dong Nai province, Vietnam (10.9830°N, 107.2531°E). The plant was taxonomically identified by Dr. Minh Thao Nguyen, and a voucher specimen (BB0121124VST) was deposited at the Biotechnology Laboratory, Institute of Biotechnology and Food Technology, Industrial University of Ho Chi Minh City, Vietnam. After shade-drying, 1.2 kg of powdered leaves were extracted with 10 L of 70% ethanol using a Soxhlet apparatus for 8 hours. The extract was filtered and concentrated under reduced pressure at 45°C to yield 89.6 g of crude B. balsamifera ethanol extract (BBEE), which was stored at 4°C until further use.

Experimental animals

The Swiss albino mice (25-30 g) were obtained from the Pasteur Institute, Ho Chi Minh City, Vietnam. Animals were acclimatized for seven days in standard laboratory conditions (24 ± 2 °C, 55-60% relative humidity, 12-hour light/dark cycle) with access to standard pellet diet and filtered water *ad libitum*. The study was approved by the Ethics Committee of the University and conducted under the OECD Guidelines for the Testing of Chemicals and the International Guiding Principles for Biomedical Research Involving Animals.

Experimental design

Mice were randomly divided into control, treatment, and satellite groups. For acute toxicity assessment, BBEE was administered orally at doses of 1000, 3000, and 5000 mg/kg, and animals were monitored for 14 days. For subchronic evaluation, BBEE was administered daily at 100, 300, and 500 mg/kg for 90 days. Satellite groups corresponding to the highest doses were observed for an additional 28 days post-treatment to assess recovery.

Body weight and food intake

Body weight, food consumption, and water intake were recorded weekly. Percent weight gain and average daily intake were calculated and compared among groups[5].

Relative organ weight
After euthanasia, major organs were excised, blotted, and weighed. Relative organ weight (organ-to-body weight ratio) was calculated to assess organ-specific responses[6].

Hematological analysis
Blood samples were collected via cardiac puncture under mild anesthesia. Hematological parameters, including RBC, WBC, hemoglobin, hematocrit, and platelet count, were determined using an automated hematology analyzer[7].

Serum biochemistry
Serum was isolated from coagulated blood by centrifugation. Parameters analyzed included alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, blood urea nitrogen (BUN), total protein, and albumin, measured using commercial diagnostic kits[7].

Urinalysis
Urine was collected using metabolic cages. Parameters such as pH, ketone bodies, and electrolytes (Na^+, K^+, Cl^-) were measured using dipsticks and ion-selective electrode methods[8].

Statistical analysis
Data were expressed as mean ± standard deviation (SD). One-way ANOVA followed by Tukey's post hoc test was used for multiple comparisons. Pearson's correlation and linear regression were employed to assess dose-response relationships. Statistical significance was set at $p < 0.05$.

Results and Discussion

Yield and phytochemical composition of BBEE
The ethanol extraction of *Blumea balsamifera* leaves (BBEE) yielded a high extraction efficiency, indicating favorable solvent compatibility for phytochemical recovery. As presented in Table 1, BBEE contained multiple classes of bioactive compounds, including flavonoids, terpenoids, polyphenols, alkaloids, saponins, and steroids, while cardiac glycosides were not detected. Among the quantified constituents, antioxidant-associated groups were predominant, supporting the extract's suitability for further investigation in dose-response toxicity models.The diverse phytochemical profile of BBEE, particularly the presence of flavonoids, polyphenols, terpenoids, and alkaloids, contributes to the biological activities observed in acute and subchronic models.

Table 1: Qualitative and quantitative phytochemical composition of BBEE

Phytochemical	Presence	Content (mg/g extract)
Flavonoids	+	40.78 ± 1.19[a]
Terpenoids	+	63.56 ± 1.63[a]
Polyphenols	+	68.45 ± 1.52[a]
Alkaloids	+	4.54 ± 0.14[a]
Saponins	+	NT[b]
Steroids	+	NT[b]
Cardiac glycosides	−	—

Note: (+) present, (−) absent, NT: not tested. [a]Values expressed as mean ± SD of three replicates. [b]Quantitative analysis not conducted.

These compounds are known to modulate oxidative stress, inflammatory signaling, and detoxification pathways, which account for protective and adaptive systemic effects at varying exposure levels[9]. Prior studies have similarly reported comparable chemical profiles in *B. balsamifera* leaf extracts, validating the consistency of bioactive content across different extraction protocols[10]. This compositional background provides a mechanistic rationale for the observed dose-dependent outcomes, especially concerning antioxidant and immunomodulatory effects.

Body weight and food intake
A significant inverse correlation was observed between BBEE administration and body weight gain, as well as food intake, in both acute and subchronic exposure models. As shown in Table 2, mice treated with BBEE exhibited dose-dependent reductions in weight gain and food consumption, supported by linear regression analysis and strong statistical correlations. Time-course data (Figure 1) and daily food intake profiles (Figure 2) further corroborate these trends. Notably, recovery was evident in the satellite groups, with body weight and intake parameters returning to levels comparable to controls post-treatment. These findings suggest that BBEE exerts modulatory effects on energy metabolism or appetite regulation, potentially mediated by its phytochemical constituents[11]. Compounds such as flavonoids and terpenoids are reported to influence satiety pathways, gastrointestinal function, and metabolic efficiency, which account for the observed reductions in food intake and weight gain[12]. Similar effects have been documented with other plant-derived extracts, such as *Hedyotis capitellata* and *Morus alba*[13,14]. The normalization of these parameters in the recovery groups highlights the transient and non-lethal nature of these effects, supporting the safety of BBEE under defined exposure conditions.

Relative organ weights
BBEE administration led to dose-dependent increases in relative liver weight (RLW) and relative kidney weight (RKW), as indicated in Tables 3A and 3B. Statistically significant positive correlations were observed across both low- and high-dose groups. Elevated RLW and RKW were detected in all treatment groups compared to controls. In contrast, satellite groups displayed normalized organ weights after the recovery phase. These findings are visually supported by the regression analyses presented in Figures 3 and 4.The increases in RLW and RKW represent adaptive physiological responses to phytochemical exposure. The liver, being a primary site of xenobiotic metabolism, undergoes hypertrophy due to increased enzymatic activity or transient cellular proliferation[15]. Similarly, kidney enlargement reflects compensatory excretory mechanisms[16]. Such changes are commonly associated with reversible functional adaptation rather than overt organ damage and have been reported in previous studies involving plant extracts[17,18]. The normalization in satellite groups underscores the non-cumulative nature of these responses.

Hematological parameters
BBEE treatment resulted in dose-dependent modulation of hematological indices. Table 4 summarizes the key findings, with RBC counts showing a significant positive correlation with increasing doses. Platelet (PLT) and white blood cell (WBC) counts also demonstrated dose-associated elevations, as depicted in Figures 5 and 6. These alterations were not sustained in the satellite groups, which showed hematological values comparable to controls by the end of the observation period. These hematological effects suggest an immunomodulatory and hematopoietic influence of BBEE, mediated by flavonoids and other phytoconstituents known to support erythropoiesis, leukopoiesis, and platelet function[19]. The underlying mechanisms involve cytokine modulation, antioxidant protection, and marrow stimulation[20]. Similar effects have been noted in the context of other phytomedicines[21,22]. The reversal of these effects supports the hematological safety of BBEE within the tested dosage range.

Serum biochemistry
As shown in Tables 5A and 5B, BBEE-treated groups exhibited dose-dependent variations in key serum biochemical markers, particularly AST, ALT, BUN, and creatinine. BUN levels showed a consistent linear increase with dose (Figure 8), while AST and ALT were variably elevated. All biochemical indices returned to baseline in the satellite groups, as seen in Figure 7. These findings suggest that BBEE induces a mild and reversible hepatic and renal response, potentially through transient modulation of

Table 2: Weight gain and dose-response in BBEE-treated mice

Group	Dose range (mg/kg)	Mean ± SD of WG (%)	R^2	R	p-value	Correlation	Comparison to control
Control	0	40.5 ± 2.2	—	—	—	Reference	—
Low-dose group	100–500	25.6 ± 3.1	0.995	–0.987	0.012	↓↓	Different
Satellite 500 (Recovery)	(500)	39.8 ± 2.0	—	—	—	Normalized	NS (p > 0.05)
High-dose group	1000–5000	5.3 ± 1.6	0.998	–0.959	0.007	↓↓	Different
Satellite 5000 (Recovery)	(5000)	40.1 ± 2.4	—	—	—	Normalized	NS (p > 0.05)

R^2 and Pearson's correlation coefficients (r) were calculated for dose-dependent trends. NS: not significant (p > 0.05). "↓↓" indicates a strong negative correlation. Values are expressed as mean ± SD (n = 6).

Table 3A: Dose-response of relative liver weight in BBEE groups

Group	Dose range (mg/kg)	Mean ± SD of RLW (%)	R^2	r	p-value	Correlation	Comparison to control
Control	0	14.3 ± 0.2	—	—	—	Reference	—
Low-dose group	100-500	15.0 ± 0.3	0.996	+0.988	0.010	↑↑	Different
Satellite 500	Recovery (500)	39.8 ± 2.0	—	—	—	Normalized	NS (p > 0.05)
High-dose group	1000-5000	14.1± 0.2	0.998	+0.991	0.006	↑↑	Different
Satellite 5000	Recovery (5000)	14.2 ± 0.3	—	—	—	Normalized	NS (p > 0.05)

R^2 and r represent linear regression and Pearson's correlation, respectively. Values are mean ± SD (n = 6).

Table 3B: Dose-response of relative kidney weight in BBEE groups

Group	Dose range (mg/kg)	Mean ± SD of RKW (%)	R^2	r	p-value	Correlation	Comparison to control
Control	0	3.1 ± 0.1	—	—	—	Reference	—
Low-dose group	100-500	3.4 ± 0.1	0.992	+0.987	0.015	↑↑	Different
Satellite 500	Recovery (500)	3.5 ± 0.1	—	—	—	Normalized	NS (p > 0.05)
High-dose group	1000-5000	3.8 ± 0.2	0.996	+0.985	0.009	↑↑	Different
Satellite 5000	Recovery (5000)	4.2 ± 0.1	—	—	—	Normalized	NS (p > 0.05)

"↑↑" indicates strong positive correlation. NS: not significant (p > 0.05). Values are mean ± SD (n = 6).

metabolic enzymes or oxidative pathways[23]. This is consistent with previous reports on *Olea europaea* and *Castanopsis costata*, where plant extracts induced temporary increases in liver and kidney biomarkers that normalized post-exposure[24,25]. The observed trends reinforce the extract's safety margin when used within therapeutic dosing limits.

Urinalysis

Urinary parameters, including ketone concentration and pH, displayed dose-dependent alterations following BBEE treatment. Table 6 and Figure 10 illustrate strong positive correlations between BBEE dose and urinary ketone and pH values. In addition, BBEE exposure was associated with transient increases in urinary electrolytes (Na^+, K^+, Cl^-), as depicted in Figure 9. All changes reverted to baseline levels in satellite groups following withdrawal. The urinary effects observed stem from the diuretic or metabolic influences of BBEE constituents. Flavonoids and essential oils are known to modulate renal ion exchange, acid-base balance, and mitochondrial metabolism[26]. The elevated ketone levels and pH shifts are indicative of increased fatty acid oxidation and temporary renal stress[27]. The full recovery observed in the satellite groups confirms the extract's reverse effect on renal function[28]. Similar patterns have been observed in studies involving *Ginkgo biloba* and *Vaccinium macrocarpon*, supporting the mechanistic plausibility of the current findings and the renal safety of BBEE under controlled administration[29,30].

Table 4: Dose-response of RBC in BBEE groups

Group	Dose range (mg/kg)	Mean ± SD of RBC ($\times 10^6$ cells/mm^3)	R^2	r	p-value	Correlation	Comparison to control
Control	0	8.33 ± 0.18	—	—	—	Reference	—
Low-dose group	100-500	8.63 ± 0.39	0.961	0.992	0.039	↑↑	Different
Satellite 500	Recovery (500)	8.35 ± 0.26	—	—	—	Normalized	NS ($p > 0.05$)
High-dose group	1000-5000	8.55 ± 0.13	0.988	0.979	0.012	↑↑	Different
Satellite 5000	Recovery (5000)	8.44 ± 0.11	—	—	—	Normalized	NS ($p > 0.05$)

R^2 and *r* represent linear regression and Pearson's correlation coefficients, respectively. "↑↑" indicates strong positive correlation. NS: not significant ($p > 0.05$). Values are expressed as mean ± SD (n = 6).

Table 5A: Dose-response of AST levels in BBEE groups

Group	Dose range (mg/kg)	Mean ± SD of AST (U/L)	R^2	r	p-value	Correlation	Comparison to control
Control	0	99.55 ± 2.99	—	—	—	Reference	—
Low-dose group	100-500	112.00 ± 3.38	0.799	0.836	0.078	↑↑	Different
Satellite 500	Recovery (500)	101.05 ± 1.71	—	—	—	Normalized	NS ($p > 0.05$)
High-dose group	1000-5000	99.00 ± 2.92	0.898	0.845	0.065	↑↑	Different
Satellite 5000	Recovery (5000)	92.78 ± 1.77	—	—	—	Normalized	NS ($p > 0.05$)

R^2 and *r* represent linear regression and Pearson's correlation coefficients, respectively. "↑↑" indicates strong positive correlation. NS: not significant ($p > 0.05$). Values are expressed as mean ± SD (n = 6).

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Table 5B: Dose-response of creatinine levels in BBEE groups

Group	Dose range (mg/kg)	Mean ± SD of Creatinine (mg/dL)	R^2	R	p-value	Correlation	Comparison to control
Control	0	0.31 ± 0.02	—	—	—	Reference	—
Low-dose group	100-500	0.35 ± 0.02	0.861	0.794	0.041	↑↑	Different
Satellite 500	Recovery (500)	0.32 ± 0.01	—	—	—	Normalized	NS ($p > 0.05$)
High-dose group	1000-5000	0.42 ± 0.02	0.788	0.846	0.014	↑↑	Different
Satellite 5000	Recovery (5000)	0.40 ± 0.01	—	—	—	Normalized	NS ($p > 0.05$)

R^2 and *r* represent linear regression and Pearson's correlation coefficients, respectively. "↑↑" indicates strong positive correlation. NS: not significant ($p > 0.05$). Values are expressed as mean ± SD (n = 6)

Table 6: Dose-response of urinary ketones in BBEE groups

Group	Dose range (mg/kg)	Mean ± SD of Ketone (mg/dL)	R^2	r	p-value	Correlation	Comparison to control
Control	0	0.82 ± 0.2	—	—	—	Reference	—
Low-dose group	100-500	0.82 ± 0.2	0.996	0.994	0.048	↑↑	Different
Satellite 500	Recovery (500)	0.79 ± 0.1	—	—	—	Normalized	NS ($p > 0.05$)
High-dose group	1000-5000	0.88 ± 0.2	0.992	0.997	0.036	↑↑	Different
Satellite 5000	Recovery (5000)	0.80 ± 0.1	—	—	—	Normalized	NS ($p > 0.05$)

R^2 and *r* represent linear regression and Pearson's correlation coefficients, respectively. "↑↑" indicates strong positive correlation. NS: not significant ($p > 0.05$). Values are expressed as mean ± SD (n = 6).

Table 7:. Summary of correlation and dose-response relationships in BBEE-treated groups

Parameter	Correlation coefficient (r)	p-value	Correlation type
Body weight gain (%)	-0.987	0.012	Pearson
Relative liver weight (RLW)	0.991	0.006	Pearson
Relative kidney weight (RKW)	0.985	0.009	Pearson
RBC	0.992	0.039	Pearson
WBC	0.985	0.009	Pearson
Creatinine	0.846	0.014	Pearson
BUN	0.926	0.009	Pearson
Ketone	0.994	0.048	Pearson
pH	0.973	0.007	Pearson

Table 7 demonstrates significant dose-response correlations between BBEE and multiple physiological, hematological, biochemical, and urinary parameters. Strong correlations ($|r| > 0.9$, $p < 0.05$) were observed in body weight gain (inverse), relative liver and kidney weights, and biomarkers such as RBC, WBC, creatinine, BUN, ketone, and urinary pH. These findings reflect a consistent and biologically relevant dose-dependent response to BBEE exposure. Importantly, all altered parameters returned to baseline values in the satellite groups following cessation of treatment, highlighting the reversible nature of BBEE-induced effects. This suggests that the extract's impact is adaptive rather than permanently toxic, underscoring its safety profile when administered within appropriate dosage limits. The overall data provide a solid foundation for further investigation into the safe and sustainable use of BBEE in medicinal applications.

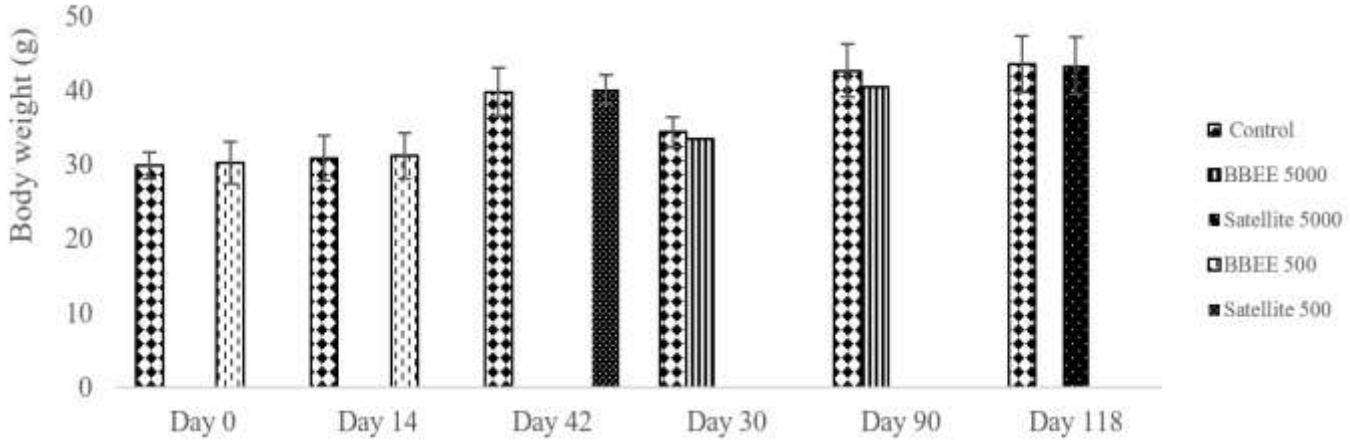

Figure 1. Changes in body weight of mice during acute and sub-chronic toxicity studies. Body weights were recorded at baseline (Day 0) and at key intervals throughout the study. Groups include control, BBEE500, BBEE5000, and their respective satellite recovery groups. Values are expressed as mean ± SD (n = 6).

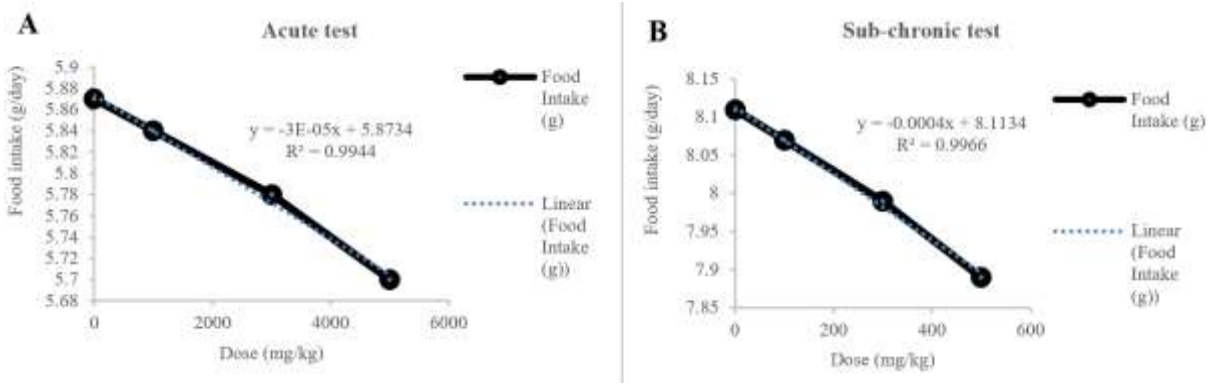

Figure 2. Dose-response relationship between BBEE administration and food intake in acute (A) and sub-chronic (B) toxicity models. Food intake (g/day) was measured and analyzed by linear regression. Both models demonstrated strong inverse correlations between BBEE dose and food consumption ($R^2 = 0.9944$ for acute; $R^2 = 0.9966$ for sub-chronic).

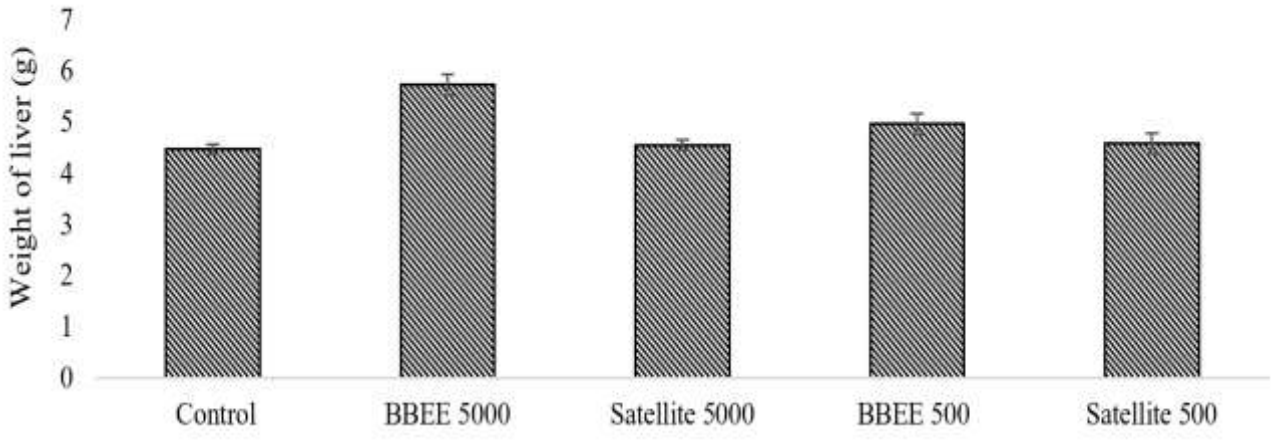

Figure 3. Effect of BBEE on absolute liver weight in mice following acute and satellite toxicity studies. Values are presented as mean ± SD (n = 6). BBEE: *Blumea balsamifera* ethanol extract.

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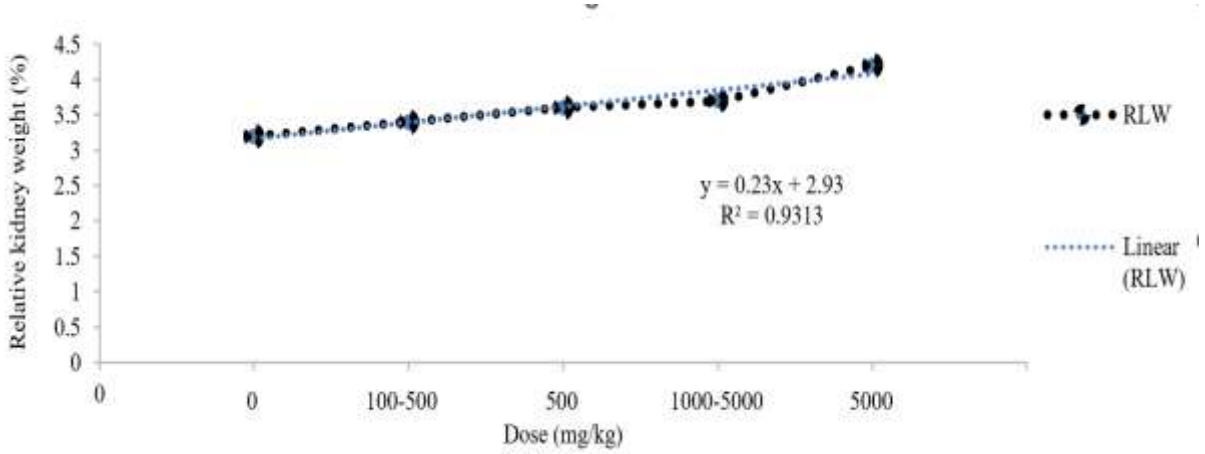

Figure 4: Linear regression analysis between BBEE dose and relative kidney weight (RLW) in acute and satellite toxicity models. Equation: y = 0.23x + 2.93; R^2 = 0.9313. RLW: relative kidney weight (%).

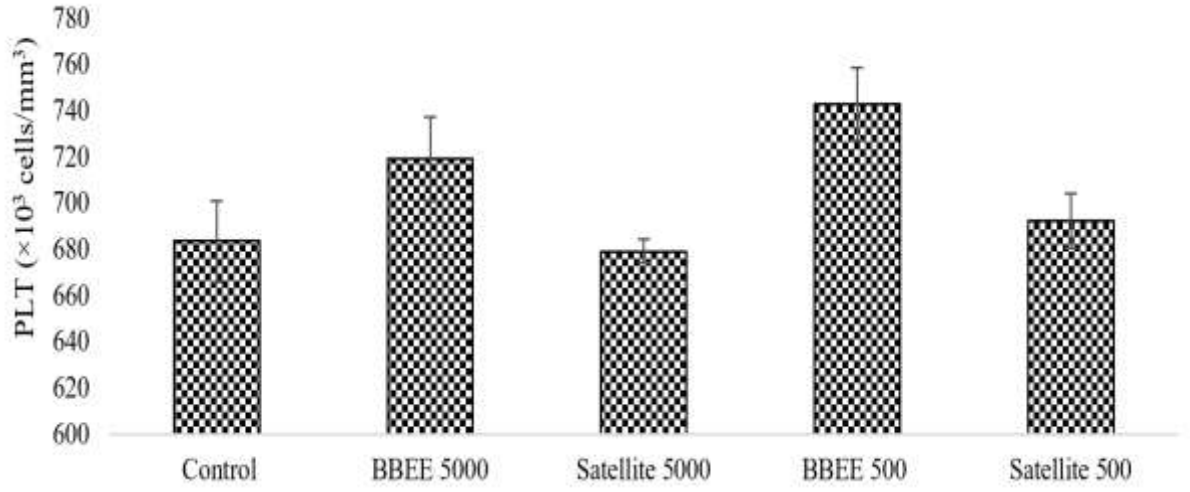

Figure 5: Effect of BBEE on platelet count (PLT) in mice across treatment and satellite groups. Values are presented as mean ± SD (n = 6). BBEE: *Blumea balsamifera* ethanol extract.

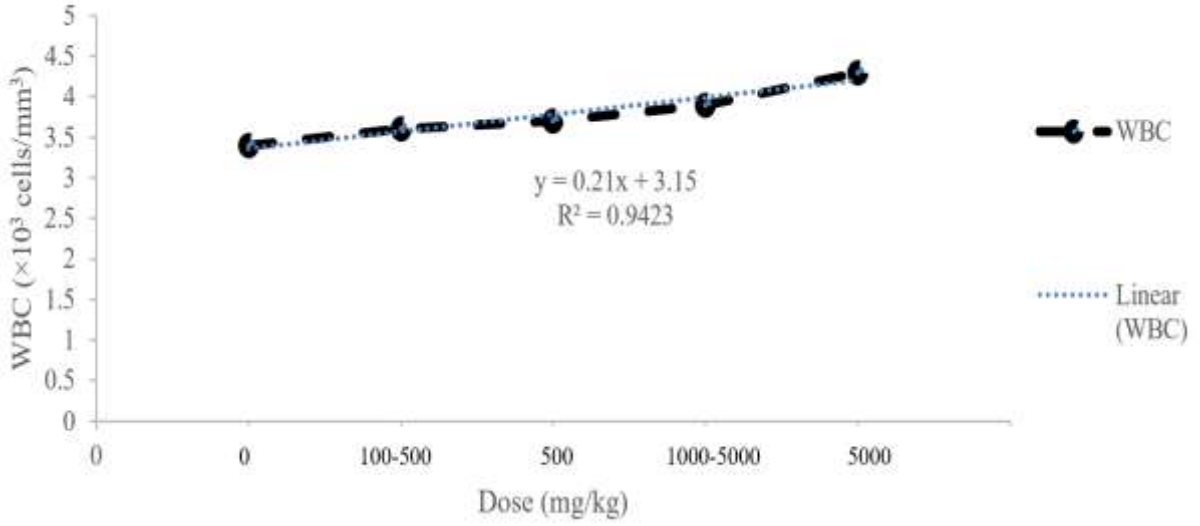

Figure 6: Linear regression analysis of white blood cell (WBC) count concerning BBEE dose. Equation: y = 0.21x + 3.15; R^2 = 0.9423. WBC: white blood cell count (×10³ cells/mm³).

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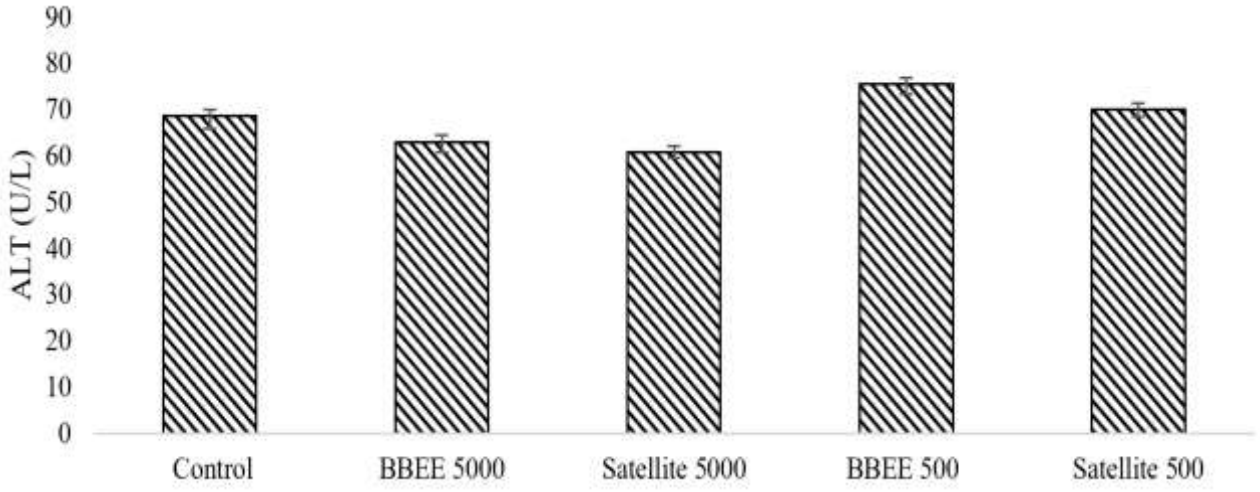

Figure 7:. Effect of BBEE on alanine aminotransferase (ALT) levels in mice across treatment and satellite groups. Values are expressed as mean ± SD (n = 6). BBEE: *Blumea balsamifera* ethanol extract.

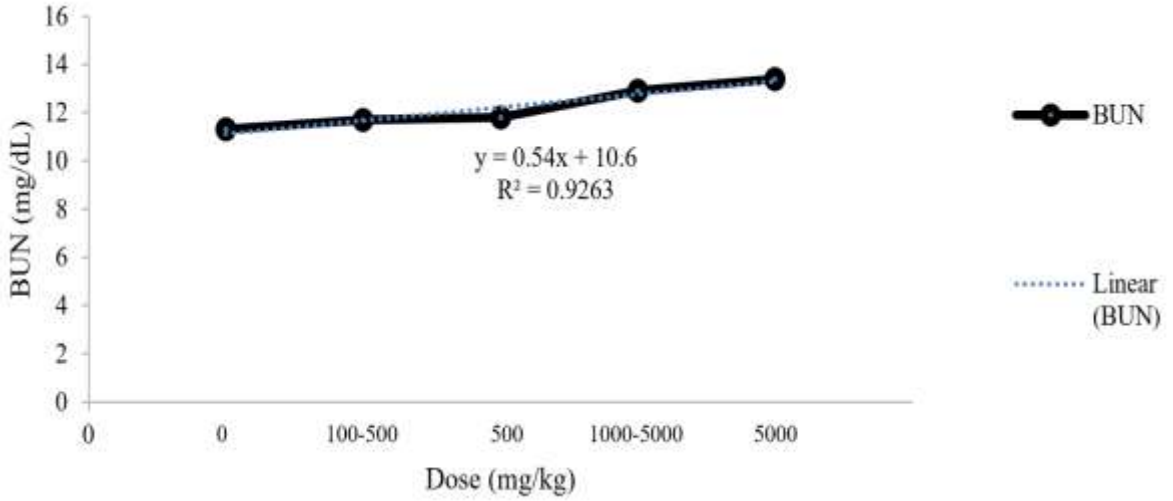

Figure 8: Linear regression analysis of blood urea nitrogen (BUN) concentration in response to BBEE administration. Equation: y = 0.54x + 10.6; R^2 = 0.9263. BUN: blood urea nitrogen (mg/dL).

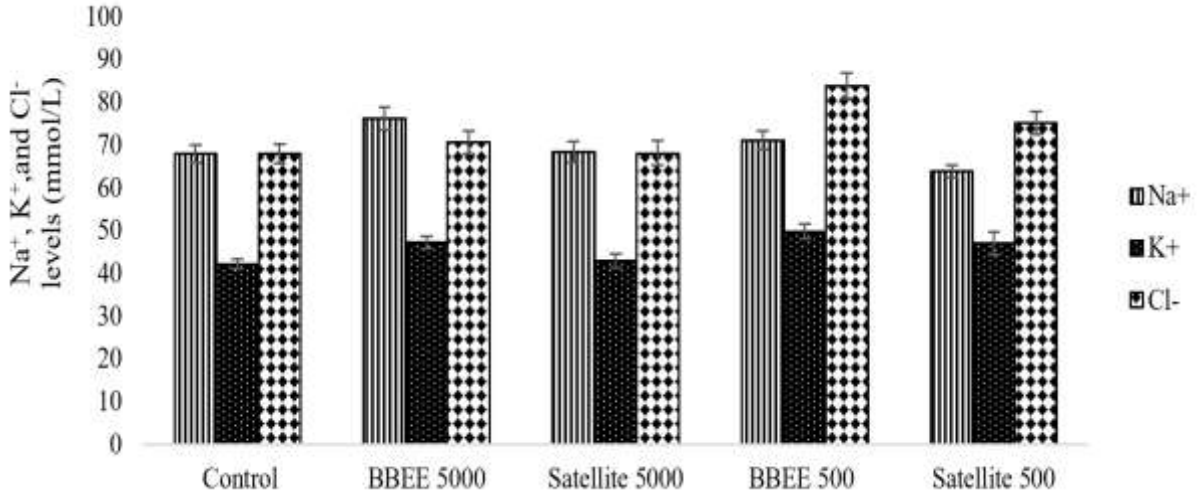

Figure 9: Effect of BBEE on urinary electrolyte (Na^+, K^+, Cl^-) levels in mice across treatment and satellite groups.

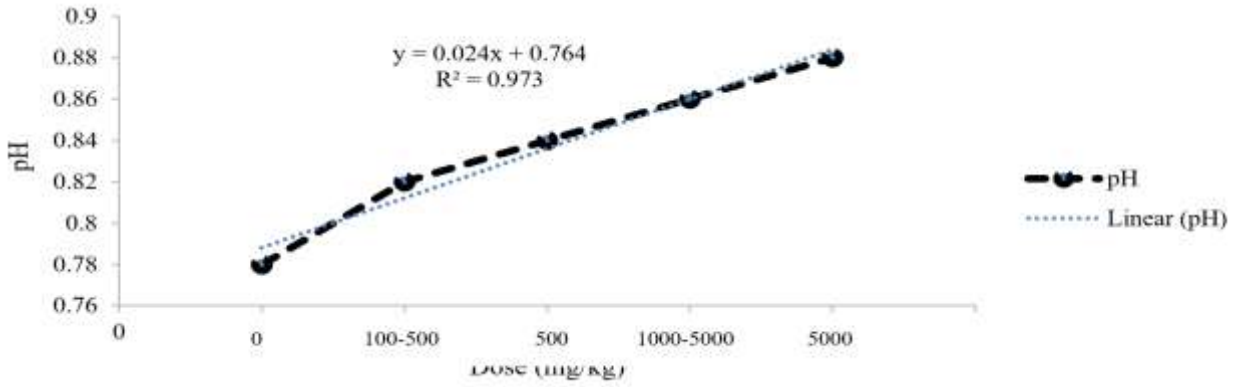

Figure 10: Linear regression analysis of urinary pH values in response to BBEE dose

Conclusion

The present study provides comprehensive evidence that *Blumea balsamifera* leaf ethanol extract (BBEE) induces dose-dependent alterations in body weight, organ coefficients, hematological, biochemical, and urinary parameters in both acute and subchronic murine models. While high-dose exposure was associated with transient physiological changes, recovery groups exhibited normalization of key indicators, indicating the extract's reversible effects and non-cumulative toxicity. These findings support the favorable safety margin and therapeutic potential of BBEE, warranting further validation for sustainable biomedical or nutraceutical use.

Conflict of interest

The author`s declare no conflict of interest.

Authors' declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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References

1. Abdallah EM, Alhatlani BY, Menezes RP, Martins CHG. Back to Nature: Medicinal plants as promising sources for antibacterial drugs in the post-antibiotic era. Plants (Basel). 2023;12(17):3077. Doi: 10.3390/plants12173077
2. Widhiantara IG, Jawi IM. Phytochemical composition and health properties of Sembung plant (*Blumea balsamifera*): A review. Vet World. 2021;14(5):1185–1196. Doi: 10.14202/vetworld.2021.1185-1196
3. Maulydia NB, Khairan K, Tallei T, Salaswati S, Musdalifah A, Nabila FF, Idroes R. Exploring the medicinal potential of *Blumea balsamifera*: Insights from molecular docking and molecular
4. dynamics simulations analyses. Malacca Pharmaceutics. 2024;2(1):33–40. Doi: 10.60084/mp.v2i1.168
5. Tran PN, Tran TTN. Evaluation of acute and subchronic toxicity induced by the crude ethanol extract of *Plukenetia volubilis* Linneo leaves in Swiss albino mice. Biomed Res Int. 2021;2021:6524658, 1–13. Doi: 10.1155/2021/6524658
6. Nhung TTP, Quoc LPT. Assessment of the acute and chronic toxicity studies of ethanol extract of *Blumea balsamifera* (L.) DC. leaves on murine models. Trop J Nat Prod Res. 2024;8(2):6224–6233. Doi: 10.26538/tjnpr/v8i2.20
7. Tran TPN, Nguyen TT, Tran GB. Anti-arthritis effect of ethanol extract of Sacha inchi (*Plukenetia volubilis* L.) leaves against complete Freund's adjuvant-induced arthritis model in mice. Trop Life Sci Res. 2023;34(3):237–257. Doi: 10.21315/tlsr2023.34.3.13
8. Tran TPN, Quoc LPT. Acute and sub-chronic toxicity studies of the ethanol extract of *Erythrina fusca* Lour. fruit via oral administration in mice. Acta Biol Szeged. 2023;67(1):111–122. http://abs.bibl.u-szeged.hu/index.php/abs
9. Janigashvili G, Chkhikvishvili I, Ratian L, Maminaishvili T, Chkhikvishvili D, Sanikidze T. Effects and medical application of plant-origin polyphenols: A narrative review. Bioact Compd Health Dis. 2024;7(8):375–385
10. Abdelrahman KN, Abdel Ghany AGA, Saber RA, Osman A, Sitohy B, Sitohy M. Anthocyanins from pomegranate peel (*Punica granatum*), chili pepper fruit (*Capsicum annuum*), and bougainvillea flowers (*Bougainvillea spectabilis*) with multiple biofunctions: Antibacterial, antioxidant, and anticancer. Heliyon. 2024;10(11):32222. Doi: 10.1016/j.heliyon.2024.e32222
11. Ulloa del Carpio N, Alvarado-Corella D, Quiñones-Laveriano DM, Araya-Sibaja A, Vega-Baudrit J, Monagas-Juan M, Navarro-Hoyos M, Villar-López M. Exploring the chemical and pharmacological variability of *Lepidium meyenii*: A comprehensive review of the effects of maca. Front Pharmacol. 2024;15:1–22. Doi: 10.3389/fphar.2024.1360422
12. Liu H, Wang S, Wang J, Guo X, Son Y, Fu K, Gao Z, Liu D, He W, Yang LL. Energy metabolism in health and disease. Signal Transduct Target Ther. 2025;10:69. Doi: 10.1038/s41392-025-02141-x
13. Nhung TTP, Quoc LPT. Efficacy of black shallot extract in analgesic and antipyretic activities in experimental mice. Trop J Nat Prod Res. 2024;8(3):6609–6616. Doi: 10.26538/tjnpr/v8i3.20
14. Tran TPN, Quoc LPT. Assessment of the toxic effects of *Hedyotis capitellata* Wall. leaves ethanol extract via biological assays in mice (*Mus musculus*). Malays J Biochem Mol Biol. 2023;1:122–134.
15. Fauzi A, Kifli N, Noor MHM, Hamzah H, Azlan A. Hematological, biochemical, and histopathological evaluation of the *Morus alba* L. leaf extract from *Brunei Darussalam*: Acute toxicity study in ICR mice. Open Vet J. 2024;14(3):750–758. Doi: 10.5455/OVJ.2024.v14.i3.1
16. Ma X, Huang T, Chen X, Li Q, Liao M, Fu L, Huang J, Yuan K, Wang Z, Zeng Y. Molecular mechanisms in liver repair and

regeneration: From physiology to therapeutics. Signal Transduct Target Ther. 2025;10:1–45.
17. Kikuchi H, Chou CL, Yang CR, Chen L, Jung HJ, Park E, Limbutara K, Carter B, Yang ZH, Kun JF, Remaley AT, Knepper MA. Signaling mechanisms in renal compensatory hypertrophy revealed by multi-omics. Nat Commun. 2023;14:3481. Doi: 10.1038/s41467-023-38958-9
18. Wahyuni I, Aulifa DL, Rosdianto AM, Levita J. Nephroprotective activity of *Angelica keiskei* (Miq.) Koidz. on cisplatin-induced rats: Reducing serum creatinine, urea nitrogen, KIM-1, and suppressing NF-kappaB p65 and COX-2. Drug Des Devel Ther. 2024;18:4707–4721. Doi: 10.2147/DDDT.S481479
19. Nhung TTP, Quoc LPT. Counteracting paracetamol-induced hepatotoxicity with black shallot extract: An animal model investigation. Trop J Nat Prod Res. 2024;8(1):5875–5880. Doi: 10.26538/tjnpr/v8i1.24
20. Intharuksa A, Kuljarusnont S, Sasaki Y, Tungmunnithum D. Flavonoids and other polyphenols: Bioactive molecules from traditional medicine recipes/medicinal plants and their potential for phytopharmaceutical and medical application. Molecules. 2024;29(23):5760. Doi: 10.3390/molecules29235760
21. Bhol NK, Bhanjadeo MM, Singh AK, Dash UC, Ojha RR, Majhi S, Duttaroy AK, Jena AB. The interplay between cytokines, inflammation, and antioxidants: Mechanistic insights and therapeutic potentials of various antioxidants and anti-cytokine compounds. Biomed Pharmacother. 2024;178:117177. Doi: 10.1016/j.biopha.2024.117177
22. Wang J, Wang L, Tan J, Chai R, Wang Y, Wang Y, Zhao S, Wang X, Bian Y, Liu J. Toxicity studies of condensed fuzheng extract in mice and rats. Heliyon. 2024;10(3):24780. Doi: 10.1016/j.heliyon.2024.e24780
23. Nouioura G, Tourabi M, Tahraoui A, El-yagoubi K, Maache S, Elfatemi H, Lyoussi B, Derwich EH. Assessment of the acute and subacute toxicity of the aqueous extract of Moroccan *Ferula communis* fruit in a mouse model. Saudi Pharm J. 2023;31(8):101701. Doi: 10.1016/j.jsps.2023.101701
24. Allameh A, Niayesh-Mehr R, Aliarab A, Sebastiani G, Pantopoulos K. Oxidative stress in liver pathophysiology and disease. Antioxidants (Basel). 2023;12(9):1653. Doi: 10.3390/antiox12091653
25. Azzi M, Laib I, Bouafia A, Medila I, Tliba A, Laouini SE, Alsaeedi H, Cornu D, Bechelany M, Barhoum A. Antimutagenic and anticoagulant therapeutic effects of Ag/Ag_2O nanoparticles from *Olea europaea* leaf extract: Mitigating metribuzin-induced hepato- and nephrotoxicity. Front Pharmacol. 2024;15:1485525. Doi: 10.3389/fphar.2024.1485525
26. Alkandahri MY, Sadino A, Abriyani E, Hermanto F, Oktoba Z, Sayoeti MFW, Sangging PRA, Wardani D, Hasan N, Sari SW, Safitri NA, Ikhtianingsih W, Safitri S. Evaluation of hepatoprotective and nephroprotective activities of *Castanopsis costata* extract in rats. Biomed Rep. 2024;22(2):24-35. Doi: 10.3892/br.2024.1902
27. Silva-Pinto PA, Costa de Pontes JT, Aguilar-Morón B, Carnero Canales CS, Pavan FR, Roque-Borda CA. Phytochemical insights into flavonoids in cancer: Mechanisms, therapeutic potential, and the case of quercetin. Heliyon. 2025;11(4):42682. Doi: 10.1016/j.heliyon.2025.e42682
28. Yamahara K, Yasuda-Yamahara M, Kuwagata S, Chin-Kanasaki M, Kume S. Ketone body metabolism in diabetic kidney disease. Kidney360. 2024;5(2):320–326. Doi: 10.34067/KID.0000000000000359
29. Adeola OE, Adewale OB, Akpor OB, Adamolekun MM, Akpor OA. Evaluation of acute and subacute toxicity of aqueous extract of *Picralima nitida* seeds in Wistar rats. Trop J Nat Prod Res. 2024;8(12):9679–9685. Doi: 10.26538/tjnpr/v8i12.48
30. Zhang Z, Tang S, Liu S, Leng Y, Fu X, Xie H, Gao H, Xie C. The efficacy and safety of *Ginkgo biloba* L. leaves extract combined with ACEI/ARB on diabetic kidney disease: A systematic review and meta-analysis of 41 randomized controlled trials. Front Pharmacol. 2024;15:1–28. Doi: 10.3389/fphar.2024.1408546
31. Moreira LSG, Teixeira KTR, Cardozo LFMF, Alvarenga L, Regis B, Brito JS, Leal VO, Borges NA, Brum ISC, Carraro-Eduardo JC, Borini GB, Berretta AA, Ribeiro-Alves M, Mafra D. Effects of cranberry extract (*Vaccinium macrocarpon*) supplementation on lipid peroxidation and inflammation in patients with chronic kidney disease (stages 3–4): A randomized controlled trial. J Nutr Metab. 2024;2024:9590066. Doi: 10.1155/2024/9590066