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ACUTE TOXICITY EVALUATION OF BREADFRUIT LEAF EXTRACT (*ARTOCARPUS ALTILIS*) FOR DYSLIPIDEMIA TREATMENT IN WISTAR RATS

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Abstract
Background: The use of herbal medicine for managing dyslipidemia is increasing globally; however, comprehensive data regarding its acute safety profile remains limited. This study aimed to evaluate the acute toxicity of the aqueous extract of breadfruit leaves (*Artocarpus altilis*) prepared via maceration to mirror traditional preparation in Wistar rats, and to determine its LD_{50} value. **Methods:** Using a laboratory experimental design, 20 male Wistar rats were randomly divided into four groups: a control group (distilled water) and three treatment groups administered single doses of 3, 5, and 10 g/kg BW. Clinical symptoms, mortality, body weight, and histopathological changes in the liver and kidneys were evaluated over 14 days. **Results**: the results showed zero mortality across all groups, establishing an LD_{50} > 10 g/kg BW. Transient clinical symptoms (lethargy, diarrhea, and tremors) appeared on Day 1 at high doses (5 and 10 g/kg BW) but completely resolved by Day 14. Significantly, body weight increased across all groups (highest gain of 17.7% at 10 g/kg BW, $p < 0.001$), suggesting that the extract did not interfere with appetite or nutrient absorption. Histopathological analysis revealed dose-dependent changes, including fatty degeneration and mild necrosis in the liver, as well as hydropic degeneration in the kidneys at ultra-high doses. **Conclusion:** the aqueous extract of *Artocarpus altilis* is practically non-toxic (LD_{50} > 10 g/kg BW). While it holds strong potential as a safe therapeutic agent for dyslipidemia, extremely high doses impose a metabolic burden on excretory organs.

Introduction

The use of herbal medicine is increasing globally because it is perceived as more affordable and fewer side effects than synthetic chemical drugs. Dyslipidemia has emerged as a major global public health challenge, with its prevalence in adults estimated to range from 20% to 80% depending on the diagnostic criteria. Despite significantly increasing the risk of cardiovascular diseases and imposing a substantial economic burden, the awareness

and clinical control of this condition remain suboptimal, particularly in low- and middle-income countries (1). Many populations, particularly in developing countries as well as in communities that still closely adhere to traditional herbal medicine practices, choose herbal medicine as an alternative treatment due to its ease of access and lower costs compared to conventional treatment (2,3). Additionally, herbal medicines are derived from natural sources and exhibit high tolerability, thereby potentially minimizing the risk of adverse effects frequently encountered with synthetic chemical drugs. This condition encourages many individuals to turn to herbal remedies for long-term treatment and as a complement to conventional medicine (4,5).

Natural compounds with antioxidant properties, such as those found in bergamot, curcumin, and olive tree extracts, have generally been shown to be beneficial in improving lipid profiles and reducing dyslipidemia-related oxidative damage (6). Following this principle, breadfruit leaves (*Artocarpus altilis*) present a strong potential as they contain active compounds such as alkaloids, tannins, flavonoids, steroids, and saponins, which act as potent antioxidants capable of scavenging free radicals (7). Empirical evidence has demonstrated that the administration of breadfruit leaf decoction significantly reduces triglyceride, total cholesterol, and Low Density Lipoprotein (LDL) levels in hyperlipidemic animal models. This lipid lowering effect is attributed to the presence of flavonoids and tannins, which enhance lipoprotein lipase activity and inhibit intestinal fat absorption (8).

Antioxidants like curcumin and olive tree extract have demonstrated lipid-lowering effects and the ability to ameliorate dyslipidemia by reducing lipid peroxidation and enhancing lipid homeostasis (9,10). These antioxidants improve total cholesterol, LDL, and triglycerides while often raising protective HDL cholesterol. Studies on compounds that combine antioxidant and anti-inflammatory effects show potential to reduce foam cell formation and vascular damage in dyslipidemic animal models, highlighting the beneficial impact of antioxidants on lipid-induced tissue injury (11).

The major barrier to utilizing herbal remedies as a therapy is the lack of sufficient scientific data regarding safety, particularly toxicity, as well as constraints in the standardization of herbal products. There is a clear gap in the literature: most previous studies have focused solely on efficacy trials (pharmacodynamics), while data regarding the acute safety profile (toxicity) on vital organs remains highly limited. Without valid toxicity data, claims of herbal efficacy cannot be medically justified for human use. To the best of our knowledge, no previous study has specifically evaluated the acute toxicity of aqueous breadfruit leaf extract prepared by maceration in relation to dyslipidemia treatment in an animal model. This water extraction method (maceration) is essential as it mirrors the most common traditional preparation such as boiling or brewing used by the community. Providing this rationale makes investigating the toxicity profile of the aqueous extract of breadfruit leaves highly crucial. This study aims to evaluate the acute toxic effects of

breadfruit leaf extract in Wistar rats and determine the LD_{50} value to ensure its safe use as a herbal medicine for dyslipidemia.

Materials and Methods

Study Design, Location, and Subjects

This study employed a laboratory experimental design using a randomized pre-posttest control group design. The study was conducted from December 2021 to February 2022 at the Laboratory of Pharmacology and Toxicology, Faculty of Pharmacy, and the Laboratory of Anatomical Pathology, Hasanuddin University Teaching Hospital. The research subjects consisted of 20 healthy and active male Wistar rats, aged 8 weeks, weighing 150–170 g. The experimental animals were randomly divided into four groups (n=5 per group): the control group administered with distilled water (K), and three treatment groups (PI, PII, PIII) administered with a single dose of breadfruit leaf extract at 3 g/kg BW, 5 g/kg BW, and 10 g/kg BW, respectively. This study was approved by the Ethics Committee of The Faculty of Public Health Hasanuddin University, with approval number 1088/UN4.14.1/TP.01.02/2022

Extraction Procedure and Intervention

Extraction Procedure and Intervention The breadfruit leaves (*Artocarpus altilis*) used in this study were collected from Maros regency**.** The breadfruit leaf extract was prepared via maceration using water as the solvent (reverse osmosis) at a ratio of 1:10 for 3 hours, with intermittent agitation. The resulting filtrate was separated using a separator at a speed of 3000 rpm, then dried using a freeze dryer at -60 °C until a solid extract was obtained. To ensure global legitimacy and adherence to regulatory frameworks, the acute toxicity protocol was conducted in compliance with the OECD Test Guideline 423 (12). The determination of the single-dose levels administered (3, 5, and 10 g/kg BW) was carefully selected based on previous literature references (13,14), which indicated this range as optimal for establishing the acute toxicity threshold. Prior to the administration of the test substances, the rats were acclimatized for 14 days and fasted for 14–18 hours. The extract was administered orally via gastric gavage, with the volume adjusted to the body weight of each animal.

Observation Parameters and Data Analysis

The acute toxicity test was conducted by observing clinical symptoms and mortality over 14 days. Clinical observations were recorded at specific frequencies: carefully during the first 30 minutes, 4 hours, and 24 hours post single dose administration, and subsequently once daily. These observations included behavioral aspects such as locomotor activity, abnormal reactions (tremors, seizures, diarrhea), changes in food and water consumption,

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and other physical abnormalities. The body weight of the rats was measured at the beginning and end of the intervention to determine the average weight gain. At the end of the observation period, the experimental animals were euthanized using ketamine/xylazine inhalation anesthesia followed by cervical dislocation to strictly comply with animal welfare principles**.** The experimental animals were sacrificed to harvest the liver and kidneys for histopathological examination using a light microscope. The histopathological analysis was performed using standard Hematoxylin and Eosin (H&E) staining. The body weight change data were tested for normality using the Shapiro-Wilk test, followed by a Paired t-test and One-way ANOVA, while the LD_{50} value was determined based on the number of mortalities at the highest administered dose.

Results

Table 1. Symptoms of Toxicity in the Form of Behavioral Changes in the Control Group and Treatment Group (n = 5)

Observation	Day 1 (Incidence Fraction)				Day 14 (Incidence Fraction)			
	K	P I	PII	P III	K	PI	PII	PIII
Lethargy	0/5	0/5	4/5	2/5	0/5	0/5	0/5	0/5
Diarrhea	0/5	0/5	3/5	2/5	0/5	0/5	0/5	0/5
Tremors	0/5	0/5	4/5	1/5	0/5	0/5	0/5	0/5
Cyanosis	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5
Physical Abnormalities	0/5	0/5	4/5	2/5	0/5	0/5	0/5	0/5
Strange Behavior	0/5	0/5	5/5	3/5	0/5	0/5	0/5	0/5
Mortality	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5

Observation results showed that the toxicity symptoms, specifically behavioral changes, were acute and dose-dependent. On Day 1 of observation, the Control Group (K) and Treatment Group I (PI) did not display any clinical symptoms across all observed parameters. Conversely, toxicity symptoms such as lethargy, diarrhea, tremors, physical abnormalities, and abnormal behavior began to appear (positive) in Treatment Group II (PII) and Treatment Group III (PIII). Interestingly, cyanosis was not observed in any of the experimental groups on the first day. Furthermore, there was zero mortality (0/5) across all experimental groups, explicitly confirming that the LD_{50} value of the extract exceeds 10 g/kg BW. Observation results on Day 14 revealed a significant change, wherein all observation parameters across all treatment groups (PI, PII, and PIII) showed completely negative results. The disappearance of the clinical symptoms that had previously appeared in the PII and PIII groups on the first day demonstrates that the toxic effects of the treatment substance are reversible. This condition indicates an effective physiological adaptation process within the animals' bodies, or suggests that their metabolic systems successfully detoxified and

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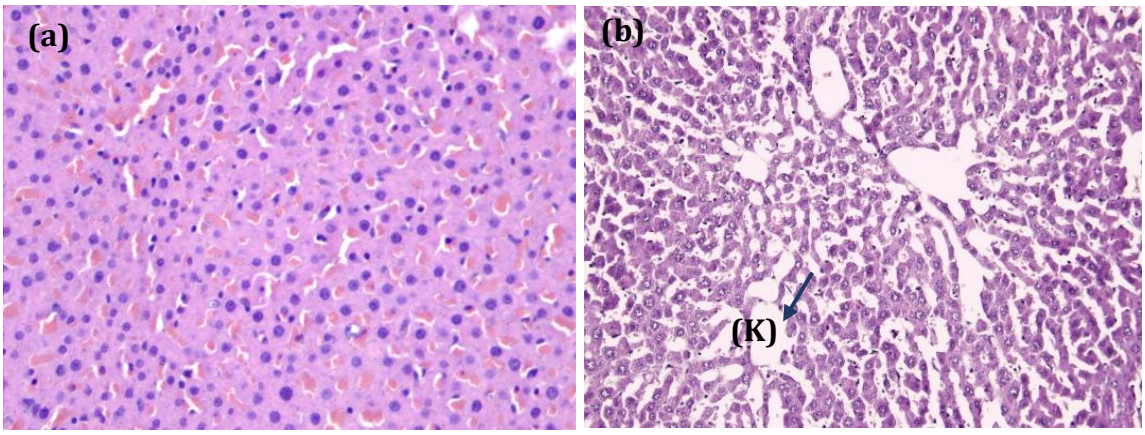
eliminated the substance over time, thereby allowing the behavioral conditions of the experimental animals to return to baseline.

Table 2. Mean Body Weight Gain of Wistar Rats Before and After Administration of Breadfruit Leaf Extract

Group	Weight			p value
	Pretest	Posttest	Δ	
Control	157 ± 4.66	170 ± 5.77	13 ± 6.28	0.010[a]
PI	162 ± 6.1	180 ± 5.45	17.8 ± 1.09	0.001[a]
PII	160 ± 7.09	177 ± 6.61	17.4 ± 1.67	0.001[a]
PIII	159 ± 5.47	187 ± 3.53	26.4 ± 7.05	0.001[a]
P Value		0.001[b]		

[a]Paired t-Test (comparing Pretest and Posttest within the same group); [b]One-Way ANOVA (comparing weight gain differences among all groups).

The analysis results in Table 2 show a significant increase in body weight across all experimental groups. Based on the Paired t-Test, there was a significant difference ($p < 0.05$) between body weight before (Pretest) and after (Posttest) the intervention, with the percentage of body weight gain (%Δ) being 8.3% in the Control group, 10.9% in PI, 10.8% in PII, and reaching the highest figure of 17.7% in the PIII group, respectively. Analysis using One-Way ANOVA yielded a value of $p = 0.001$, confirming a highly significant difference in the average weight gain among the treatment groups. The trend of higher weight gain in the treatment groups, particularly PIII, indicates that despite the initial appearance of clinical symptoms (Day 1), long-term administration of breadfruit leaf extract did not interfere with appetite or nutrient absorption, but rather potentially supported metabolic improvement and general health status in Wistar rats.



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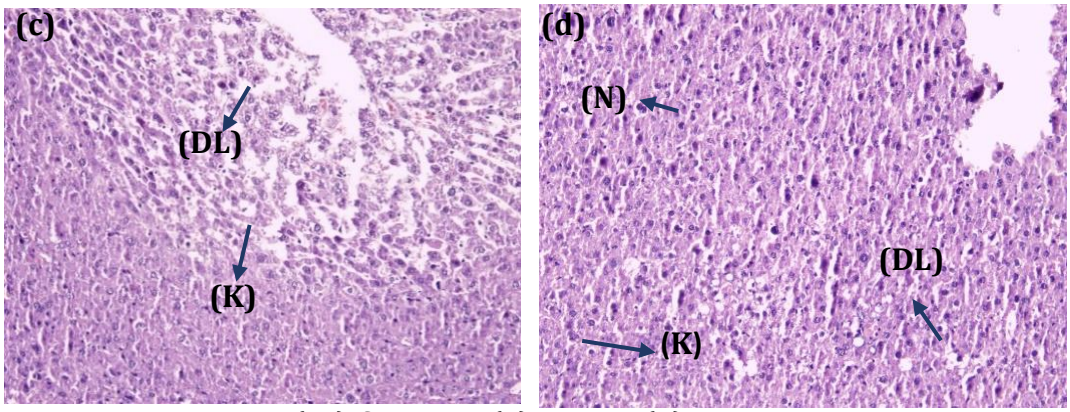
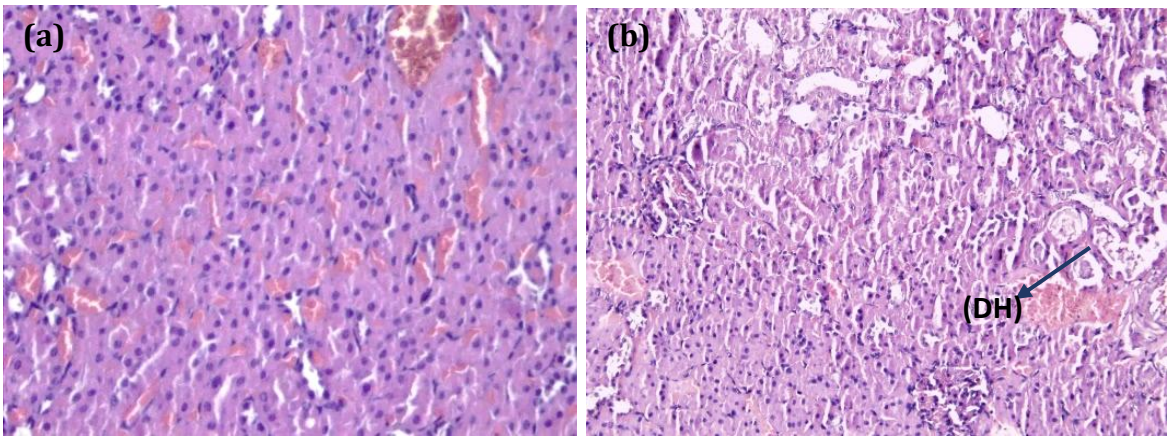


Note: Fatty Degeneration (DL), Congestion (K), Necrosis (N)

Figure 1. Effect of breadfruit leaf extract on the histopathology of the liver of Wistar rats, (a): Control group, (b): group I dose 3 g/kg bw, (c): group II dose 5 g/kg bw and (d) group III dose 10 g/kg bw.

Observation results in Figure 1 regarding the histopathology of Wistar rat livers reveal that the administration of breadfruit leaf extract exerts varying effects depending on the dose. In the control group (a) and the 3 g/kg BW treatment group (b), the liver cells (hepatocytes) appear normal, displaying a well-organized radial arrangement alongside well-preserved nucleus and cytoplasm conditions. Changes begin to appear in the 5 g/kg BW group (c), where moderate congestion (blood accumulation in the veins) and mild fatty degeneration in the cytoplasm are observed. The most visible damage occurs in the 10 g/kg BW group (d), which exhibits severe congestion, higher accumulation of fatty degeneration, and the onset of mild cell necrosis. Overall, the severity of hepatocyte damage is directly proportional to the increase in dosage, indicating that a higher extract dose imposes a greater metabolic burden on the liver; nevertheless, the extract is still generally categorized as practically non-toxic as it caused no mortality.



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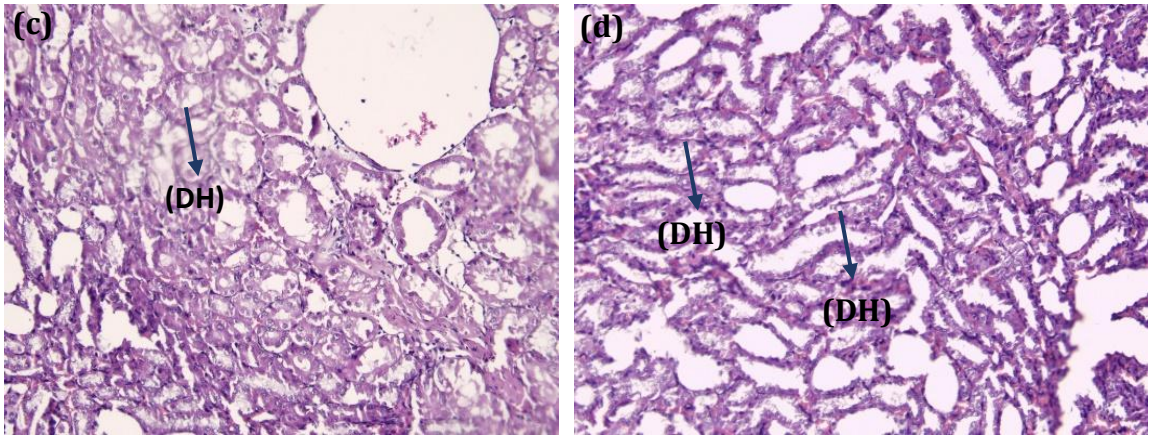

Note: Hydrophilic Degeneration (DH)

Figure 2. Effect of breadfruit leaf extract on the histopathology of the kidneys of Wistar rats, (a): Control group, (b): group I dose 3 g/kg bw, (c): group II dose 5 g/kg bw and (d) group III dose 10 g/kg bw

Observation results in Figure 2 show that the administration of breadfruit leaf extract exerts varying effects according to the administered dose. The control group (a) displays normal kidney tissue without any structural abnormalities. In treatment group I with a dose of 3 g/kg BW (b), abnormalities in the form of Hydropic Degeneration (HD) begin to be observed, though still within the mild category. Damage increases in treatment group II with a dose of 5 g/kg BW (c) and group III with a dose of 10 g/kg BW (d), where moderate abnormalities are found, including hydropic degeneration, glomerular atrophy, and dilation of several renal tubules.

DISCUSSION

The absence of mortality at a very high dose (10 g/kg BW) categorizes the aqueous extract of breadfruit leaves as practically non-toxic (LD_{50} > 10,000 mg/kg BW). This high safety margin is consistent with previous toxicity studies on other *Artocarpus* species. A study on *Artocarpus chama* leaf extract demonstrated the presence of phytochemical compounds such as flavonoids, tannins, alkaloids, and steroids, as well as antioxidant and neuropharmacological activities, without any reported adverse acute toxicity at the tested doses (200-500 mg/kg) (15,16). Furthermore, the use of water as an extraction solvent (maceration) likely contributed to this high safety profile. Aqueous extraction tends to isolate polar compounds while leaving behind more toxic, non-polar constituents often extracted by organic solvents like methanol or hexane. This high LD_{50} value provides a strong scientific basis that the therapeutic potential of breadfruit leaves for dyslipidemia does not compromise its acute safety aspects. Biochemically, the active compounds in *Artocarpus altilis* such as flavonoids, saponins, and tannins are considered relatively safe in the short

term because their antioxidant properties effectively neutralize immediate oxidative stress without overwhelming the cellular defense mechanisms.

During the first 30 minutes following the administration of high doses (5 g/kg BW and 10 g/kg BW), the rats exhibited clinical symptoms such as lethargy, diarrhea, tremors, and abnormal behaviors, including nose-scratching and rearing. Rather than merely reflecting generalized glucocorticoid-induced physical stress (17), these acute symptoms are likely linked to the specific phytochemical profile of the extract. For example, high concentrations of saponins can induce temporary gastric irritation and alter gut permeability, leading to diarrhea and gastrointestinal discomfort. Additionally, a sudden influx of certain alkaloid compounds may cause mild, transient neurotoxic effects or Central Nervous System (CNS) overstimulation, manifesting as tremors and rearing. However, after 14 days of observation, all experimental animals returned to normal, healthy, and active behavior. This rapid physiological adaptation indicates that the metabolic system successfully detoxified and eliminated these water-soluble compounds before irreversible systemic failure could occur.

In this study, all experimental groups demonstrated a significant increase in body weight following the intervention, with the highest gain (17.7%) observed in the 10 g/kg BW group. This finding indicates that the administration of breadfruit leaf extract does not interfere with appetite or nutrient absorption. In fact, leaf extracts rich in antioxidants and phytochemicals can play a crucial role in improving metabolic health, thereby indirectly contributing to healthy weight gain, particularly under conditions of oxidative stress or metabolic disorders (18). This outcome sharply contrasts with general toxicological theories, where exposure to toxic substances typically causes a significant decrease in body weight (often >10%) due to physiological stress, gastrointestinal discomfort, or disruption of the gut microbiota leading to nutrient malabsorption (19). Furthermore, toxicity usually triggers dysfunction in energy and lipid metabolism in the liver, exacerbated by oxidative stress and systemic inflammation (20).

The histopathological analysis of the liver showed that the 3 g/kg BW dose group displayed a normal liver architecture. However, at doses of 5 g/kg BW and 10 g/kg BW, congestion (blood accumulation) and fatty degeneration (lipid accumulation within the cytoplasm) were observed. At the highest dose (10 g/kg BW), the onset of mild necrosis (cell death) was even detected. While elevated Reactive Oxygen Species (ROS) generally trigger cell death (21,22), these specific hepatic changes can be attributed to the metabolic burden of processing ultra-high doses of phytochemicals. The accumulation of alkaloid metabolites in the liver can overwhelm the detoxification capacity of hepatocytes, directly burdening the tissue. Furthermore, excessive amounts of saponins possess surfactant properties that can interact with and disrupt the lipid bilayer of cell membranes, potentially leading to cell lysis and the observed mild necrosis at the 10 g/kg BW dose.

The histopathological analysis of the kidneys showed the presence of hydropic degeneration across all treatment groups, ranging from mild to moderate categories at high doses. Similarly, this hydropic degeneration represents a cellular response to the intense filtration burden of excreting high concentrations of plant metabolites, such as tannins and flavonoids. While flavonoids are highly beneficial at therapeutic doses for treating dyslipidemia, an excessive acute load requires intensive mitochondrial metabolic activity for excretion, which can temporarily disrupt ion regulation and cause cell swelling (23). Nevertheless, no necrosis was observed in the kidney tissue across all groups. This study has certain limitations, primarily that it solely evaluates acute toxicity over a short 14-day observation period following a single-dose administration, and utilizes an animal model which may not entirely reflect human physiological responses. It is recommended that further sub-chronic or chronic toxicity studies be conducted to evaluate the effects of long-term use before the extract is widely applied as a herbal therapy for dyslipidemia.

Conclusion

Based on the results, the aqueous extract of Artocarpus altilis leaves, a potential therapeutic agent for dyslipidemia, is demonstrated to be practically non-toxic, exhibiting an LD_{50} value exceeding 10 g/kg BW. Clinical symptoms appearing on the first day at high doses were reversible and did not negatively impact weight gain, which increased significantly across all treatment groups. However, microscopic analysis showed dose-dependent histopathological changes in the liver and kidneys, such as fatty degeneration, mild necrosis, and hydropic degeneration. This indicates that while safe from the risk of sudden death, very high doses may affect the tissue integrity of excretory organs.

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