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Acute oral toxicity test and determination of lethal dose (LD_{50}) of *Garcinia forbesii* King leaf extract in wistar rats

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ABSTRACT

Garcinia forbesii King, an endemic plant from Sumatra and Kalimantan, is traditionally used for treating skin infections and inflammation. Its potential use as a raw material for medicines needs to be supported by safety tests. The purpose of this study is to assess the acute toxicity of its 70% leaf extract in male Wistar rats, evaluating clinical symptoms, body weight changes, organ indices, and the lethal dose (LD_{50}). The study administered extract doses orally at 5 (G2), 50 (G3), 300 (G4), and 2,000 (G5) mg/kg BW, monitoring toxicity signs over 14 days. Symptoms such as piloerection, respiratory distress, and soft feces were noted. Significant weight loss was observed at doses of 2,000 mg/kg BW. There was no significant effect on the kidney index, but the liver and heart indices exhibited significantly lower changes compared to the control. The LD_{50} value was estimated to be between 2,000-5,000 mg/kg BW. Further studies are recommended to assess histopathological effects and identify harmful chemicals in the plant.

Keywords: *Garcinia forbesii* King, acute toxicity test, lethal dose, LD_{50}, methanol

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INTRODUCTION

Garcinia forbesii King, a tropical and subtropical plant, is prominently cultivated in the forests of Kalimantan, Sumatra, and certain regions of Malaysia. This specific species, classified within the Garcinia genus, is commonly referred to as red mangosteen or Mundar fruit in the Kalimantan region. While the fruit is mainly appreciated for its delightful sweet and sour flavor, it is a common practice for individuals to discard the skin. However, in certain areas, the pericarp is employed as a traditional remedy for treating skin infections and inflammations (Hadi & Nastiti, 2023; Rosida & Panghiyangani, 2023; Sutomo et al., 2021).

Phytochemical research has focused on investigating secondary metabolites extracted from various parts of *G. forbesii* King, including the pericarp, branches, tree bark, and leaf (Figure 1) Upon conducting phytochemical screening, xanthones, flavonoids, terpenoids, and polyphenols were found to be present in the pericarp, demonstrating their potential anticancer properties (Joharman et al., 2021). Notably, rubraxanthone extracted from the bark has shown antibacterial and antiplasmodial activity in studies conducted by Alen et al. (2008) and Wairata et al. (2022). On the other hand, the leaf of *G. forbesii* King contains phenylpropanoid compounds, known for their high antioxidant activity, and steroids, which are believed to possess anti-inflammatory properties (Perdana, 2023; Sutomo et al., 2020). In fact, a recent study by Sutomo et al. (2020) demonstrated that the antioxidant activity of *G. forbesii* leaf surpassed that of the fruit skin.

Drawing upon prior studies that have investigated the antioxidant and anti-inflammatory properties of the G. *forbesii* King leaf, it is rather intriguing to note that conducting toxicity tests is essential in order to determine the safety levels associated with the medicinal use of G. *forbesii* King leaf. Test animals are used in these studies to determine the preparation's average dose-response data and to detect any harmful effects on biological systems (BPOM RI, 2022).

An acute oral toxicity test is designed to identify harmful effects that manifest shortly after oral administration of a test drug or after repeated doses within a 24-hour period. Finding a substance's inherent toxicity, obtaining information on hazards following acute exposure, establishing initial dose levels, and figuring out a substance's or formulation's LD_{50} are the goals of the oral acute toxicity test (BPOM RI, 2022; OECD, 2001). As there is no existing research on the acute toxicity tests or LD_{50} determination of *G. forbesii* King leaf, conducting an oral acute toxicity test of *G. forbesii* King leaf is essential prior to their commercial use. Therefore, the goal of this study is to ascertain the leaf toxic effects and LD_{50} of *G. forbesii* on male white rats. The findings from this study are expected to serve as a foundation for further toxicity tests and as a reference for the development of *G. forbesii* King leaf formulations as novel natural-based drug candidates.

MATERIALS AND METHOD

Materials

Fresh *G. forbesii* King leaves were taken from Biih Kampong, Karang Intan sub-district, Banjar Regency, South Kalimantan Province in December 2023 (Figure 1) Methanol (CV. Eralika mitra persada), aquadest. The taxonomic determination of the *G. forbesii* King plant was carried out in the Lab of the Faculty of Mathematics and Natural Sciences at Universitas Lambung Mangkurat, with the taxonomic determination number 281/LB.LABDASAR/XI/2023.

Methods

G. Forbesii King leaf extract

Fresh *G. forbesii* King leaves are air-dried at room temperature until the leaves can be crushed. After drying, the leaves are pulverized using a blender to obtain simplisia in powder form. A 70% methanol solvent was used in the maceration process to extract 200 g of Garcinia leaf powder. The extraction process lasted for a full day, repeated three times for twenty-four hours each, with an eight-hour stirring interval and a solvent change every 24 hours. The liquid extract obtained was filtered,

evaporated in a rotary evaporator, and thickened at 50°C in a water bath to produce a viscous extract with a consistent weight (Sutomo et al., 2020).

Figure 1. (A) *G. forbesii* King tree; (B) *G. forbesii* King branch; (C) *G. forbesii* King fruits

Source: https://home.banjarkab.go.id/mundar-banjar-dinobatkan-sebagai-buah-langka-terenak-2/ and personal photograph.

Experimental animals

A total of 25 male Wistar rats, each aged between 8 and 12 weeks and weighing in the range of 160 to 200 grams, were utilized for the study. The rats were carefully selected to ensure they had no weight variation of more than 20% and were in good health. Rats were maintained in characteristic laboratory settings, with a twelve-hour light-dark cycle, ad libitum meal, water feeding, and cage room temperatures between 20 ±2°C. The experimental animal protocols received approval from the Animal Ethics Committee of the Faculty of Medicine at Universitas Lambung Mangkurat, located in South Kalimantan, with the ethical clearance number being 075/KEPK-FKIK ULM/EC/VI/2024.

Acute oral toxicity test

The Food and Drug Administration's Regulation Number 10 of 2022 was followed when performing the acute oral toxicity test, employing a fixed-dose procedure. The test is divided into two distinct stages: the initial stage and the main stage. The initial stage aims to establish the suitable starting dose for use in the following main stage, where only one rat is used for the initial evaluation. Based on BPOM regulations for acute oral toxicity tests, used fixed doses are 5 (G2), 50 (G3), 300 (G4), and 2,000 (G5) mg/kgBB body weight, which are expected to cause toxic effects. The main stage is carried out at the dose level, where death occurs in the preliminary stage or the highest dose reached in the initial stage. In this main stage, the conducted to find the LD_{50}, 5 test animals at the test dose. These five test animals consisted of 1 from the preliminary test and 4 additional test animals (BPOM RI, 2022).

Observations were made after a single administration of *G. forbesii* King leaf extract for 30, 60, 120, and 240 minutes within the first 24 hours. Furthermore, observations were conducted once a day for 14 days. Body weight was assessed before treatment and prior to sacrifice on the 14th day. Rats that remained alive were dissected to retrieve liver, kidney, and cor organs for organ index calculation. Toxicity symptoms and organ indices were compared with those of the control group.

Data Analysis

The statistical analysis was conducted with SPSS version 25. The Shapiro-Wilk test was applied to evaluate the normality of the data. If the data showed a normal distribution, the paired t-test was used to analyze weight changes before and after the intervention. Conversely, the Wilcoxon test was used for data that did not conform to a normal distribution. If the data did not meet the assumption of normality, the Kruskal-Wallis test was employed at a confidence level of 95%.

RESULT AND DISCUSSION

Toxic effects of the 70% methanol extract of *G. forbesii* King.

Acute toxicity tests conducted on Wistar rats during the initial 24-hour observation period showed no significant behavioral changes (Table 1). Breathing is monitored as an indicator of toxicity and its effect on respiratory function. Piloerection remained until 240 minutes, while in group 4 (300 mg/kg dose), piloerection occurred at the 240th minute. Piloerection refers to the phenomenon in which feathers become erect due to tension, a process regulated by sympathetic nerves innervating the pili arrector muscles, crucial for maintaining body temperature (Nurbaeti et al., 2021; Ubang et al., 2022).

Table 1. Signs of toxicity are observed when doses of 5 (G2), 50 (G3), 300 (G4), and 2,000 (G5) mg/kg BW are applied within a span of 4 hours

Signs of toxicity	Time (minutes)				
	30	60	120	180	240
Piloerection	G5*1	G5*1	G5*1	G5*1	G4-5*1
Ptosis	N	N	N	N	N
Seizures	N	N	N	N	N
Lacrimation	N	N	N	N	N
Grooming	N	N	N	N	N
Hyperactivity	N	N	N	N	N
Respiration	N	G5*1	N	N	N
Writhing	N	N	N	N	N
Defecation	N	N	N	N	N
Death	N	N	N	N	N

Description
N = All normal groups G5 = 2,000 mg/kg BW
G4= 300 mg/kg BW *1 = Number of rats

In Table 2, it can be seen that no deaths occurred with the administration of *G. forbesii* King leaf extract doses of 5 (G2), 50 (G3), 300 (G4), and 2,000 (G5) mg/kg BW for 14 days.

Table 2. Potential toxic effects of the 70% methanol extract from leaf *G. forbesii* King in wistar rats

Group	N	Mortality	% Mortality
	Initial Stage		
G1	1	0	0
G2	1	0	0
G3	1	0	0
G4	1	0	0
G5	1	0	0
Group	**Main stage**		**% Mortality**
G1	4	0	0
G2	4	0	0
G3	4	0	0
G4	4	0	0
G5	4	0	0

Description
G1 = Control group G4 = 300 mg/kg BW
G2 = 5 mg/kg BW G5 = 2,000 mg/kg BW
G3 = 50 mg/kg BW

After the preliminary test findings showed no fatalities at any of the administered dose levels, the main test continued with four specific doses: 5 mg/kg BW (G2), 50 mg/kg BW (G3), 300 mg/kg BW (G4), and 2,000 mg/kg BW (G5). The behavioral patterns of the experimental animals were meticulously observed at intervals of 30, 60, 120, 180, and 240 minutes, followed by a subsequent observation period lasting 24 hours after the extract was administered via oral sonde. The behaviors observed in the rats included piloerection, ptosis, convulsions, lacrimation, grooming, hyperactivity, variations in breathing, writhing, and defecation.

During the 14-day observation period, certain symptoms indicative of toxicity were still evident, particularly manifesting as piloerection in the dose groups of 50-2,000 mg/kg BW (G3-5); however, it is noteworthy that piloerection ceased to occur following the fifth day of administration. Ptosis was found in the 2,000 and 300 mg/kg BW dose groups (G4-5) but was not found after day 7 of observation. Ptosis refers to drooping eyelids caused by decreased motor activity. On the second day of administration, it was observed that the feces' consistency in the experimental animals had slightly softened and showed a darker brown color; this alteration was consistent across all dose groups and lasted until the fourteenth day.

Table 3. Signs of toxicity were observed over a period of 14 days

Signs of toxicity	Day							
	2	**3-4**	**5**	**6**	**7**	**8-9**	**10-11**	**12 -14**
Piloerection	G4-5*2	G3-5*2	G3*2	N	N	N	N	N
Ptosis	N	G5*1	G5*1	G4-5*1	G4*1	N	N	N
Seizures	N	N	N	N	N	N	N	N
Tremor	N	N	N	N	N	N	N	N
Lacrimation	N	N	N	N	N	N	N	N
Grooming	N	N	N	N	N	N	N	N
Hyperactivity	N	N	N	N	N	N	N	N
Respiration	N	N	N	N	N	N	N	N
Writhing	N	N	N	N	N	N	N	N
Weakness	N	N	N	N	G2*1	G4*2	N	N
Defecation	G2-5*3	G2-5*3	N	N	G2-4*1	N	N	G2-3*2
Death	-	-	-	-	-	-	-	-

Description
N = All normal groups
G1 = Control group
G2 = 5 mg/kg BW
G3 = 50 mg/kg BW
G4 = 300 mg/kg BW
G5 = 2,000 mg/kg BW
* = Number of rats

Defecation is the physiological process by which the intestines are emptied, resulting in the removal of waste material from the body. An atypical increase in the frequency of defecation is commonly referred to as diarrhea. Changes in stool consistency may indicate mild toxicity, necessitating further investigation to determine the mechanism of toxicity and toxic dose. Based on the the analysis “Liquid Chromatography-High Resolution Mass Spectrometry” (LC-HRMS), methanol 70% s extract of *G. forbesii* King leafs contains several secondary metabolites, including oxalosuccinic acid (Rosida, 2024). Oxalosuccinic acid is a crucial intermediate in the TCA (Tricarboxylic Acid) cycle, which plays a role in intermediate metabolism and energy production. While not directly linked to causing diarrhea, its metabolite succinate has been associated with diarrhea under specific conditions. The accumulation of succinate in the gut can lead to increased colonic fluid secretion and inflammatory responses, contributing to diarrhea (Kaczmarczyk et al., 2021; Zhou et al., 2022).

Additional signs of toxicity include seizures, a neurological disorder marked by excessive brain electrical activity brought on by an increase in the excitatory neurotransmitters glutamate and aspartic acid and a decrease in the inhibitory neurotransmitter GABA. Excessive tear production is termed lacrimation, which can be influenced by autonomic nerves. Grooming is a behavior displayed by rats to clean their bodies, particularly the face, and an increase in its frequency may suggest pain. Hyperactivity, alterations in the central nervous system, or fear of being touched can also indicate pain. Writhing, characterized by abnormal twisting movements, is a sign of pain and discomfort in animals. Rats employ pain as a defensive mechanism in response to potentially harmful stimuli; however, following the administration of the methanol extract derived from G. *forbesii* King leaves, none of the typical indicators of toxicity was observed. Detailed observations can be found in Table 2 & Table 3 (Nurbaeti et al., 2021; Ubang et al., 2022).

Weight change

Data on changes in rat body weight were collected prior to treatment and after the administration of the test extract for 14 days. The findings of the paired t-test analysis showed no significant difference in body weight before and after 14 days of treatment in the control and 300 mg/kg BW groups ($p = 0.624$ and 0.452, respectively). Nevertheless, the 5 and 50 mg/kg BW dose groups exhibited a significant increase in body weight ($p = 0.001$ and 0.013). Conversely, the test group receiving a dose of 2,000 mg/kg BW displayed a significant decrease in body weight prior to and after treatment, as evidenced by the Wilcoxon rank test results ($p = 0.042$), depicted in Figure 2 below.

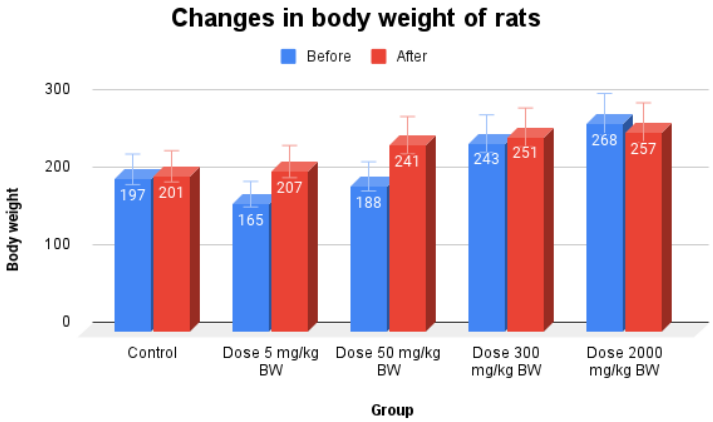

Figure 2. Effect of *G. forbesii* King leaf extract on changes in body weight of rats

It is crucial to acknowledge that changes in body weight in rats can be influenced by various factors, including internal and external factors of the experimental animals, and the composition of the test preparation. In a study conducted by Rosida (2024), it was found that the methanol extract of *G. forbesii* leaf contains hydroxycitric acid (HCA). HCA has been shown to inhibit extramitochondrial citrate lyase, which plays a role in cellular fatty acid synthesis, thereby inhibiting lipogenesis (Onakpoya et al., 2011; Tutunchi et al., 2023). This is in accordance with the 2,000 mg/kg BW dose group, where there is a significant decrease in body weight.

Organ index

The organ index serves as an indicator of the relative changes in organ weight of experimental animals after dosing with the test substance, and it is used to assess the toxic effects of that substance on the organs. To calculate the organ index, one divides the weight of the organ by the body weight of the experimental animal and subsequently multiplies the resulting figure by 100. In Table 4, the organ

index of the liver, kidney, and cor was calculated. The results showed significant differences in liver and heart indices (p = 0.01 and 0.02, respectively). It is suspected that *G. forbesii* King leaf extract has a toxic effect on the liver and heart. The organ index can be used as an indicator to determine the toxic effect of a material or test sample, whether there is enlargement or shrinkage of an organ, although it cannot be used as a standard for determining damage (Ubang et al., 2022).

Table 4. The effect of *G. forbesii* King leaf extract on average organ index

Index Organs	Control	Dose 5 mg/kg BW	Dose 50 mg/kg BW	Dose 300 mg/kg BW	Dose 2000 mg/kg BW	p
Kidney mean ± SD	0,0074 (±0.0009)	0.0068 (±0.0004)	0.0066 (±0.0009)	0.0071 (±0.0011)	0.0064 (±0.0004)	0.60 (NS)
Liver mean ± SD	0.0314 (±0.0043)	0.0368 (±0.0014)	0.0292 (±0.0032)	0.0322 (±0.0031)	0.0312 (±0.0015)	0.01(S)
Cor median (min-max)	0.0040 (0.0031-0.0043)	0.0033 (0.0031-0.0033)	0.0030 (0.0025-0.0032)	0.0030 (0.0030-0.0034)	0.0030 (0.0027-0.0033)	0.02 (S)*

The results of the ANOVA test for kidney index are not significant (NS), while the liver index is significantly (S) different; the* Kruskal-Wallis test for organ index shows a significant difference.

LD_{50} determination

Preparation of a single test preparation was carried out by mixing the methanol leaf extract test preparation with distilled water. In this study, the doses administered were determined using the fixed dose method, specifically consisting of 5 mg/kg BW (G2), 50 mg/kg BW (G3), 300 mg/kg BW (G4), and 2,000 mg/kg BW (G5). Observations were conducted throughout both the preliminary and main tests at the mentioned doses, with all rats surviving until the fourteenth day. The death of test animals was noted during the observation, so the determination of the acute toxicity LD_{50} value of the methanol extract of *G. forbesii* King leaf could not be determined using the probit method. Therefore, the determination of acute toxicity in this study uses pseudo LD_{50}, where the toxicity benchmark is seen from the value of the highest dose given to the test animal (Abrori et al., 2019). In this study, the LD_{50} value of the preparation of 70% methanol extract of *G. forbesii* King leaf in male rats Rattus norvegicus is greater than 2,000 mg/kg BW or is in category 5, namely no deaths but found ≥1 symptom of toxicity, which means LD_{50} > 2,000-5,000 mg/kg BW is mildly toxic according to Hodge and Sterner (1995) in the Guidelines for Nonclinical Toxicity Tests In Vivo by BPOM. Several studies of toxicity tests on the leaves of the genus Garcinia show varying results. Santa-Cecília et al., 2011 reported the administration of 0.5-5 g of *Garcinia brasiliensis* leaf extract orally to male Wistar rats for 7 days showed no symptoms of toxicity or death. Similarly, Pachare & Garge, 2022, reported acute oral toxicity tests of *Garcinia indica* leafs in Albino female rats up to a dose of 2,000 mg/kg BW orally, which showed no signs of toxicity. Meanwhile, the acute toxicity test of the aqueous extract of *Garcinia hombroniana* leaves by Dyary et al., 2016, in female Sprague Dawley rats showed little toxicity in terms of body weight, clinical biochemistry, hematology, relative organ weight, and tissue histology (cor, kidney, liver, and spleen), with LD_{50} > 5,000 mg/kg BW.

Different aspects of the toxicity test of *Garcinia cowa* leaves were explored in the research conducted by Wahyuni et al., 2017. They administered the ethyl acetate fraction of *Garcinia cowa* leaf extract to Swiss albino mice of both sexes and observed significant effects on creatinine levels, SGPT, and the weight ratio of liver and kidney organs at doses of 80, 500, 1000, and 2,000 mg/kg BWrat. In a different investigation, Nweke et al., 2019 male Wistar rats were orally administered Garcinia kola leaf extract at doses of 300, 600, and 900 mg/kg BW rat for 28 days. This caused histopathological damage to the testes and potentially led to infertility in male rats. The variations in toxicity test results among different Garcinia species may be attributed to differences in compound content, which necessitate further research.

CONCLUSION

The outcomes of the methanol oral acute toxicity test of *G. forbesii* King leaves showed signs of toxicity within the first 24 hours at doses of 2,000 and 300 mg/kg. The results of the oral acute toxicity test of the methanol extract of *G. forbesii* King leaves showed signs of toxicity in the first 24 hours at doses of 2,000 and 300 mg/kg BW in the form of piloerection and respiratory distress. Additionally, changes in stool consistency were also observed, becoming more mushy. There was a significant increase in body weight observed at doses of 5 and 50 mg/kg BW; moreover, a notable rise in body weight was also recorded at the 2,000 mg/kg dose throughout the 14-day observation period. The LD_{50} value of *G. forbesii* King leaves is 2,000-5,000 mg/kg BW, which indicates mild toxicity. Additional investigation is required to examine the compounds found in the leaves of *G. forbesii* King and to examine the histopathologic changes in test animals after administration of *G. forbesii* King extract.

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