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Biotolerance Study of the Hydroalcoholic Extract of *Terminalia mantaly* H. Perrier on Rat Renal Activity

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Abstract

Terminalia mantaly H. Perrier is one of the plants of the Combretaceae family that is widely used in traditional African medicine for its antibacterial, antifungal, and especially in the treatment of malaria. In this study, we evaluated the effect of the hydroalcoholic extract of *Terminalia mantaly* (HAETM) on the tissue and kidney biochemical markers of rats. Forty (40) rats were randomly divided into 4 groups, assigning 10 animals within each group (5 males and 5 females per group). Animals in group 1 received distilled water and were used as the control group; on the other hand, groups 2, 3, 4 received by gavage a volume of the extract corresponding to 1 ml/100g body weight at 150 mg/kg, 300 mg/kg, 600 mg/kg, respectively. The hydroalcoholic extract was administered at the same time daily for 28 days, and blood was collected once a week to evaluate renal biochemical parameters; the kidney tissues were used to perform the histopathological study. The creatinine rate increased significantly ($p < 0.001$). The analysis of the serum electrolytes reveals a significant decrease in the levels of sodium, potassium, and creatinine ($p < 0.005$). The kidney micrograph did not show any adverse effects in the different groups of animals treated with the hydroalcoholic extract. Hydroalcoholic extract of *Terminalia mantaly* should be globally well tolerated by the body when used in doses ranging from 150 to 600 mg/kg of the body weight in animals (for this study, rats). However, further in-depth studies would be needed to get a more thorough and complete picture of the safety profile of the extract.

Keywords

Terminalia mantaly, Biotolerance, Biochemical Markers

1. Introduction

The use of phytomedicines is constantly increasing in several developing countries [1]. In West African countries, 80% of the population uses traditional medicine and medicinal plants as their primary health care [1]. In addition, in Cote d'Ivoire, 70% of the Ivorians rely on plants to heal themselves. This enthusiasm for the use of medicinal plants is linked to several factors, in particular, the low cost of phytomedicines compared to modern drugs and the perception that plants are of natural origin and do not pose health risks [1] [2] [3].

Despite the strengths of traditional medicine, it faces barriers that can impede its effectiveness; one such example is the consistency and accuracy of the doses used in the preparation and administration of drugs [4]. This confirms that insufficient knowledge of the adverse effects and toxicity of long and repeated use, amplified by user error, exposes them to the real risks of herbal therapeutic accidents, which can sometimes be tragic [5] [6]. With this situation in mind, it is strongly recommended that all plants used traditionally in the treatment of diseases should be subjected to toxicological studies to prove their safety [2].

Case in point, *Terminalia mantaly* H. Perrier, the subject of our study, is a plant from the Combretaceae family that is traditionally used in several medicinal recipes [4] [7] [8]. In fact, in Madagascar, its barks and leaves are used for the treatment of dysentery, oral and digestive candidiasis, and postpartum care [9] [10]. In Côte d'Ivoire, its leaves are used in the treatment of malaria [4]. Recent studies conducted by several researchers in our laboratory have revealed that the aqueous and the hydroalcoholic extracts on the bark of this plant have excellent antibacterial and antifungal benefits that inhibit the activities of *Plasmodium falciparum* [11]-[16]. To ensure the safety in the usage of *Terminalia mantaly* (*T. mantaly*) H. Perrier on the populace, an early study was conducted to evaluate the hematological parameters and hepatic tolerance, and it revealed that the plant's hydroalcoholic extract could be well tolerated by the rats' blood cells and liver [17]. It is important to note, though, that several studies have uncovered revealed toxicological risks and incidences of nephrotoxicity linked to the use of medicinal plants [18]. These toxicological risks of nephrotoxicity, in particular are caused by interactions, errors by confusion of plant species, but also by their metabolites can thus modify the main functions of the kidney [3] [18] [19] [20]. Therefore, it would be wise to carry out further studies on other vital organs, such as the kidneys, which are one of the main routes for drug elimination [18] [21]. Based on this observation, we have undertaken this study to contribute to the enhancement of Ivorian pharmacopoeia. It, therefore, aims to evaluate the effect of the hydroalcoholic extract of *Terminalia mantaly* H. Perrier on certain biochemical markers and kidney tissues.

2. Materials and Methods

2.1. Plant Material

The barks from the trunk of the *Terminalia mantaly* H. Perrier plant, collected

in the region of Azaguié (southern area of Abidjan), were used in this study [17]. The collected specimens were harvested, cut, and dried in the shade. After the drying process, the pieces of this plant were finely ground using an electric grinder, IKAMAG-RCT® type. The powder obtained was brown. The extracts were prepared according to the method described by Zihiri *et al.* [22]. In the preparation of hydroalcoholic extracts, 70%, 100 g of plant powder was extracted and placed in a blender along with one litre of distilled water or a mixture of ethanol-water (729 ml of ethanol 96% and 271 ml of distilled water); the process is repeated 3 times. After crushing, the mixture obtained was first spun in a clean square fabric and then filtered twice successively with cotton wool and once with Whatman 3 mm paper. The filtrate was concentrated using a rotary evaporator at 70˚C. The concentrate was evaporated at 50˚C in an oven for 48 hours. The extract obtained is the 70% hydroalcoholic extracts.

2.2. Experimental Animals

The animal selection was in accordance with the Organization of Economic Co-operation and Development (OECD) guidelines no. 423 [23]. Healthy, young, and nulliparous, non-pregnant Wistar rats that weigh 100 - 120 mg, were 8 - 10 weeks old, and were obtained from the animal house of pharmaceutical science, Abidjan (Côte d'Ivoire), were selected. The animals are picked randomly, marked to permit individual identification. Animals were kept in plastic cages with wood shavings that were changed every other day for 5 days before dosing. This allows animals acclimatization to laboratory conditions (ambient temperature 25˚C, ±3˚C; humidity ranged from 35% to 60%; light and dark period, 12/12 hours, bedding cleaned and sterilized). All animals had a regular supply of drinking water and food.

2.3. Treatment with Plant Material

A repeated oral dose of toxicity study was carried out according to the OECD Guideline 407 [24]. The rats were divided into four groups of 10 animals each (5 males and 5 females). Group 1 received 1 ml/100g body weight of distilled water and served as the control group. Groups 2, 3, and 4 received extract doses of 150, 300, and 600 mg/kg body weight, respectively. Mortality, body weight, food and water consumption, as well as observation for general toxicity signs of the animals were evaluated daily for 28 days.

2.4. Blood Sample and Organ Collection

At the end of each week, the animals were anesthetized with diethyl ether. The blood was drawn through cardiac puncture and collected in sterile tubes without anticoagulant. Plasma was obtained in one set by centrifuging the blood at 3000 revolutions/min for 10 min and stored at −20˚C in Eppendorf bottles until it required enzymatic activities and concentration of biochemical metabolites assays. The kidneys were collected and fixed with 10% buffered formalin for fur-

ther analysis [25].

2.5. Determination of Renal Parameters in Rat Serum

Blood from the dry tubes centrifuged at 3000 rpm for 5 min in the Humanlyser 2000 robot was used for the analysis of the biochemical and electrolyte parameters. Thus, the quantitative determination of metabolites urea and creatinine was made at wavelengths of 500 nm and 600 nm respectively and the dosage of sodium and potassium electrolytes with wavelengths of 587 nm and 767 nm respectively (**Table 1**).

2.6. Preparation of Tissue Sections and Histopathology

The kidney tissues were cut into transverse blocks. An automatic processor (RH-12EP Sakura, Fine Technical Co. Ltd., Tokyo, Japan) was used to further process the blocks. About 12 hours were required for dehydration (96% alcohol for one hour × four changes, and 100% alcohol for one hour × one change).

The clearing was done in three changes of toluene for one hour each. Tissues were impregnated in two changes of paraffin wax with a melting point of 50˚C for a period of 2 hours. Embedding of tissue was done in paraffin using L-shaped metallic moulds. These blocks were put in the refrigerator for a period of 4 - 6 hours. Each block was cut on a rotary microtome (MicromGmbh, Waldorf, Germany). About 5-micrometer-thick tissue section was obtained and placed in the water bath with a temperature of 50˚C below the melting point of paraffin wax. The cut ribbons of tissues were placed on the albumenized glass slide. The sample slides were subsequently stained with haematoxylin-eosin (HE) and examined under a light microscope; photomicrographs of the samples were recorded [26].

2.7. Statistical Analysis

The results are presented as mean ± standard deviation (SD). Analysis of variance (ANOVA) with repeated measures was employed to compare the results according to the administered doses and times of treatment. ANOVA was considered significant when the level of probability (p) was < 0.05; if $p < 0.01$, this difference is considered very significant; if highly significant, $p < 0.001$.

Table 1. Biochemical parameters for the quantitative determination of metabolites and electrolytes.

Parameters metabolites and electrolytes	Colorimetric Method	Wavelength (nm)
Creatinine	Alkaline picrate	500
Urea	Urease	600
Sodium	Temperature (2000˚ K)	589
Potassium	Temperature (2000˚ K)	767

3. Results

3.1. Biochemistry Results

3.1.1. Urea Concentrations

Figure 1 shows the rate of change in mean urea concentrations per week. Mean values of urea concentrations after one week of treatment were 0.28 ± 0.08 g/L in batch T and 0.28 ± 0.08 g/L at 0.29 ± 0.16 g/L in animals treated lots. They were equal to 0.31 ± 0.01 g/L in the control group and ranged between 0.31 ± 0.01 g/L and 0.32 ± 0.02 g/L in the treated animals at the end of four weeks of experimentation (Figure 1). The statistical analysis revealed that the rate of urea variations was not significant ($p > 0.05$) in all treated animals compared to the control animals regardless of the dose administered.

3.1.2. Creatinine Concentrations

Figure 2 shows the rate of change in average creatinine concentrations per week. After one week of treatment, mean values of creatinine concentrations were 7.5 ± 0.77 mg/L for animals in the T-lot while animals in the treated lots ranged from 6.55 ± 1.44 mg/L to 6.95 ± 0.68 mg/L. At the end of four weeks of testing, creatinine rate was 7.50 ± 0.70 mg/L in T-lot, whereas in the treated lots, they ranged from 7.15 ± 0.1 mg/L to 7.85 ± 0.7 mg/L. However, an increase of more than 19.84% in the level of creatinine was observed in the animals treated with 600 mg/kg per body weight after 4 weeks of treatment. Statistical analysis showed that the variation of creatinine rate was not significant ($p > 0.05$) in all treated animals compared to the control animals regardless of the dose administered, except during the exposure time for the 600 mg/kg dose, during which, the changes in creatinine levels was significant ($p < 0.001$).

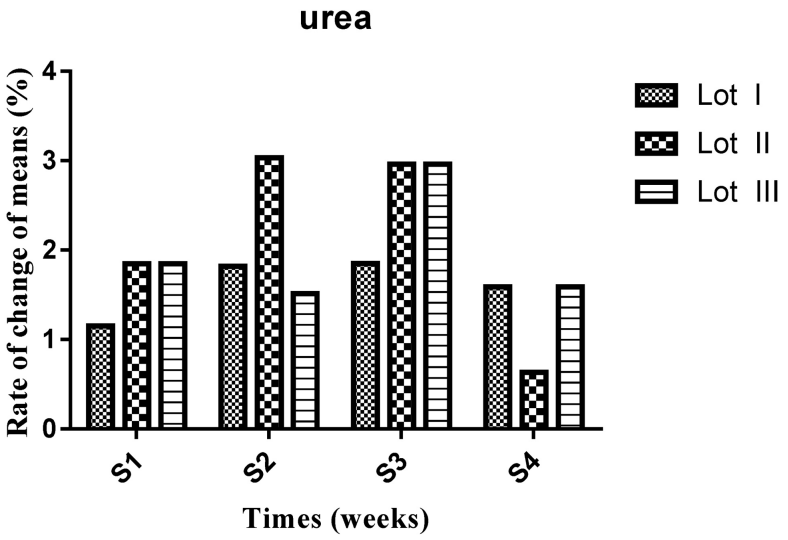

Figure 1. Rate of change in mean urea concentrations per week. Each bar represents the rate of change, n = 10 with Lot I = 150 mg/kg; Lot II = 300 mg/kg; Lot III = 600 mg/kg body weight of the animal; S, S2, S3, S4: first, second, third, fourth week of study. Differences observed between batches are not significant for $p > 0.05$.

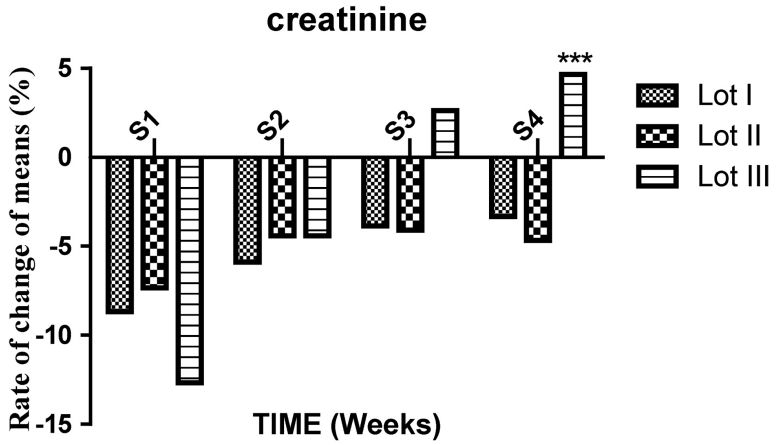

Figure 2. Rate of change in mean creatinine concentrations per week. Each bar represents the rate of change of the mean, n = 10 with Lot I = 150 mg/kg; Lot II = 300 mg/kg; Lot III = 600 mg/kg body weight of the animal; S1, S2, S3, S4: weeks of study; the asterisks indicate the significant differences of each group of animals treated in each week for $p < 0.001$.

3.1.3. Sodium Concentration

The rate of change in mean sodium concentrations per week is presented in Figure 3. Mean values of potassium concentrations after one week of sodium were 143.80 ± 2.38 mEq/L in the animals in batch T and ranged from 142 ± 90 mEq/L to 143.3 ± 2 mEq/L in the animals from lot I to lot III. They were 143 ± 4.58 mEq/L in lot T and ranged from 140 ± 3.21 mEq/L to 141.5 ± 1.15 mEq/L in the lots treated by the end of the four weeks of testing.

The decrease in the highest sodium rate of change was observed at the fourteenth week of treatment in the treated animals with −2.09% at a dose of 600 mg/kg of body weight. Statistical analysis showed that the observed decreases in sodium variation rates were significant ($p < 0.05$) compared to the control.

The sodium variation rates obtained after four weeks of treatment decreased by −2.64% in animals that are treated with 600 mg/kg per body weight. These variations in sodium levels are significant ($p < 0.001$) in the animals that are treated with a dose of 600 mg/kg per body weight during the time of the experiment.

3.1.4. Potassium Concentration

Variation in average potassium concentrations per week is shown in Figure 4. After one week of treatment, the mean values of treatment were 4.10 ± 0.29 mEq/L in the control animals and ranged from 3.90 ± 0.15 mEq/L to 4 ± 0.2 mEq/L in animals treated with HAETM. The highest decreases were observed in the first week of treatment in animals treated at doses 150 and 300 mg/kg of body weight with variation rates of −4.87%. Statistical analysis showed that the observed decrease in potassium levels was significant ($p < 0.05$) compared to the control for these doses of HAETM. Statistical analysis revealed that these rates of variation were not significant ($p > 0.05$) in all animals after 4 weeks of experimentation.

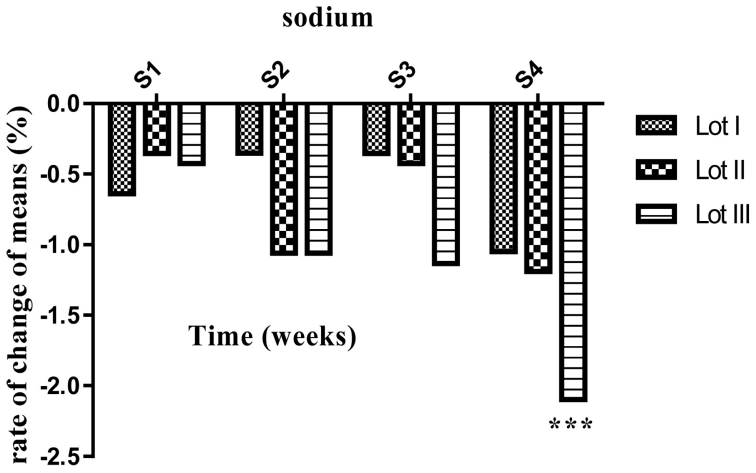

Figure 3. Rate of change in mean sodium concentrations per week. Each bar represents the rate of change of the mean, n = 10 with Lot I = 150 mg/kg; Lot II = 300 mg/kg; Lot III = 600 mg/kg body weight of the animal; S1, S2, S3, S4: weeks of study. The asterisks indicate significant differences in each group of animals treated per week for $p < 0.001$.

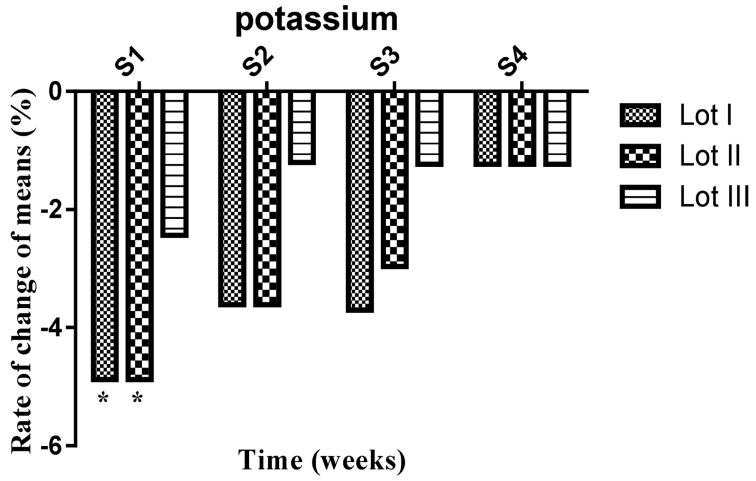

Figure 4. Rate of change in average potassium concentrations per week. Each bar represents the rate of change of the mean, n = 10 with Lot I = 150 mg/kg; Lot II = 300 mg/kg; Lot III = 600 mg/kg body weight of the animal; S1, S2, S3, S4: weeks of study. Asterisks indicate significant differences in each group of animals treated per week (*$p < 0.05$).

3.2. Histological Study of the Kidney

All the sections of **Figure 5** show that the histological organization of the kidney is normal in the rats of the control group and in those lots treated with HAETM.

In the cortical zone around the glomeruli, we observed contoured portions or tubes that are distinguished by distal proximal, and the distal tubes are clearly visible and distinct. The proximal convoluted tubule (TCP) is observed with an epithelium and a brush border that almost completely fills the lumen. The distal convoluted tubule (TCD), on the other hand, does not have a brush border and has a larger and better-defined lumen.

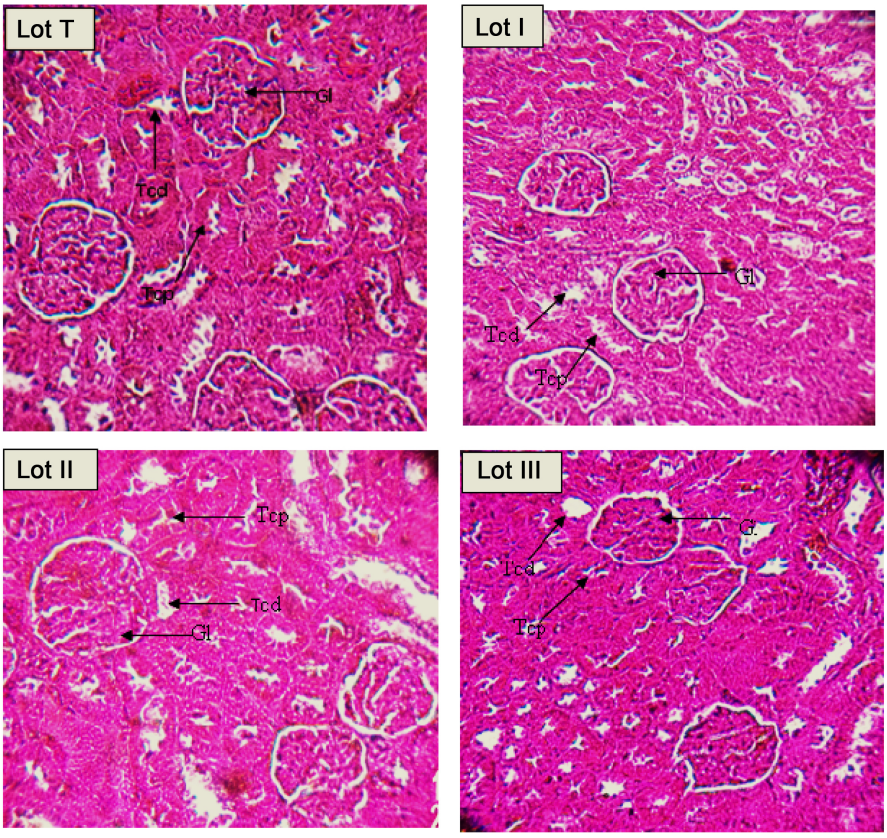

Figure 5. Portion of the kidney of rats. Hemalun-eosin stain; magnification: ×100 T-lot (control): portion of control rat kidney tissue; Lot I (150 mg/kg PC), Lot II (300 mg/kg PC), and Lot III (600 mg/kg PC); portions of kidney tissue from rats treated at different doses. Gl: Glomerulus; Tcp: Proximal by pass tube; Tcd: Distal convoluted tube.

4. Discussion

We analysed the influence of HAETM at the structural level and at the level of renal function by following the evolution of specific markers such as urea, creatinine, sodium, and potassium. Any substance capable of modifying these different renal functions (glomerular filtration, tubular secretion, and reabsorption) inevitably leads to changes in the plasma concentrations of urea, creatinine in the metabolites, and sodium, potassium, and electrolyte level [26] [27] [28]. An increase in creatinine concentration at high concentrations of *Terminalia mantaly* after 4 weeks of exposure indicates that *Terminalia mantaly* has a significant effect on creatinine metabolism. Indeed, creatinine is excreted exclusively by the kidneys. Its high level is considered an indicator of kidney damage [29]. Our results corroborate with those of Kone *et al.* [30] who indicated a decrease in serum creatinine level in rats treated with the aqueous extract of the debarked roots of *Rauvolfia vomitoria* Afzelius (Apocynaceae) at a dose of 700 mg/kg of body weight. The decrease in the level of creatinine showed that a dose of 600 mg/kg of body weight of HAETM would not alter the proper functioning of the kidneys. However, our results differ from those of Gbogbo *et al.* [31] who observed a significant difference in the increase of creatinine levels in rats treated

with aqueous stem bark extract of *Spondias mombin* with a dose of 500 and 1000 mg/kg body weight compared to the spleen observed in the controls. They also noticed that the levels of creatinine and urea of treated rats remained lower compared to controls during the first three weeks of the study. In general, the average creatinine values obtained with all the doses of the extract are in the range of the values of the control animals and those of the normal values found in the rats [32]. Therefore, the hydroalcoholic extract of *Terminalia mantaly* would not constitute as dangerous for renal function.

Our results are consistent with those of Lohoues *et al.* [33] who showed that blood electrolytes should be known in the absorption of sodium and the secretion of potassium by the distal convoluted tube and the collector tube are under the hormonal control of aldosterone. Aldosterone is a hormone produced by the adrenal cortex at the latex of *Calotropis procera* and could not result in a disruption of glomerular filtration.

It is stimulated by the action of renin via angiotensin. Its target cells are the main cells of the collecting tube [34]. It not only activates the reabsorption of sodium to maintain its balance but also stimulates the excretion of potassium in the urine. It is the main route of the excretion of potassium in the urine [35] [36]. The reabsorption of sodium also leads to the reabsorption of water, correcting a decrease in blood volume [37]. In our study, the significant decrease in serum concentration of sodium and potassium ions could be explained by the disruption of the renin-angiotensin-aldosterone system, which controls the regulation of sodium and potassium. However, it should be noted that the mean values of the metabolite and electrolyte concentrations obtained with all the doses of the extract are in the range of the values of the control rats and that of the normal values found in the rats [32]. Therefore, *Terminalia mantaly* would not significantly disrupt renal function.

In the present study, the kidney micrograph did not exhibit any adverse effects in the different groups of animals treated with HAETM. Indeed, the glomeruli and capsules appeared normal, and Bowman's space was also clearly visible. These results show that the hydroalcoholic extract of *Terminalia mantaly* will not damage the kidney tissue. The effects of HAETM established in this study are similar to those found by Akanmu *et al*. [38] but with an extract of cloves of the garlic fistula. These authors revealed that there were no changes in the kidney histology of the rat treated with the extract at a dose of 1000 mg/kg. The same observation was made with *Morinda morindoides* by Tra-Bi *et al.* [39].

5. Conclusions

The aim of this study was to evaluate the renal biotolerance of the hydroalcoholic extract of *Terminalia mantaly* (HAETM). At the end of our work, it was found that urea did not vary significantly; on the other hand, creatinine, sodium, and potassium parameters have varied significantly in relation to the dose per week and to their initial values over time. However, all these variations were moderate

and transient, with values that remained within their standard. In addition, the histological analysis performed on the kidneys showed no abnormality in the structure and functional integrity of the target organs that were studied during the prolonged administration of HAETM.

The study showed that hydroalcoholic extract of *Terminalia mantaly* is generally well tolerated by the body when used at doses ranging from 150 to 600 mg/kg of body weight. However, it would be necessary to carry out more in-depth studies, including ones pertaining to cardiovascular tolerance to obtain a fuller picture of the safety profile of the extract.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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