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Research Article

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Acute Toxicity Evaluation and Phytochemical Screening of *Morinda citrifolia* L. Leaf Infusion in Mice

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ABSTRACT

Background: *Morinda citrifolia L.* is a medicinal plant widely distributed in Indonesia and other tropical regions. However, studies on the phytochemical constituents of its leaf infusion and its acute toxicity are still limited.

Aims: This study aimed to evaluate the acute toxicity profile and phytochemical characteristics of *Morinda citrifolia* L. leaf infusion in mice.

Methods: A total of 25 mice were randomly assigned to one control group and four treatment groups receiving doses of 1,000, 5,000, 10,000, and 15,000 mg/kg. Observations were conducted for 14 days, assessing clinical signs, changes in body weight, absolute organ weight, relative organ weights, and mortality. To detect the presence of secondary metabolite compounds in the leaf infusion, phytochemical screening was performed using standard qualitative methods.

Results: One incidental mortality occurred at the 1,000 mg/kg dose. Although initial body weights differed prior to treatment, no significant differences were observed among the groups on days 7 and 14. The continuous increase in body weight until day 14 indicates that the treatment did not interfere with normal growth. Analysis of absolute and relative weights of major organs revealed no significant differences except for the heart, which showed no toxicological relevance.

Conclusion: Phytochemical screening revealed the presence of alkaloids, saponins, flavonoids, and tannins. Overall, these findings indicate that L. leaf infusion did not produce evident acute toxic effects in mice within the tested dose range under the conditions of this study.

INTRODUCTION

Morinda citrifolia L., also known as noni fruit or mengkudu, is a medicinal plant widely recognized for its various health benefits (Wang et al., 2002). This tropical plant is widely distributed across Australia, the Pacific Islands, and Southeast Asia, including Indonesia (Nelson & Elevitch, 2006). Traditionally, noni fruit has been associated with anti-inflammatory properties, prevention of infections, treatment of various digestive disorders, and enhancement of the immune system (Assi et al., 2017). In Java and Sumatra, this plant is commonly referred to as "pace." The fruit is frequently used as a primary complementary ingredient in the traditional dish "rujak bebek" due to its distinctive flavor.

In practice, noni fruit has been extensively utilized for both medicinal purposes and as a food source. However, the leaves of the plant have not been widely

developed as herbal products. The leaves of *Morinda citrifolia* L. are known to contain various secondary metabolites, including alkaloids, flavonoids, saponins, and tannins (Parida, 2022). These compounds indicate potential pharmacological activities such as antioxidant, antibacterial, and anti-inflammatory effects (Hou et al., 2025). Rohman et al. (2007) reported that noni leaves contain phenolic and flavonoid compounds that correlate with their antioxidant activity. Nevertheless, utilization of natural products is not always inherently safe. Any natural substance intended for consumption still requires toxicity evaluation to ensure its safety limits, particularly if it is to be further developed as a raw material for phytopharmaceutical preparations.

An essential initial step in assessing the safety of a natural substance is acute toxicity testing. Within a specified period, toxicity testing can provide an overview of potential adverse effects resulting from the administration of a single dose or a series of single doses of a natural substance. The primary indicators used to assess the toxic potential of a substance in experimental animals include changes in body weight, relative and absolute organ weights, clinical signs, and mortality (Parasuraman, 2011). The data obtained serve not only as a reference for determining safety levels but also as a foundation for more complex subsequent studies.

Although *Morinda citrifolia* L. has long been recognized in traditional medicine, scientific information regarding the acute toxicity profile of its leaf infusion remains limited. Therefore, this study was conducted to evaluate the acute toxicity potential in female mice and to identify the phytochemical constituents of *Morinda citrifolia* L. leaf infusion. The results of this study are expected to provide scientific contributions to the safety aspects of noni leaf utilization and to support its development in a more responsible manner.

MATERIALS AND METHODS

Ethical Approval

The experimental procedures were conducted following ethical approval from the Animal Ethics Committee of the School of Veterinary Medicine and Biomedical Sciences, IPB University, with reference number 390/KEH/SKE/X/2025.

Study Period and Location

The study was carried out from Oktober to December 2025 at the School of Veterinary Medicine and Biomedical Sciences, IPB University, Indonesia. *Morinda citrifolia* L. Leaf simplicia was obtained from Laboratory of Pharmacology and Toxicology IPB University. Preparation for *Morinda citrifolia* L. leaves infusion was. Performed by boiling 500 grams of dried leaves in 1000 ml of water at approximately 100°C for 15 min, then filtered using a strainer. The administered doses were calculated based on the dry weight of the leaf simplicia used for infusion preparation (Andriyanto et al., 2025).

Experimental Animals

The study utilized 25 strain DDY male mice, aged eight weeks with body weights ranging from 20 to 25 g. The animal models were allowed to acclimate for one week before the treatment begin. To eliminate possible parasitic infections that might affect the validity of the outcomes, praziquantel was given at a dosage of 0.03 mg per gram of body weight as a preventive intervention.

Acute Toxicity Assesment

Animals were observed daily over a 14-day period to identify any changes in their clinical condition (OECD, 2022; OECD, 2019). Feed and water intake were monitored regularly throughout the study. A thorough physical examination was also carried out, including assessment of the hair coat and skin, the condition of the eyes and mucous membranes, as well as evaluation of respiratory and nervous system function. Any signs suggestive of toxic effects, such as tremors, seizures, excessive salivation, diarrhea, or reduced activity, were carefully recorded from the beginning until the end of the observation period.

Body weight was measured on day 0 prior to treatment and subsequently on days 7 and 14. On day 14, all surviving mice were euthanized in accordance with established procedures, followed by examination of the major organs. The organs evaluated included the liver, kidneys, spleen, heart, and lungs. Organ weights were documented to obtain both absolute values and relative weights in relation to body weight. If any animal died during the study, a necropsy was performed to assess macroscopic findings, and the organs were weighed accordingly.

Phytochemical Screening

Phytochemical screening of the *Morinda citrifolia* L. leaf infusion was carried out qualitatively using established standard procedures (Trease & Evans, 2002). Alkaloids were tested using Mayer, Wagner, and Dragendorff reagents. Flavonoids were identified through the Shinoda reaction, while steroids and

terpenoids were examined using the Liebermann Burchard method.

Saponins were evaluated by the froth test, and tannins were assessed with ferric chloride reagent. The presence of each compound was determined based on characteristic color changes or the formation of specific precipitates.

Data Analysis

Statistical analyses were performed using Microsoft Excel (Microsoft Corp., Redmond, WA, USA). The data were presented as mean ± standard deviation (SD). Differences among treatment groups were analyzed using one-way analysis of variance (ANOVA) for each parameter and observation time. When the ANOVA indicated significant differences, Tukey's multiple comparison test was performed to determine intergroup differences. A p-value of less than 0.05 was considered statistically significant.

RESULTS AND DISCUSSION

Acute Toxicit Assessment

Acute toxicity evaluation of *Morinda citrifolia* leaf infusion is essential to identify potential adverse effects of following administration. One mortality was observed in the 1000 mg/kg group on day 13. The animal exhibited weight loss, conjunctivitis, and abdominal breathing prior to death. However, gross necropsy examination of the dead mice revealed no remarkable macroscopic abnormalities in the major organs. No mortality occurred at higher doses, and no dose-dependent pattern was observed. Therefore, the death was considered incidental and not treatment related.

Body weight is considered a sensitive indicator of systemic toxicity. In acute or subacute toxicity studies, a body weight reduction of ≥10% in treated groups is often regarded as an early indication of potential adverse effects of a tested substance (Dorato & Engelhardt, 2005). Body weight changes in mice were observed on days 0, 7, and 14 to monitor the delayed effects of *Morinda citrifolia* leaf infusion. The data on body weight changes are presented in Table 1.

Baseline body weight data are important for interpreting subsequent changes and derived parameters (Bailey et al., 2004; Michael et al., 2007). Table 1 shows that on Day 0, there was a significant difference in body weight among groups ($p = 0.0023$), with the 1000 mg/kg dose group having a lower initial body weight compared to the other groups. In contrast, no significant differences were observed on Day 7 ($p = 0.832$) or Day 14 ($p = 0.074$). Although a significant difference in body weight was present at Day 0 due to the lower weight of the 1000 mg/kg group, the lack of significant differences on Days 7 and 14 indicates that administration of the infusion did not affect growth and did not produce toxic effects in mice. All groups exhibited minor fluctuations in body weight without a consistent dose–response pattern.

Body weight changes relative to baseline are presented in Table 2. Changes in body weight (Δ) from Day 0 to Day 7 and Day 14 are presented in Table 2 for each dose group. On Day 7, the p-value was 0.23, indicating that the initial response to exposure was relatively uniform. The lack of significant change on Day 7 suggests that infusion administration did not notably affect body weight during the first week. The absence of significant and persistent weight loss indicates that the test substance did not induce severe metabolic stress, anorexia, or impairment of nutrient absorption, conditions commonly associated with systemic toxicity (Sellers et al., 2007; Gad, 2016).

Table 1. Mean body weight (g) of mice administered various doses of *Morinda citrifolia* leaf infusion at baseline (Day 0), Day 7, and Day 14 following treatment

Dose (mg/Kg)	Day 0 (Mean ± SD)	Day 7 (Mean ± SD)	Day 14 (Mean ± SD)
0	27.6 ± 1.342[a]	28.0 ± 4.95[a]	25.6 ± 2.793[a]
1000	26.6 ± 2.074[a]	25.2 ± 6.979[a]	31.75 ± 3.202[a]
5000	25.8 ± 1.304[a]	27.6 ± 1.140[a]	30.0 ± 1.181[a]
10000	23.2 ± 1.304[b]	26.4 ± 2.408[a]	27.2 ± 3.114[a]
15000	25.4 ± 1.140[a]	27.4 ± 2.702[a]	28.4 ± 2.881[a]
P Value	0.0023	0.832	0.074

Superscript letters within the same column indicate significant differences (Tukey post hoc, p<0,05)

On Day 14, the p-value was 0.004, indicating significant differences between groups. Interestingly, the control group showed an average weight loss of −2.0 ± 2.35 g, whereas the treated groups exhibited weight gains ranging from 3.0 to 4.75 g. An increase in body weight is not generally considered an indicator of toxicity unless it is associated with pathological fluid retention or edema, which is typically confirmed through clinical observations or histopathological findings. Overall, the absence of a consistent decrease in body weight, the lack of an adverse dose–response relationship, and the overall tendency for body weight to increase until the end of the observation period suggest that the tested compound did not negatively affect nutritional status or metabolic function during the 14-day observation period. Therefore, based on body weight parameters, the compound can be considered not to induce detectable acute systemic toxic effects during the observation period.

In addition to body weight, changes in absolute and relative weights of major organs are sensitive indicators of adaptive responses such as hypertrophy, atrophy, congestion, or degeneration resulting from exposure to test substances. Interpretation of these changes should be considered in the context of dose–response patterns and their biological relevance.

Based on Table 3, unlike other major organs, the heart showed a statistically significant difference compared to the control at Day 14 for all tested doses. The p-values were 0.041 for the heart, 0.067 for the liver, 0.080 for the kidney, 0.052 for the spleen, and 0.118 for the lungs. However, the statistical significance observed in the heart did not follow a dose-dependent pattern.

Compared to absolute organ weight, relative organ weight is calculated as the ratio of the measured organ weight to the actual body weight, providing a more accurate interpretation of the systemic effects of a xenobiotic compared to absolute weight (Sellers et al., 2007). Based on Table 4, similar to the absolute organ weight data, the relative weight of the heart showed a significant difference compared to other organs. The relative heart weight had a p-value of 0.049, indicating a significant difference without dose–dependent pattern, whereas the liver (p = 0.071), kidney (p = 0.094), spleen (p = 0.058), and lungs (p = 0.676) did not show significant differences.

A substance is typically considered toxic when significant changes occur in both absolute and relative organ weights and when these changes follow a clear dose–response trend (Wallace, 2022). In both absolute (p = 0.041) and relative (p = 0.049) organ weight observations, the heart showed a statistically significant difference among the treatment groups, particularly at the 5000 mg/kg dose, where the heart weight differed significantly from the control. However, when all dose levels are considered collectively, this pattern appears inconsistent (Andersen et al., 1999). At the higher dose of 10000 mg/kg, the heart weight returned to values close to the control group, and at 15000 mg/kg no significant difference was observed. This indicates that the observed change did not follow a dose-dependent pattern.

If a substance truly exerts toxic effects, organ alterations typically become more pronounced with increasing dose (Lazic et al., 2020). Since such a pattern was not observed in this study, the increased heart weight at 5000 mg/kg is more likely attributable to normal biological variation or a mild adaptive physiological response rather than a toxic effect. This finding could partially be influenced by inter-individual differences and variations in baseline body weight among experimental groups. In the present study,

Table 2. Body weight change from baseline in mice treated with various doses of *Morinda citrifolia* leaf infusion on Days 7 and 14

Dose (mg/Kg)	Δ Day 7 (Mean ± SD)	Δ Day 14 (Mean ± SD)
0	0.4 ± 3.65[a]	-2.0 ± 2.35[a]
1000	-1.4 ± 6.07[a]	4.75 ± 4.35[a]
5000	1.8 ± 1.30[a]	4.2 ± 1.92[a]
10000	3.2 ± 3.19[b]	3.8 ± 3.56[a]
15000	2.0 ± 2.45[a]	3.0 ± 3.00[a]
P Value	0.23	0.004

Superscript letters within the same column indicate significant differences (Tukey post hoc, p<0,05)

significant differences in body weight were already observed before treatment administration at Day 0 (p = 0.0023), indicating pre-existing variability among animals that may affect absolute organ weight measurements. The increased heart weight may be related to temporary changes in metabolic activity or circulatory dynamics rather than structural damage to cardiac tissue. It was not accompanied by mortality, clinical signs of toxicity, or alterations in other vital organs. Therefore, the observed change is not considered sufficiently strong to be interpreted as evidence of toxicity. It can be tentatively concluded that *Morinda citrifolia* leaf infusion does not induce acute toxicity in major organs. To further strengthen this conclusion, additional evaluations such as histopathological examination and serum biochemical parameters are recommended in accordance with international guidelines for acute toxicity testing (Hall et al., 2012).

The liver is considered one of the primary target organs in toxicity studies due to its central role in the biotransformation of xenobiotics through the cytochrome P450 enzyme system (Klaassen & Watkins, 2015). Activation of this enzymatic system may lead to mild hepatocellular hypertrophy as an adaptive response to enzyme induction. However, substances that exert hepatotoxic effects typically produce progressively greater alterations in liver weight as the administered dose increases. The minor fluctuations observed in liver weight in this study did not demonstrate a consistent dose-dependent pattern. Therefore, the observed variations are more likely to reflect normal biological variability or mild adaptive responses rather than evidence of hepatotoxicity.

Changes in kidney weight are often associated with nephrotoxicity when accompanied by tubular degeneration, congestion, or alterations in biochemical biomarkers such as creatinine and blood urea nitrogen (BUN) (Frazier et al., 2012). In the present observation, no significant differences were detected and no dose–response trend was identified.

The spleen plays an important role in immune regulation and hematopoiesis. Both the absolute and relative spleen weights tended to increase, particularly at doses of 5000 and 15000 mg/kg; however, this pattern was not dose dependent. In general, an increase in spleen weight may be associated with immune stimulation or splenic congestion (Elmore,

Table 3. Comparison of absolute organ weights among experimental groups on day 14

Dose (mg/Kg)	Heart (g)	Liver (g)	Kidneys (g)	Spleen (g)	Lung (g)
0	0.136 ± 0.08^{a}	1.368 ± 0.33^{a}	0.308 ± 0.04^{a}	0.142 ± 0.08^{a}	0.206 ± 0.05^{a}
1000	0.196 ± 0.09^{ab}	1.542 ± 0.47^{a}	0.326 ± 0.08^{a}	0.195 ± 0.09^{a}	0.212 ± 0.06^{a}
5000	0.320 ± 0.12^{b}	1.798 ± 0.24^{a}	0.348 ± 0.06^{a}	0.320 ± 0.12^{a}	0.264 ± 0.04^{a}
10000	0.174 ± 0.070^{a}	1.304 ± 0.18^{a}	0.290 ± 0.06^{a}	0.174± 0.07^{a}	0.214 ± 0.05^{a}
15000	0.302 ± 0.134^{a}	1.710 ± 0.34^{a}	0.378 ± 0.08^{a}	0.302 ± 0.13^{a}	0.206 ± 0.05^{a}
P Value	0.041	0.067	0.089	0.052	0.118

Superscript letters within the same column indicate significant differences (Tukey post hoc, p<0,05)

Table 4. Comparison of relative organ weights among experimental groups on day 14

Dose (mg/Kg)	Heart (g)	Liver (g)	Kidneys (g)	Spleen (g)	Lung (g)
0	0.005 ± 0.003^{a}	0.053 ± 0.010^{a}	0.012 ± 0.001^{a}	0.005 ± 0.003^{a}	0.008 ± 0.002^{a}
1000	0.007 ± 0.002^{a}	0.053 ± 0.011^{a}	0.011 ± 0.002^{a}	0.007 ± 0.002^{a}	0.008 ± 0.002^{a}
5000	0.010 ± 0.003^{a}	0.060± 0.006^{a}	0.012 ± 0.002^{a}	0.010 ± 0.003^{a}	0.009 ± 0.001^{a}
10000	0.006 ± 0.002^{a}	0.048 ± 0.004^{a}	0.011 ± 0.001^{a}	0.006 ± 0.002^{a}	0.008 ± 0.001^{a}
15000	0.010 ± 0.003^{a}	0.060 ± 0.007^{a}	0.013 ± 0.002^{a}	0.010 ± 0.003^{a}	0.007 ± 0.001^{a}
P Value	0.049	0.071	0.094	0.058	0.676

Superscript letters within the same column indicate significant differences (Tukey post hoc, p<0,05)

2006; Haley et al., 2005). In addition, such findings should be supported by hematological data, such as differential leukocyte counts or erythrocyte indices.

In the present study, lung weight did not show significant differences in either absolute or relative measurements. In systemic oral toxicity studies, the lungs are not typically considered a primary target organ for early-stage evaluation (Sellers et al., 2007). Observation of the lungs is generally conducted as secondary supporting data to help confirm whether systemic toxicity has occurred. When a substance is toxic, pulmonary changes are often characterized by systemic inflammatory responses or secondary edema.

Phytochemical Screening

Based on Table 5, the phytochemical screening results indicated that the leaf infusion of *Morinda citrifolia* tested positive for the presence of alkaloids, flavonoids, saponins, and tannins, while steroids and terpenoids were not detected.

In general, the presence of flavonoids, tannins, and saponins is frequently associated with antioxidant, anti-inflammatory, and tissue-protective activities, whereas alkaloids exhibit a broad spectrum of biological effects that may be either therapeutic or toxic depending on their chemical structure (Harborne, 1998; Evans, 2009; Wink, 2018). The presence of these secondary metabolites may enhance metabolic efficiency, reduce oxidative stress, and improve appetite (cory et al., 2018), which could contribute to the observed increase in body weight in the treated groups (table 2). However, since oxidative stress markers and quantitative feed intake were not evaluated in the present study, the underlying mechanism responsible for the body weight increase remains unclear and requires further investigation.

The absence of significant body weight reduction or a dose-dependent suppression pattern in the treated groups observed in this study may be partly attributed to the presence of flavonoids. Flavonoids are widely reported to possess strong antioxidant activity through free-radical scavenging mechanisms and modulation of phase II detoxification enzymes (Pietta, 2000; Kumar & Pandey, 2013). These biological properties may contribute to protecting hepatic and other tissues from oxidative stress (Middleton et al., 2000).

Saponins have been reported to modulate the immune system and interact with cholesterol in cell membranes, thereby influencing membrane permeability. It may potentially lead to cellular damage and alterations in organ function. (Francis et al., 2002). In the present study, observations of major organs showed no significant alterations (Tables 3 and 4). Therefore, the concentration of saponins in the *Morinda citrifolia* leaf infusion was likely insufficient to induce damage to target organs.

Several tannins have been reported to possess notable astringent and antioxidant properties (Smeriglio et al., 2017). Furthermore, tannins are capable of binding proteins and scavenging free radicals, thereby reducing oxidative damage in biological tissues (Okuda, 2005). However, at high concentrations, tannins may reduce feed intake, which can ultimately lead to decreased body weight (Francis et al., 2002; Makkar, 2003). In the present study, no significant reduction in body weight was observed, suggesting that the tannin content was within a range that did not adversely affect nutrient intake or systemic metabolism.

The presence of alkaloids is often associated with the possibility of toxic manifestations such as behavioral changes, reduced activity, alterations in body weight, or changes in organ weight when present at sufficiently high concentrations. In cases of significant alkaloid-induced cardiotoxicity, consistent and dose-dependent alterations in relative heart weight are typically observed and may be

Table 5. Phytochemical Screening of *Morinda citrifolia* L. Leaf Infusion

Phytochemical Constituent	Result
Alkaloids	+
Flavonoids	+
Steroid & Terpenoids	-
Saponin	+
Tannins	+

accompanied by clinical manifestations (Klaassen, 2021). These findings suggest that the alkaloid content in the *Morinda citrifolia* leaf infusion is likely present at relatively low concentrations or in forms that are not toxic, thereby not producing detectable physiological disturbances under the conditions of this study.

The lack of plant steroids (certain phytosterols) reduces the likelihood of metabolic alterations that could influence body weight. In addition, the oxidative metabolism of some terpenoids may exhibit hepatotoxic or nephrotoxic effects at high doses due to the formation of reactive metabolites (Guengerich, 2020). The absence of these compound classes may partly explain the stability of liver and kidney weights observed in Tables 3 and 4. Collectively, these results indicate that the leaf infusion is relatively safe under the conditions of this acute oral toxicity study and may have a wide margin of safety at the tested dose range.

CONCLUSION

Morinda citrifolia L. leaf infusion did not show significant acute systemic toxicity in mice. No dose-dependent mortality or clinical signs of toxicity was observed, and no adverse effects were detected on body weight or major organs weight. Phytochemical screening revealed the presence of several compounds, including alkaloids, flavonoids, saponins, and tannins. These findings indicate that the infusion is relatively safe based on short-term studies and has a good potential for further pharmacological investigation.

AUTHORS CONTRIBUTION

All authors contributed to this manuscript as follows: AM, AB, ASS collected the data, drafted the manuscript, and designed the tables and graphs. AA developed the main conceptual ideas and critically revised the article. AA proofread the manuscript. All authors discussed the results and contributed to the final version of the manuscript.

"The author declares that there is no conflict of interest with the parties involved in this research".

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