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Original Article

The Impact of Sub Acute Administration of Purified Gambier (*Uncaria gambir Roxb.*) to The Liver and Kidney Functions and its Reversibility on Rats

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ABSTRACT

Introduction: The impact of sub-acute administration of purified gambier (*Uncaria gambir Roxb.*) to the liver and kidney function and its reversibility had been studied on rats. **Methods:** Rats at the aged of 2-3 months and the bodyweight of ±250 g were treated with water solution of purified gambier at the dose of 5 mg/kg10 and 20 mg/kg for 7 to 14 consecutive days. Plasma ALP, AST activities, creatinine clearance, liver and kidney ratios were determined on the day 1, 7, 14 one week after the doses stopped. All data on each parameter were analyzed using two-way ANOVA followed by Duncan's multiple T-test and significance was taken at $p<0.05$. **Results:** The results showed that all parameters was not affected significantly ($p>0.1$), except ALT activity and liver organ ratio decreased significantly ($p<0.05$). **Conclusion:** These indicated that purified gambier is relatively non-toxic to the liver and the kidney of the rats at doses of 5-20 mg/kg BW for 14 days.

Key Words: Purified gambier, Liver function, Renal function, ALP, ALT, CrCl.

INTRODUCTION

Indonesia is a country rich in flora and fauna. One of the plants that are being developed to become herbal medicinal plants is the gambier plant. This plant is spread in Aceh, North Sumatra, Riau, West Sumatra, Bangka, Belitung, and West Kalimantan. In West Sumatra this plant spreads throughout the region, such as in 50-kota, Pesisir Selatan, Tanah Datar, Pariaman, Sawahlunto, Pasaman and Solok.[1]

Traditionally, people have used gambier (*Uncaria gambir Roxb.*) to treat burned, headache diarrhea and dysentery, as a mouthwash for sore throats. Gambier extract also potential as antibacterial, antinematode, gastric ulcersreliever, antioxidants, antihypertension, prevent heart disease and hyperlipidemia. Gambier contain catechins of 7-33%, 20-55% of kathechu tannic acid, 20-30% of pyrocathecol, 1-3% of fluorescent gambier, 3-5% of red katechu, 2-4% of quercetin, fixed oil of 1-2%, and wax of 1-2%. From these chemical contents, our local government promotes the development of gambier to be to becoming a standardized herbal medicine.[2]

In the contrary, in 1985 a patented drug containing catechins, namely Catergen®, was withdrawn from the market due to its immunohemolysis effect to the patients.[3] According to Flavonoid Pharmacokinetics Book, catechins and their metabolites at a certain dose can bind to red blood cells allowing the production of autoantibodies to cause hemolytic anemia and kidney failure.[4] According to Ningsih (2017), herbal formulas contained gambier and Caesalpiniasappan extracts at doses of 300mg and 1200mg / KgBW produced lesions in the liver, kidneys and heart in male and female mice, large doses indeed.[5] In addition, research conducted by Takami et al reported that catechins content in green tea at a concentration of 0.5% (or equal with 3535 mg / KgBW) reduce rat body weight and increase ALT and ALP biomarkers.[6]

According to WHO, a drug, include herbal medicine, not only must be effective, but also meet the safety and quality requirement. Therefore, data on the safety of herbal medicines is needed, such as data evaluation of general toxicity, specific toxicity (on certain organs) and other tests (teratogenic, carcinogenic and mutagenic tests).[7]

In this paper, multiple doses of purified gambier (*Uncaria gambir Roxb.*) toxicity to the liver and kidney functions and its reversibility will be explore.

MATERIALS AND METHODS

A number 27 male rats at the aged of 2-3 months and the body weight of ±250 g was divided into 9 groups (3 rats per group). Group 1-3 were treated with water solution of purified gambier at the dose of 5 mg/kg., group 4-6 at dose of 10 mg/kg and the last 3 group were treated at dose of 20. Another group of 3 rats were used as control and its data was used repeatedly from day 1 to day 21. The gambier was given orally once a day for 14 days. During the experimental period, the animals were fed and drunk ad libitum, 24 hourly urine output was collected, measured to determine the urine creatinine and specific gravity. Three of the rats were killed and the blood sample and the liver and kidney were taken to measure the ALP, AST activities, creatinine plasma, liver and kidney ratios respectively on the day 1, 7, 14 and 21. Urine and plasma creatinine was determine using creatinine kit (Greiner®), while AST and

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ALP activities were determined using ALT KIT DiaSys® and Alkaline phosphatase KIT DiaSys® respectively. All of these three parameters were measured by photometer (Photometer 5010 V5+). The creatinine clearance, the liver and kidney ratioswere then calculated. All data on each parameter were analyzed using two-way ANOVA followed by Duncan's multiple T-test and significance was taken at P<0.05. For the experimental, the ethics code approval of the was obtained from ethics committee of the Faculty of Medicine, Andalas University, Padang - Indonesia (The registration numbers are 156/KEP/FK/2020 and 159/KEP/FK/2020).

RESULTS

Animal ALT activity was significantly decreased by the doses ($p<0.05$) and duration ($p<0.05$) of purified gambier administration but not by the interaction of these two variables ($p>0.1$). However, ALT activity remain unchanged after gambier was stopped. The averages of ALT activities of the animal on the day 1, 8, 15 and 22 were 150.333 ± 10.4 ; 93.5 ± 10.4 ; 99.3 ± 10.4 ; 108.2 ± 10.4 while the averages of animal ALT activities of control group and the group treated with gambier at doses of 5, 10, and 20 mg/KgBW were 150.3 ± 10.4 ; 104.0 ± 10.4; 97.0 ± 10.4 ; 100.0 ± 10.4 respectively. There was no significant responses between doses and duration of administration (Table 1 and Figure 1).

The data showed that the ALT activities of all animals are in the normal ranges (52-224 IU/L) (52).

On the other hands, animal ALP activities did not significantly affected by the doses and duration of purified gambier administration nor the interaction of these two variables ($p>0.1$) (Table 2 and Figure 2). The averages of animal ALP activities on day 1, 8, 15, dan 22 were 221.3 ± 27.0; 242.7 ± 27.0; 204.7 ± 28.7 and 221.7 ± 28.7 IU/L and the animal ALP activities of control and the animal treated with purified gambier at doses of 5, 10, and 20 mg/KgBW were 221.3 ± 27.0; 224.2 ± 28.7; 199.9 ± 27.0 and 245.1 ± 28.7 IU/L (Table 2 and Figure 2).

From the above data we can see that these numbers are still in a normal range, even though those in the animal treated with purified gambier at dose of 20 mg/kg BW for 8-14 days, the level is a bit higher and remain higher even 7 days after gambier administration had been stopped. Actually, the normal ALP activity is vary, depends on the animal age. In his study, we use rats at the age of 8 – 10 weeks. During this period, ALP activity is higher, as reported by Hoffmann et al., (1994) was of 343 - 353 IU/L in female and more higher in male (>500 IU/L).[8]

The animal liver ratio was significantlyaffected by purified gambier dose and duration of administration ($p<0.05$) but not by interaction of these two variables ($p>0.1$). The liver ratio of animal treated with gambier

Table 1: The impact doses and duration of administration and after stopping of purified gambier to the rat ALT activities.

Doses (mg/Kg BW)	The averages ALT activities (IU/L) on days ± SE				Averages ± SE
	1	7	14	21	
Control	150.3 ±20.9	150.3 ± 20.9	150.3 ± 20.9	150.3 ± 20.9	150.3±10.4[q]
5	150.3 ± 20.9	78.3 ± 20.9	74.0 ± 20.9	113.6 ± 20.9	104.0±10.4[p]
10	150.3 ± 20.9	69.6 ± 20.9	69.3 ± 20.9	98.6 ± 20.9	97.0±10.4[p]
20	150.3 ± 20.9	75.6 ± 20.9	103.6 ± 20.9	70.3 ± 20.9	100.0±10.4[p]
Averages ± SE	150.3±10.4[b]	93.5±10.4[a]	99.3±10.4[a]	108.2±10.4[a]	

Table 2: The impact doses and duration of administration and after stopping of purified gambier to the rat ALP activities.

Doses (mg/Kg BW)	The averages ALP activities (IU/L) on days ± SE				Averages ± SE
	1	7	14	21	
Control	221.3 ± 54.1	221.3 ± 54.1	221.3 ± 54.1	221.3 ± 54.1	221.3 ± 27.0
5	221.3 ± 54.1	288.0 ± 54.1	189.0 ± 54.1	198.5 ± 66.3	224.2 ± 28.7
10	221.3 ± 54.1	205.3 ± 54.1	169.3 ± 54.1	203.6 ± 54.1	199.9 ± 27.0
20	221.3 ± 54.1	256.3 ± 54.1	239.0 ± 66.3	263.3 ± 54.1	245.1 ± 28.7
Averages ± SE	221.3 ± 27.0	242.7 ± 27.0	204.7 ± 28.7	221.7 ± 28.7	

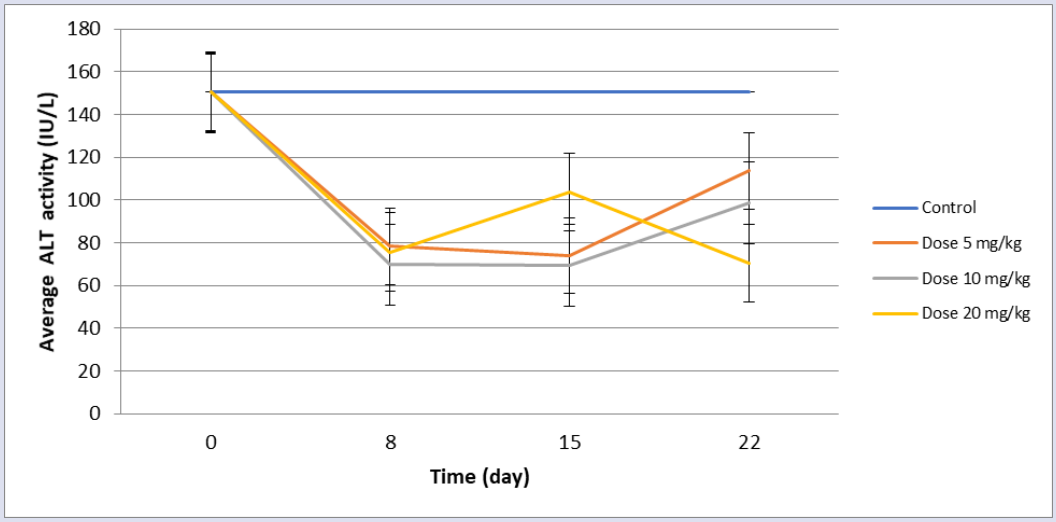

Figure 1: The impact doses and duration of administration and after stopping of purified gambier to the rat ALT activities.

was lower compared to that of control group, especially after treated for 7 – 14 days. However, most of the animal showed increases in the liver ratio after gambier administration was stopped. The averages liver ratio of the animals on the day 0, 8, 15 and 22 were 0.042 ± 0.001; 0.037 ± 0.001; 0.034 ± 0.001 and 0.040 ± 0.001 and this averages ratio of control animal and the animal treated with purified gambier at the doses of 5, 10 and 20 mg/KgBW were 0.042 ± 0.001; 0.038 ± 0.001; 0.037 ± 0.001 and 0.037 ± 0.001 respectively (Table 3 and Figure 3).

Creatinine clearance (CCr) of the animals was not significantly affected by administration of purified gambier based on dose (p>0.1) nor by duration of administration (p>0.1) or interaction of both variables (p>0.1). This stand to reason not change the renal function significantly (Table 4 and Figure 4), The averages of renal CCr of the control animals and the animal treated with the purified gambier at doses of 5, 10 and 20 mg/kgBW were 0.103 ± 0.029; 0.135 ± 0.029; 0.115 ± 0.029 and 0.122 ± 0.029 mL/min while the averages of renal CCr on day 1, 7, 15 and 22 were 0.103 ± 0.029; 0.095 ± 0.029; 0.106 ± 0.029 and 0.172 ± 0.029 ml/min.

Kidney ratio of the animal did not significantly affected by the dose and duration of purified gambier administration and the interaction of these two variables (p>0.1). The averages of kidney ratio of control animals and the animals treated with gambier at doses of 5, 10 dan 20 mg/kg BW were 0.007562 ± 0.000174; 0.007987 ± 0.000174; 0.007455 ± 0.000174 and 0.007565 ± 0.000174, while the averages ratio of this organ on day 1, 8, 15 and 22 were 0.007562 ± 0.0174; 0.7661 ± 0.0174; 0.779 ± 0.0174 and 0.7555 ± 0.0174 (Table 5 and Figure 5)

DISCUSSION

Alanine aminotransferase (ALT) and alkaline phosphatase (ALP) are among the main parameters for determining the liver function that were used in this study.[9,10] ALT is also referred to as glutamate: pyruvate aminotransferase (GPT), is a pyridoxal59-phosphate (PLP) enzyme that catalyzes the reversible transfer of the amino group of alanine to 2-oxoglutarate to form glutamate and pyruvate.[11] ALT levels are very useful in diagnosing liver damage.[12] ALP is an enzyme biomarker for monitoring the integrity and damage to liver structures and helps in

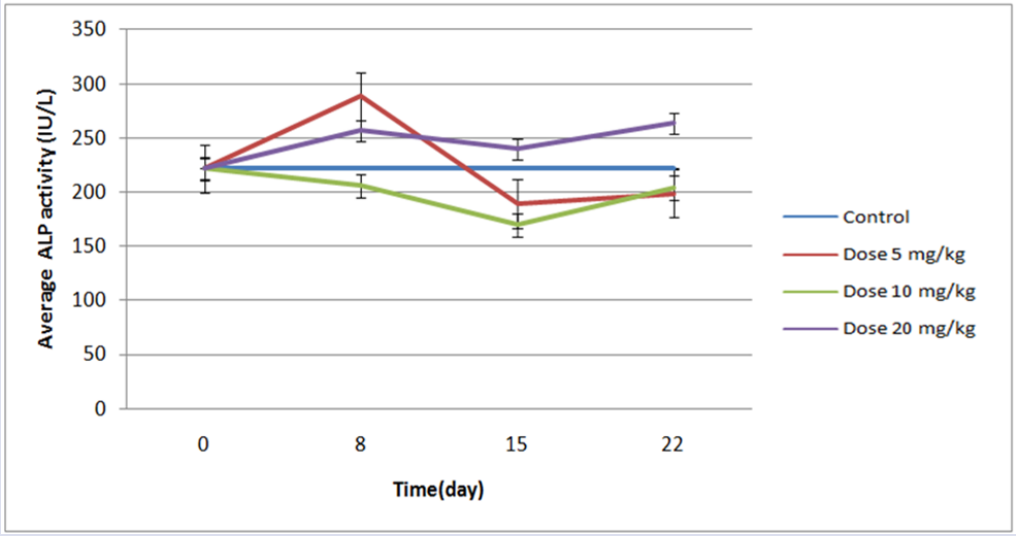

Figure 2: The impact doses and duration of administration and after stopping of purified gambier to the rat ALP activities.

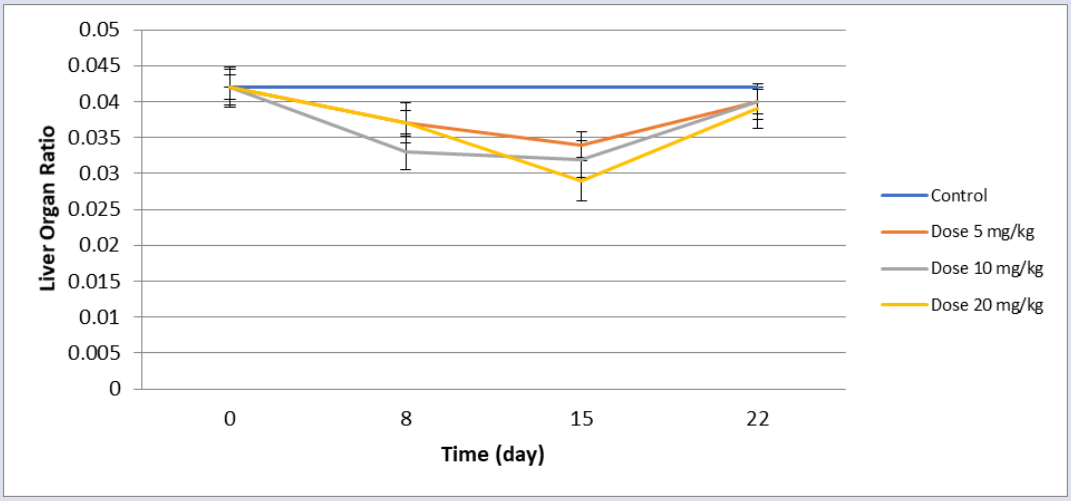

Figure 3: The impact of doses and duration of administration and after stopping purified gambier to the rat liver ratio.

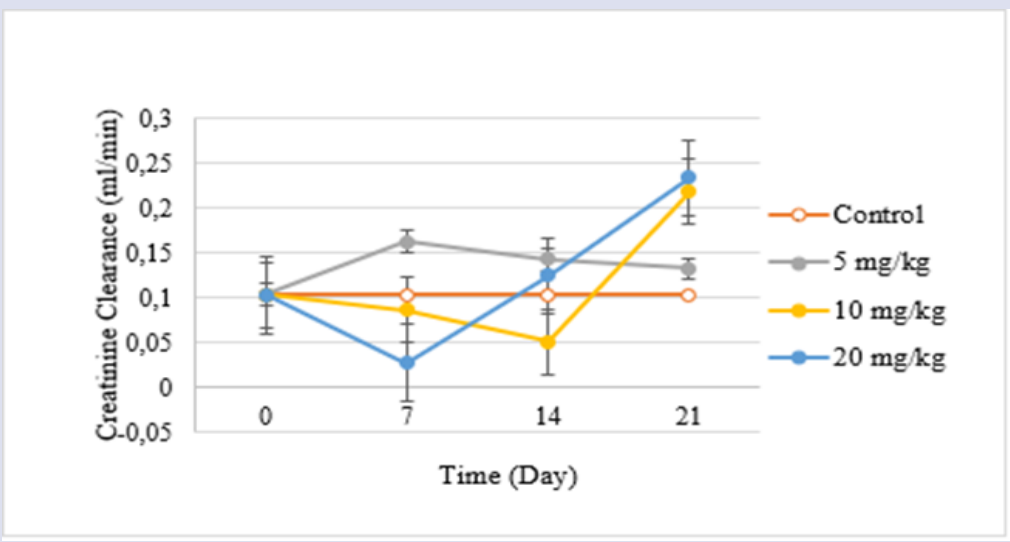

Figure 4: The impact of doses and duration of administration and after stopping purified gambier to the rat renal creatinine clearance.

Table 3: The impact of doses and duration of administration and after stopping purified gambier to the rat liver ratio.

Doses (mg/Kg BW)	Averages liver ratio (x10^{-2}) ± SE on day				Averages ± SE
	1	7	14	21	
Control	4,2 ± 0,2	4,2 ± 0,2	4,2 ± 0,2	4,2 ± 0,2	4,2 ± 0,1^{q}
5	4,2 ± 0,2	3,7 ± 0,2	3,4 ± 0,2	4 ± 0,2	3,8 ± 0,1^{p}
10	4,2 ± 0,2	3,3 ± 0,2	3,2 ± 0,2	4 ± 0,2	3,7 ± 0,1^{p}
20	4,2 ± 0,2	3,7 ± 0,2	2,9 ± 0,2	3,9 ± 0,2	3,7 ± 0,1^{p}
Averages ± SE	4,2 ± 0,1^{c}	3,7 ± 0,1^{b}	3,4 ± 0,1^{a}	4.0 ± 0,1^{c}	

Table 4: The impact of doses and duration of administration and after stopping purified gambier to the rat renal creatinine clearance.

Doses (mg/Kg BW)	Averages renal CCr (mL/min) ± SE on day				Averages ± SE
	1	7	14	21	
Control	0.103 ± 0.059	0.103 ± 0.059	0.103 ± 0.059	0.103 ± 0.059	0.103 ± 0.029
5	0.103 ± 0.059	0.162 ± 0.059	0.143 ± 0.059	0.132 ± 0.059	0.135 ± 0.029
10	0.103 ± 0.059	0.086 ± 0.059	0.051 ± 0.059	0.218 ± 0.059	0.115 ± 0.029
20	0.103 ± 0.059	0.028 ± 0.059	0.125 ± 0.059	0.233 ± 0.059	0.122 ± 0.029
Averages ± SE	0.103 ± 0.029	0.095 ± 0.029	0.106 ± 0.029	0.172 ± 0.029	

Table 5: The impact of doses and duration of administration and after stopping purified gambier to the rat renal ratio.

Doses (mg/Kg BW)	Average renal ratio (x 10^{-2}) ± SE on day				Averages (x 10^{-2}) ± SE
	1	7	14	21	
Control	0.7562 ± 0.0349	0.7562 ± 0.0349	0.7562 ± 0.0349	0.7562 ± 0.0349	0.7562 ± 0.0174
5	0.7562 ± 0.0349	0.7679 ± 0.0349	0.8530 ± 0.0349	0.8177 ± 0.0349	0.7987 ± 0.0174
10	0.7562 ± 0.0349	0.7454 ± 0.0349	0.7475 ± 0.0349	0.7328 ± 0.0349	0.7455 ± 0.0174
20	0.7562 ± 0.0349	0.7950 ± 0.0349	0.7594 ± 0.0349	0.7153 ± 0.0349	0.7565 ± 0.0174
Averages ± SE	0.7562 ± 0.0174	0.7661 ± 0.0174	0.7790 ± 0.0174	0.7555 ± 0.0174	

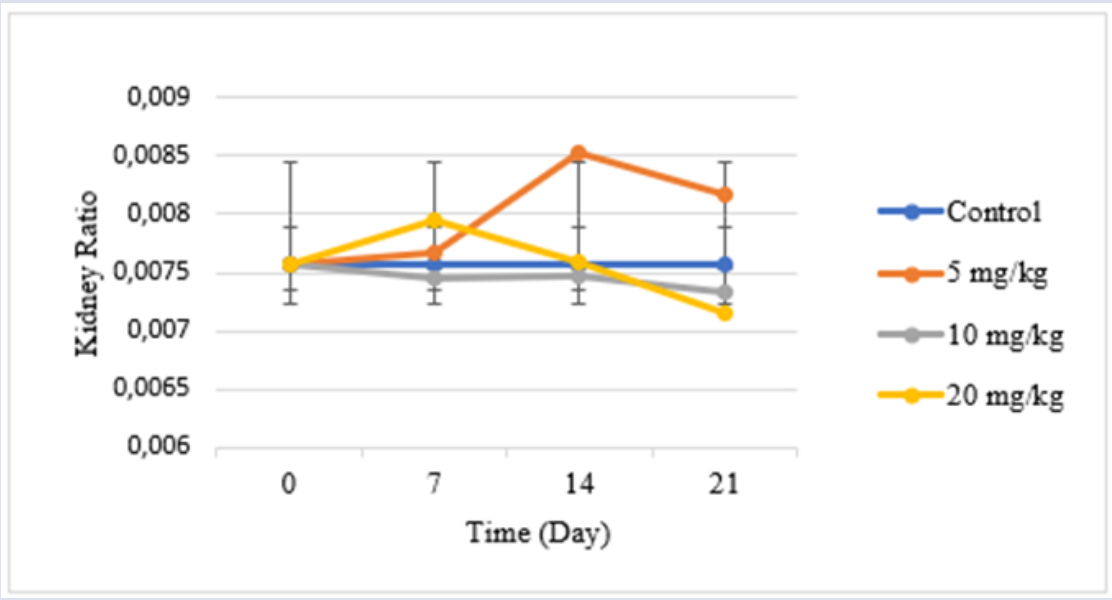

Figure 5: The impact of doses before, during and one week after administration of the purified gambier was stopped to the rat kidney ratio

the clinical diagnosis of liver toxicity conditions.[10] ALP activity also is routinely determined in most toxicological studies involving mice. This enzyme is found histochemical in the bile microvilli of the canaliculi and on the sinusoidal surface of hepatocytes.[13]

Data showed that animals treated with purified gambier had lower ALT activity values compared to that of control. This indicated that the purified gambier is not toxic to the liver. It rather protect the liver from the damage. This is agreement with a previous study, whom reported that the catechin content of gambier (a flavonoid) an active substanceis potential as antioxidant and hepato-protector.[14] Indeed, normal value of ALT activity in this study is quite higher compared to those reported elsewhere.[10,15,16] But this still in the common range value in rat (52-224 IU/L).[9]

This data is supported by serum ALP activity, in this study which not significantly changed under purified gambier treatment. ALP is a marker enzyme for the plasma membrane and endoplasmic reticulum. ALP is often used to assess the integrity of the plasma membrane, so that if the ALP value is high in the tissue and serum it indicates possible damage to external cells (plasma membrane). Elevated in ALP levels are likely a manifestation of membrane damage because ALP is a membrane-bound enzyme. High levels of serum ALP activity are commonly seen in liver damage, cancer, and heart infections. High levels of serum ALP activity are commonly seen in liver damage, cancer, and heart infections.[17] Even though serum ALP activity in this study is much higher than some reported previously,[10,15,16] but is in agree with Hoffmann (1994) where the ALP activity may vary with age, sex, and breastfeeding. In this study, we used the 8-10 week age rat, where the ALP activity values is highest compare to the other ages.[8]

In the other hand, animal liver ratios under gambier treatment animal was lower compared with control, but the ratio was returned to normal one week after gambier was stopped. The differences in body weights are often accompanied by differences organ ratio. This made more difficult to interpret the data of this parameter.[18] That's why organ ratio parameter cannot be used as the main parameter in assessing liver function but is only used as supporting data. In this study the liver organ ratio decreased due to the increase in animal body weight during the testing period. To approve the damage of the liver tissue based on the liver ratio data, histologically assessment should be studied further.

From the above explanations, it is indicated that purified gambier is relatively non-toxic to the liver function of white rats. This is evidenced by the value of the ALT, ALP and liver ratio. These results is in agreement with Bachtiar, whose reported that gambier and gambier's properties is hepatoprotector,[3] and so as with one reported by Evi Ainun Fitrianingsih (2019).[19]

Furthermore, similar result is also found in the renal data, where there was no significant change in the value of creatinine clearance and the percentage of renal function of the gambier treated rats compared to the control group. All treated animals in each group had normal kidney function (> 90%). This data is supported by an unchanged kidney ratio showed in this study. Catechins content of gambier plays a role in reducing oxidative stress, and prevent liver and kidneys damage.[20] Our previous study also showed that gambier prolong the animal death from the renal damage induced by glycerol.[21] Further study on liver and kidney histopathology is still on going.

CONCLUSION

From this study we can concluded that purified gambier is relatively safe to the liver and kidney when it is used for 14 consecutive days.

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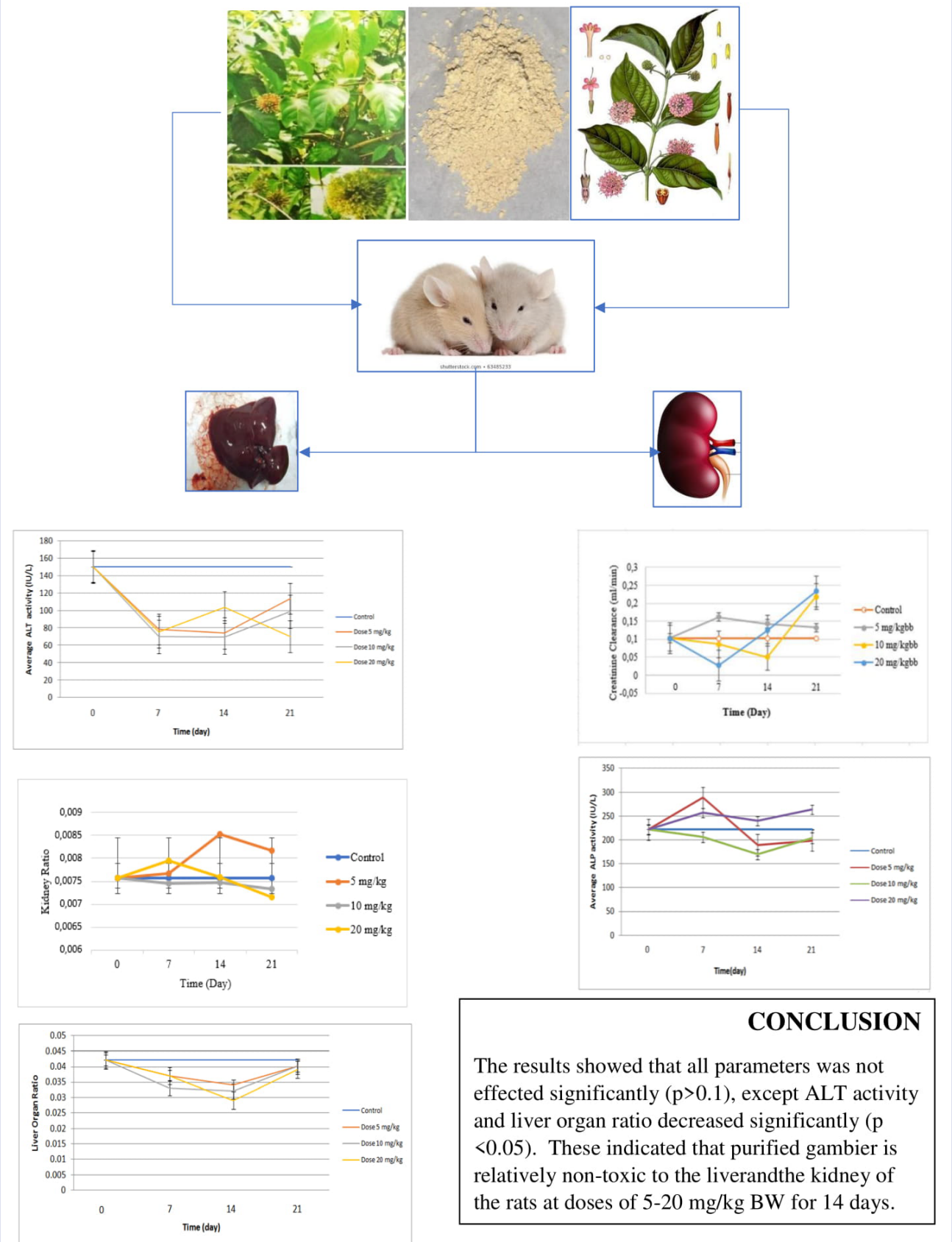
GRAPHICAL ABSTRACT



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Lathifah Putri Sinamar, S.Farm.: She is a student at the Faculty of Pharmacy, Andalas University, who has been involved in research that studies the sub-acute toxicity of purified gambier (*Uncaria gambir* Roxb.) on rat kidney function.

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Prof. Dr. Almahdy A., M.Si., Apt.: is a senior lecturer of Pharmacy Andalas University. Graduated from the Faculty of Pharmacy, Andalas University in 1985, then the Master's Program in 1990 at the Bandung Institute of Technology School of Pharmacy (ITB) and the Doctoral Program at Andalas University in 2006. Interest in pharmacology and toxicolgy as many reseaches he has conducted with colaborative with some colleages in pharmacy andalas university and other universities.

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