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**TOXICITY AND HISTOLOGICAL ANALYSIS OF PINEAPPLE CORE
EXTRACT (*Ananas comosus*) IN MALE WISTAR RAT**

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ABSTRACT

Background: Pineapple core (*Ananas comosus*) contains bromelain enzyme, which is known to remove dead skin tissue and promote the formation of new tissue. Pineapple fruit and core are also rich in bioactive compounds with potential pharmacological effects. In the oral cavity, it is beneficial in increasing salivary flow. **Objective:** This study aimed to analyze the toxicity and histological effects of pineapple core extract (*Ananas comosus*) in male Wistar rats (*Rattus norvegicus*) using control and treatment groups. **Methods:** This experimental study used 30 male Wistar rats (*Rattus norvegicus*), which were administered pineapple core extract supplementation for 14 days. The feed formulation contained pineapple core extract at concentrations of 75% and 90%, with doses ranging from 5,000 mg/kg body weight (BW) to 10,000 mg/kg BW. Histological examination of rat liver tissue was performed at the end of the study. **Results:** Observation of the control group demonstrated normal liver histology, in which hepatocytes were radially arranged within the hepatic lobules. Similar findings were observed in treatment group (K1), where most hepatocytes appeared normal, with only mild degeneration and necrosis, as well as congestion in the sinusoidal area. **Conclusion:** Pineapple core extract did not demonstrate toxic effects up to a dose of 10,000 mg/kg BW, although minimal histological alterations in liver tissue were observed.

Keywords: Histology; Male wistar rats; Pineapple core extract (*Ananas comosus*); Toxicity

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INTRODUCTION

Indonesia is a country rich in plant biodiversity, with an estimated 30,000 plant species. Approximately 9,600 of these species are believed to possess medicinal properties. However, limited public knowledge regarding traditional medicine remains a major challenge, resulting in its underutilization.^{1,2} Pineapple (*Ananas comosus*), a plant native to Brazil and Paraguay, is commonly consumed fresh, canned, or as juice, and is frequently served as a dessert.³ Bromelain, a proteolytic enzyme derived from pineapple, has been reported to accelerate wound healing, exert analgesic effects, and reduce pain and bruising after surgery.⁴

The pineapple core, commonly regarded as agricultural waste due to its difficult processing characteristics, contains valuable compounds, including bromelain.⁵ Bromelain extracted from the pineapple core has been reported to contain a higher concentration of cysteine proteinase compared to bromelain obtained from pineapple juice.^{6,7} Bromelain also functions as an anti-inflammatory agent and possesses antithrombotic and antiplatelet aggregation properties.⁸

Toxicity testing is performed to evaluate the toxic effects of a compound following single-dose administration within a specific period. This test aims to determine the LD50 (lethal dose), defined as the dose

causing death in 50% of experimental animals under predetermined conditions. Qualitative data obtained include clinical and morphological observations, as well as the mechanisms underlying toxic effects. Histological examination of vital organs, particularly the liver, is also conducted to identify structural alterations associated with impaired liver function due to toxicity.^{9,10} Histological assessment includes microscopic observation of liver tissue to detect inflammation, necrosis, and cellular degeneration caused by exposure to specific compounds.¹¹

Previous studies demonstrated that pineapple core extract influenced growth and salivary flow rate in stunted male Wistar rats.¹² Growth improvements included increases in body weight, body length, and tail length following administration of 75% pineapple core extract (*Ananas comosus* [L.] Merr). Previous study reported that the pineapple core extract contains several bioactive compounds, including flavonoids, saponins, alkaloids, tannins, steroids, and glycosides.¹³ Based on the above findings, this study aimed to identify the toxic effects of pineapple core extract, including histological examination of liver tissue, to evaluate liver function as an important indicator of the extract's safety.

MATERIALS AND METHODS

Material

The instruments used included dissection trays, minor surgical sets, 3 cc syringes, alcohol (70%, 80%, 90%, absolute), collection tubes, micropipettes, measuring cylinders, incubators, scissors, analytical balances, microscopes, scalpels, forceps, and cameras. The materials used consisted of pineapple core extract, 96% ethanol, experimental animal feed, distilled water, and alcohol. The samples consisted of pineapple cores (*Ananas comosus*) obtained from Central Aceh Regency and male Wistar rats with stunted body weight, aged less than 2 months and weighing less than 70% of normal body weight. A total of 30 rats were divided into four treatment groups.

Methods

This experimental study employed a post-test only control group design to evaluate the effects of pineapple core extract on male Wistar rats. The study was conducted at the Basic Chemistry Laboratory, Faculty of Mathematics and Natural Sciences, Universitas Syiah Kuala, where the pineapple core extract (*Ananas comosus*) was prepared. Toxicity and cellular histology examinations were performed at the Histology Laboratory, Faculty of Veterinary Medicine, Universitas Syiah Kuala, from February to March 2024. This study was approved by the Research Ethics Commission, Faculty of Veterinary Medicine, Syiah Kuala University, with ethical clearance number of 341/KEPH/IX/2024.

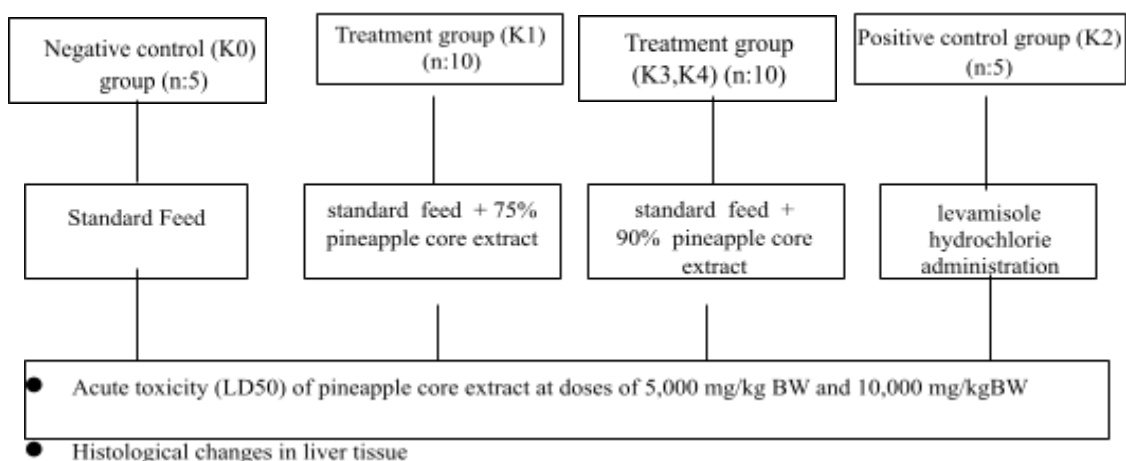


Figure 1 Experiment Design

Research Procedure

All equipment was sterilized to ensure cleanliness and safety. Pineapple cores were collected after peeling the fruit. The cores were dried at 40°C for 3 days, weighed, and ground into powder. Extraction was performed using a maceration method with 96% ethanol as the solvent at a 1:10 ratio for 24 hours at 4°C. The solvent was replaced three times within 24 hours, after which the extract was filtered and evaporated at 40°C.

The macerated extract was then stored in a refrigerator at 4°C. Subsequently, 500 g of pineapple core extract was prepared. The concentrated extract was diluted with distilled water to obtain concentrations of 75% and 90%.¹⁴

Male Wistar rats weighing less than 70% of normal body weight and aged 30 days were acclimatized in plastic cages for 10 days at a temperature of 22–24°C under a 12-hour light/dark cycle. The cages were equipped with food containers, water bottles, and bedding to collect feces and spilled feed. Cage positions were rotated every two days to ensure adequate air circulation.

Toxicity testing was conducted using the OECD 425 Up-and-Down Procedure (UDP), consisting of a main test and a limit test. The main test was performed by observing dose levels associated with mortality during the preliminary test. Dose escalation was determined based on the onset of toxic symptoms. Administration of the next dose was postponed until the survival or death of the experimental animal was confirmed.¹⁰ The experimental animal initially received a dose of 5,000 mg/kg BW. If no mortality occurred within 24 hours of observation, the same dose was administered to another animal. This procedure was repeated until a maximum of five animals had been tested. The 24-hour observation period represented the acute toxicity test. Dose administration was discontinued if mortality occurred. Animals that passed the 5,000 mg/kg BW limit test for 3 days were subsequently subjected to a 10,000 mg/kg BW limit test to determine whether the LD50 value was within the range of 5,000–10,000 mg/kg BW or exceeded 10,000 mg/kg BW. Observations included behavioral and motor activity, body weight, and organ index measurements. The findings were compared with those of the control group.¹⁰

Liver histological examination was subsequently performed. Following toxicity testing, the rats were euthanized by cervical dislocation and necropsied for liver sample collection. Liver tissues were immersed in 10% neutral buffered formalin (NBF) for 24 hours. Fixed tissues were dehydrated and cleared using graded alcohol concentrations (70%, 80%, 90%, and absolute alcohol) and toluene. Tissue samples were then embedded in paraffin and cooled. The paraffin blocks were sectioned using a microtome at a thickness of approximately 4–5 µm and stained with hematoxylin-eosin (HE). Histological examination was performed microscopically at 100× magnification. Liver tissues were evaluated for congestion, degeneration, inflammation, and necrosis.¹⁵ The data were analyzed using one-way ANOVA followed by Duncan's Multiple Range Test to determine differences between the control and treatment groups based on toxicity and liver histological findings.

RESULTS

Observations conducted over 14 days demonstrated that administration of 75% and 90% pineapple core extract at doses ranging from 5,000 mg/kg BW to 10,000 mg/kg BW did not produce toxic effects in the experimental animals. (Table 1)

Table 1. The Result of observation of toxicity symptoms and mortality in male wistar rats with stunting

Group	Toxicity symptoms	Sample	Mortality (1-14 days)
K0 (Control)	None	T1-T5	0
K1 (75% extract, 5000 mg/KgBW)	None	T1-T5	0
K2 (75% extract, 10,000 mg/KgBW)	Piloerection, incoordination, Depressive symptoms	T1-T5	0
K3 (90% extract, 5000 mg/KgBW)	None	T1-T5	
K4 (90% extract, 10,000 mg/KgBW)	None	T1-T5	0

Table 2. Body Weight data (g)

Group	Day 0	Day 14
K0	157,4	203,8
K1	157,0	205,4
K2	155,8	205,2
K3	155,4	210,0

K4	156,6	214,2
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Tabel 3. Liver Weight data (g)	
Group	Liver Weight
K0 T1	3,2
K1 T1	3,8
K2 T1	3,7
K4 T1	3,7

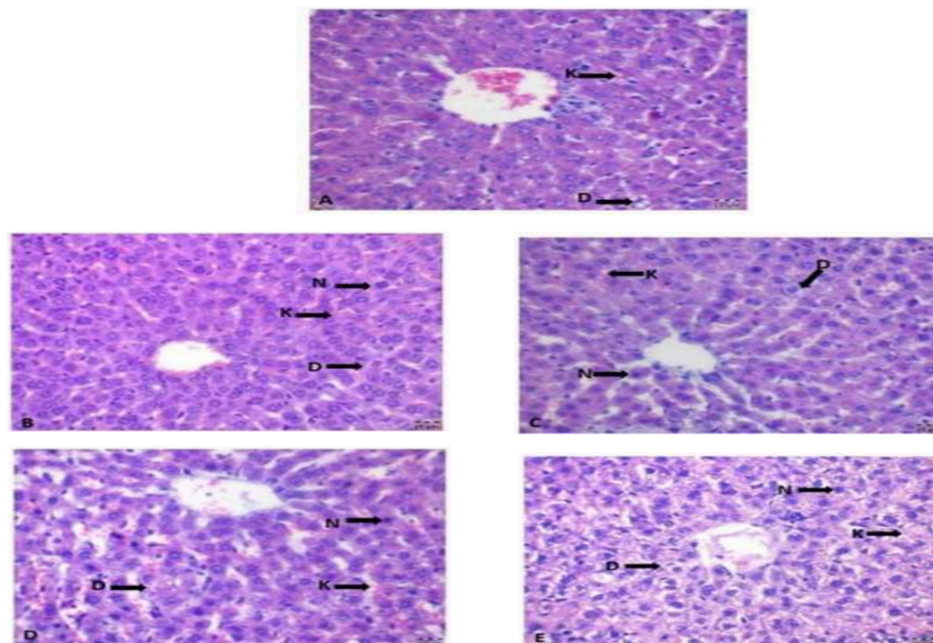


Figure 2 Histological Analysis of Liver Tissue in 4 groups (A) Control (B) K1 (C) K2 (D) K3 (E) K4

Histological examination demonstrated that the control group exhibited normal liver architecture, with hepatocytes arranged radially within the hepatic lobules. Similar findings were observed in group K1, where most hepatocytes appeared normal, although mild degeneration, necrosis, and sinusoidal congestion were observed.

In group K2, mild tissue damage was observed, characterized by hepatocyte necrosis with pyknotic nuclei and cellular degeneration. Degeneration represents temporary hepatocellular injury caused by toxic exposure, which may recover after discontinuation of the toxic agent. In group K3, necrotic cells were more prominent, and the sinusoidal areas appeared congested with blood. Microscopically, congestion was characterized by vascular dilation. In group K4, severe tissue damage was observed, with more than 75% of the microscopic field showing necrotic cells.

Table 4. Anova Test Results Comparison of Body Weight Before and After Extract Administration					
Perlakuan	0 Hari	14 Hari	Rata-rata	SEM	Sig.
K0	157,4	203,8	180,60 ^a	0.43	0.010
K1	157	205,4	181,20 ^a	0.86	
K2	155,8	205,2	180,50 ^a	0.45	
K3	155,4	210	182,70 ^{ab}	1.19	
K4	156,6	214,2	185,40 ^b	1.48	

^{ab} = Notasi huruf serupa artinya tidak ada perbedaan (5%)

SEM : Standart Error Means

The ANOVA results demonstrated that pineapple core extract administration significantly affected body weight in male Wistar rats ($p < 0.05$). Duncan's Multiple Range Test showed that the K4 group (90% extract, 10,000 mg/kg BW) had significantly different body weight values compared to groups K0, K1, and K2, whereas K3 did not differ significantly from the other groups. The Standard Error of the Mean (SEM) values were relatively low, indicating that the sample means accurately represented the population means.

Table 5. Results of Histological Data Analysis of Wistar Rat Cells

Histological Test Parameters	Intervention					SEM	Sig.
	K0	K1	K2	K3	K4		
Congestion	1,00 ^a	1,33 ^a	1,33 ^a	2,22 ^b	2,78 ^c	0,181	0,00
Cell Degeneration	0,89 ^a	1,11 ^a	1,22 ^a	2,22 ^b	3,56 ^c	0,268	0,00
Necrosis	0,67 ^a	1,33 ^b	1,33 ^b	2,44 ^c	3,33 ^d	0,262	0,00

^{ab}= Letter notation implies that there is no difference (5%)

SEM : *Standart Error Means*

ANOVA analysis demonstrated that treatment significantly affected congestion, cellular degeneration, and necrosis parameters ($p < 0.05$). Duncan's Multiple Range Test indicated that groups K3 and K4 showed significantly greater histological alterations compared with groups K0, K1, and K2. SEM values were relatively low, indicating good representation of the population mean by the sample mean.

Table 6. Results of Extract Administration Data Analysis Test on liver organ weight

Perlakuan	Hati	SEM	Sig.
K0	3,2 ^a	0.03	0.00
K1	3,8 ^b	0.06	
K2	3,7 ^b	0.05	
K4	3,7 ^c	0.08	

^a= Letter notation implies that there is no difference (5%)

SEM : *Standart Error Means*

ANOVA analysis demonstrated that pineapple core extract significantly affected liver weight in male Wistar rats ($p < 0.05$). Duncan's Multiple Range Test revealed significant differences between K1 and K0 compared with K2 and K4. The SEM values were relatively low, suggesting reliable representation of the population means.

DISCUSSION

Study on the toxicity and histological analysis of pineapple core extract (*Ananas comosus*) began with the collection of pineapple cores obtained from pineapple plantations in Kelaping Village, Pegasing District, Central Aceh Regency. The subsequent stage involved the preparation of feed supplemented with pineapple core extract at concentrations of 75% and 90%, which was then administered to male Wistar rats.

The selection of pineapple core as the primary material was based on its bioactive compounds, including bromelain, flavonoids, and phenolic compounds, which are known to possess pharmacological properties such as anti-inflammatory, antibacterial, and antioxidant activities. Previous studies conducted by Fitri et al. (2023) and Ahmad et al. (2024) reported that pineapple core extract exhibits considerable antioxidant activity, which may protect cells from oxidative damage.^{16,17}

The present study demonstrated that no mortality occurred in male Wistar rats administered pineapple core extract at doses up to 10,000 mg/kg body weight (BW). All experimental animals survived throughout the 14-day observation period, indicating that the extract did not exhibit acute lethal toxicity. These findings are consistent with those reported by Diina et al. (2022), who demonstrated that pineapple core extract did not induce acute toxicity in mice at doses up to 10,000 mg/kg BW.¹⁸ Similarly, Oktafia et al. (2022) reported that pineapple extract administered at 5,000 mg/kg BW did not produce acute toxic effects during administration

periods exceeding 14 days.¹⁹ Therefore, further long-term toxicity studies are required to evaluate the chronic safety profile of the extract.

During the 14-day treatment period, all groups, including the treatment groups, demonstrated increased body weight. This finding suggests that pineapple core extract did not significantly impair metabolism or suppress appetite. These findings are in agreement with Yenice et al. (2019), who reported that bromelain supplementation in experimental animals improved protein digestion efficiency, thereby supporting body weight gain.²⁰ Nevertheless, increased body weight alone cannot be considered a definitive indicator of health status, as subclinical damage to vital organs may still occur, as demonstrated by the liver histological findings in the present study.

One of the major findings of this study was the occurrence of liver alterations, both macroscopically (organ weight) and microscopically (histological examination). Although no substantial differences in liver weight were observed, histological analysis revealed significant liver tissue damage in the treatment groups, particularly in the high-dose group (K4). Histological examination demonstrated signs of congestion, cellular degeneration, and hepatocyte necrosis. These findings indicate potential hepatotoxic effects associated with high-dose administration of pineapple core extract. This observation is supported by Salasa et al. (2021), who reported that excessive exposure to phenolic compounds may induce oxidative stress in the liver, leading to inflammation and cellular damage.²¹ Similarly, Fitrya et al. (2025) reported that administration of plant extracts at doses reaching 10,000 mg/kg BW caused mild-to-moderate hepatic inflammation, necrosis, and steatosis in rats.²² Although these histological changes were not considered clinically severe, they occurred sporadically and indicated potential toxicological effects.

Furthermore, Ma et al. (2023) reported that exposure to herbal extracts did not cause overt clinical toxicity symptoms or body weight reduction but induced significant alterations in liver histological structure, similar to the findings observed in groups K3 and K4 in the present study.²³ These findings emphasize the importance of microscopic examination as a sensitive method for detecting early toxicity that may not yet be reflected in physiological parameters such as body weight or mortality. Therefore, the findings of this study are consistent with previous literature indicating that although pineapple core extract contains beneficial bioactive compounds, its administration at high doses should be carefully monitored.²² These findings highlight the need for further investigation regarding the safe dosage range of pineapple core extract for nutritional and pharmaceutical applications.

Although no mortality was observed, the liver histological damage identified in this study suggests a potential risk associated with long-term consumption at high doses.^{23,24} Statistical analysis demonstrated that pineapple core extract significantly affected body weight, liver histology, and liver weight in male Wistar rats. Significant body weight gain was observed in group K4 (90% extract, 10,000 mg/kg BW), suggesting that the nutritional components and bromelain content of pineapple core may enhance metabolism and protein absorption.²⁵ However, histopathological analysis revealed increased scores of congestion, degeneration, and necrosis with increasing extract doses, with the most severe damage observed in group K4. These findings indicate potential toxic effects associated with the accumulation of active compounds and oxidative stress.¹⁵ Significant increases in liver weight were also observed, particularly in groups K1 and K4, which may reflect adaptive responses related to metabolism and detoxification processes.²⁶

Overall, although high doses of pineapple core extract may promote body weight gain, these effects were accompanied by pathological alterations in liver tissue, indicating the need to determine a safe dosage threshold or No Observed Adverse Effect Level (NOAEL) for future applications.¹⁰ These findings support the hypothesis that the active compounds present in pineapple core extract exert dose-dependent effects. At low-to-moderate doses, the extract may be safe or even beneficial; however, at high doses, it may induce hepatotoxic effects.²⁷

This study has several limitations, including the relatively short duration of observation (14 days) and the exclusive focus on acute toxicity effects. Previous studies demonstrated that although short-term administration may not produce severe organ damage, prolonged exposure for 30 days may induce mild hepatic fibrosis. Therefore, long-term studies involving biochemical parameters such as serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), and serum bilirubin are required to support the histological findings obtained in this study.^{28,29}

CONCLUSION

Based on the 14-day toxicity observation of pineapple core extract (*Ananas comosus*) at 75% and 90% concentrations (doses of 5,000 and 10,000 mg/kg BW) caused no mortality or clinical toxicity symptoms in male Wistar rats. However, histological examination revealed liver tissue alterations, indicating potential hepatotoxicity at high doses.

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