Scientific Research Publishing

American Journal of Molecular Biology, 2024, 14, 126-137
https://www.scirp.org/journal/ajmb
ISSN Online: 2161-6663
ISSN Print: 2161-6620

Cardiac Tolerance of Hydroalcoholic Extract of Bark of *Terminalia mantaly* H. Perrier (HAEBTM) in Wistar Rats

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How to cite this paper: Kamo, I.L.B.E., Kouassi, K.S., Atto, V., Djaman, A.J., N'guessan, J.D. and Dosso, M. (2024) Cardiac Tolerance of Hydroalcoholic Extract of Bark of *Terminalia mantaly* H. Perrier (HAEBTM) in Wistar Rats. *American Journal of Molecular Biology*, **14**, 126-137.
https://doi.org/10.4236/ajmb.2024.143010

Received: March 23, 2024
Accepted: May 28, 2024
Published: May 31, 2024

Abstract

Terminalia mantaly H. Perrier is a plant used in traditional medicine for the treatment of various pathologies. However, *Terminalia mantaly* H. Perrier could present potential health effects on patients. In order to determine the possible cardiotoxic effects of the hydro-alcoholic extract of the bark of *Terminalia mantaly* H. Perrier, (HAEBTM) forty (40) rats distributed randomly into 4 groups, including 10 animals per group (5 males and 5 females) were used. Animals in group 1 received distilled water and were used as a control group. On the other hand, groups 2, 3, 4 received oral administration a volume of the hydroalcoholic extract of *Terminalia mantaly* H. Perrier corresponding to 1 mL/100g of body weight at 150 mg/kg, 300 mg/kg, 600 mg/kg, respectively. The extract was administered daily at the same time for 28 days and serum was collected once a week to evaluate cardiac biochemical markers using spectrophotometric methods using a Cobas C311® HITACHI biochemistry system. After one month of study, all rats were euthanized by overdose of ether, and the hearts of the rats were removed for gross morphological and histopathological analysis. Results were analysed using variance analysis (ANOVA) to compare outcomes as a function of doses administered and treatment times. The biochemical parameters ALT, LDH, CPK, CPKMB showed no significant change ($p < 0.05$) in the group of treated rats compared to the controls. However, the activities of ALAT, LDH experienced variations over time and an increase in CPK and CPKMB were observed. Microscopic observations of heart tissue sections from rats treated with the hydroalcoholic extract of *Terminalia mantaly* showed no lesions, edema and necrosis. These results suggest that the hydroalcoholic extract of *Terminalia mantaly* did not interfere with the functioning or alter the integrity of the heart.

Keywords

Terminalia mantaly, Bio Cardiac Tolerance, Biochemical Markers, Histopathology

1. Introduction

Many people around the world live without health care or with little health coverage due to poverty and the lack of adequate health infrastructure [1]. In developing countries, for example, millions of people unfortunately still suffer from various pathologies such as infectious diseases, malnutrition, complications linked to childbirth due to financial difficulties and the increasingly high cost of medicines moderns [2]. These populations therefore only resort to medicinal plants as means of treating themselves. Also, the great richness of the Ivorian pharmacopoeia and especially traditional habits mean that populations are increasingly resorting to medicinal plants from the pharmacopoeia for treatment [3] [4]. Moreover, the WHO has asked the governments of developing countries to revalorize traditional medicine in order to meet the health needs of disadvantaged populations. This development aims to develop improved traditional medicines and the integration of traditional medicine into the healthcare and public health system [1].

As such, *Terminalia mantaly* H. Perrier, a pharmacopoeial plant used in several medicinal recipes was the subject of our study [5] [6] [7]. This plant from the Combretaceae family is well known in the practice of traditional medicine in many African countries. In Madagascar, for example, the bark and leaves of *Terminalia mantaly* H. Perrier are used for the treatment of dysentery, oral and digestive candidiasis [8] [9].

In Ivory Coast, its leaves are used in the treatment of malaria [6]. Moreover, *in vitro* and *in vivo* studies of *Terminalia mantaly* H. Perrier have shown antibacterial and antifungal activities by inhibiting the action of Plasmodium falciparum [10]. However, lack of knowledge of the toxic effects of medicinal plants hinders their used [11]. Therefore, it seems appropriate to carry out toxicological research aimed at clarifying the biosafety and safety of *Terminalia mantaly* H. Perrier, in order to allow its more rational and reassuring use. Thus, a first study was carried out to evaluate the hematological parameters and hepatic tolerance, renal tolerance. This study found that the hydroalcoholic extract of the plant could be well tolerated by rats, blood cells, liver and kidney [12] [13]. The present study aims to explore the effects of the hydroalcoholic extract of T. mantaly on certain biochemical markers of rats heart 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 [12] [13]. 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.* [14]. 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 to the Organization of Economic Cooperation and Development (OECD) guidelines no. 423 [15]. 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 are 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 [16]. 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 weights, 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 3,000 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 heart was collected and fixed with 10% buffered formalin for further

analysis [12] [17].

2.5. Determination of Cardiac Biomarkers of the Rat

Cardiac enzyme activities were determined using a Cobas C311® HITACHI biochemistry system (Roche Diagnostics, France). Tests were performed using commercial kits (Roche Diagnostics, France) based on the manufacturer's instructions, summarized in Table 1.

2.6. Preparation of Tissue Sections and Histopathology

The cardiac 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).

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 [18].

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

Table 1. Operating parameters for the quantitative determination of serum cardiac markers.

cardiac biochemical markers	Methods (Spectrophotometry)	Wave length (nm)
Alanine aminotransferase (ALT)	Absorption kinetics (Disappearance of NADH)	340
Aspartate aminotransferase (AST)	Absorption kinetics (Disappearance of NADH)	340
Creatine phosphokinase (CPK)	Absorption kinetics (Formation of NADH/H+)	340
Creatine phosphokinase (CPK_{MB})	Absorption kinetics (Formation of NADH/H+)	340
Lactate dehydrogenase (LDH)	Absorption kinetics (Disappearance of NADH)	340

considered significant when the level of probability (p) was <0.05; if $p < 0.01$, this difference is considered as very significant; if highly significant, $p < 0.001$.

3. Results

3.1. Biochemistry Results

Alanine aminotransferase (ALAT)

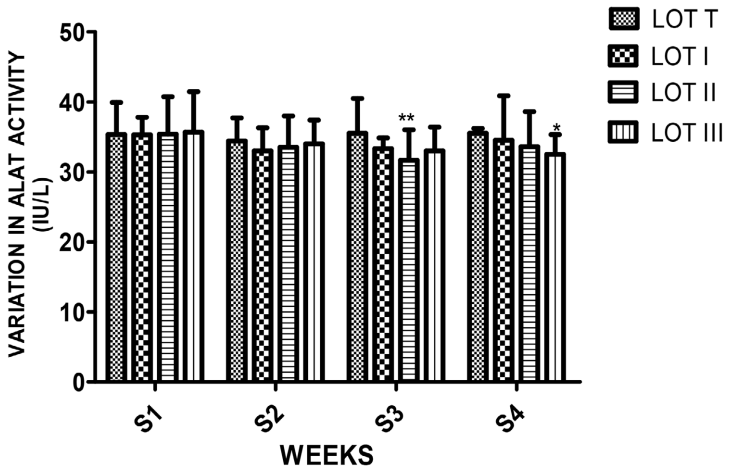
Figure 1 and Table 2 show the ALT activity of rats exposed to HAEBTM extract. ALAT activity did not vary significantly ($p > 0.05$) in the treated animals compared to the control animals. However, depending on the evolution over time, the activity of ALAT decreased significantly in the treated animals of lot II from 35.40 ± 10.39 IU/L (S1) to 31.67 ± 6, 35 IU/L (S3) ($p < 0.01$); of batch III from 35.67 ± 10.79 IU/L (S1) to 32.50 ± 2.82 (S4) ($p < 0.05$) (Figure 1), which corresponded to variations of −19.47% and −18.18% decrease.

Aspartate aminotransferase (ASAT)

Figure 2 and Table 2 show the influence of (HAEBTM) on ASAT activity. The results show a decrease in ASAT activity from 218 ± 28.30 IU/L (S1) to 188 ± 39 IU/L (S3). This reduction is not significant ($p > 0.05$) in the treated animals compared to the control animals and according to the evolution over time.

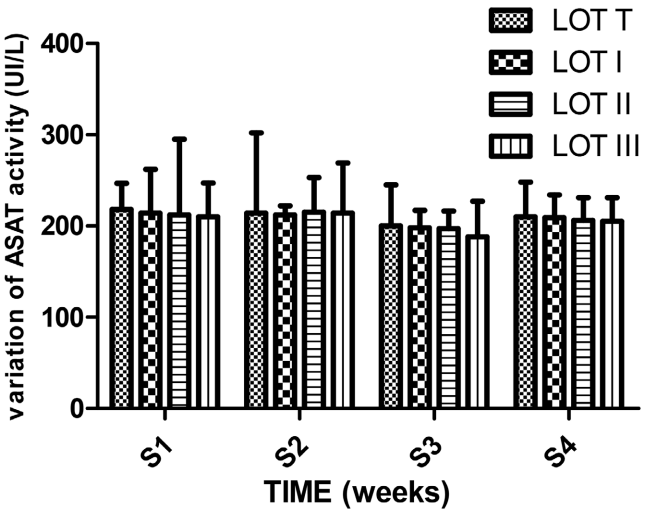
Lactate dehydrogenase (LDH)

Figure 3 and Table 2 show the influence of (HAEBTM) on LDH activity. LDH activity did not vary significantly ($p > 0.05$) in the treated animals compared to the control animals. However, depending on the evolution over time, we observe a slight significant decrease ($p < 0.05$) in the LDH activity of batch II from 869 ± 70.60 (S1) to 809 ± 83.73 (S3) ($p < 0.05$) and from 862 ± 29 (S2) to 790 ± 32 (S4) ($p < 0.05$). Likewise, LDH activity decreased in rats from batch III from 874 ± 52.12 (S1) to 796 ± 46 (S3) ($p < 0.05$) and from 870 ± 52.12 (S2) to



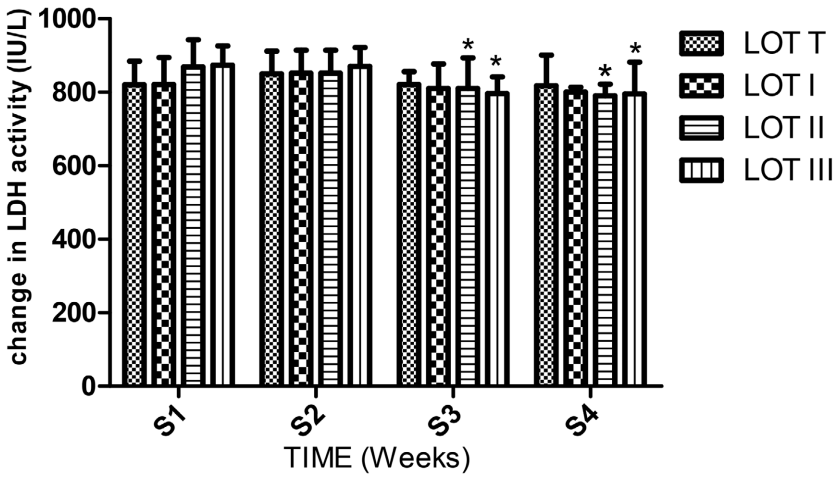
Each bar represents the mean ± standard deviation, n = 10 with Lot T = control; Lot I = 150 mg/kg; Lot II = 300 mg/kg; Lot III = 600 mg/kg of body weight of the animal; the asterisk indicates the significant differences of each group of animals treated according to the time of each week (*$p < 0.05$; **$p < 0.01$).

Figure 1. Effects of EHAT on ALT activities as a function of time.



Each bar represents the mean ± standard, n = 10 with Lot T = control; Lot I = 150 mg/kg; Lot II = 300 mg/kg; Lot III = 600 mg/kg of body weight of the animal; S1; S2; S3; S4: weeks of study, The differences observed between batches and over time are not significant: $p > 0.05$.

Figure 2. Effects of EHAT on ASAT activity as a function of time.



Each bar represents the mean ± standard, n = 10 with Lot T = control; Lot I = 150 mg/kg; Lot II = 300 mg/kg; Lot III = 600 mg/kg of body weight of the animal; S1; S2; S3; S4: weeks of study; the asterisk indicates the significant differences of each group of animals treated according to the time of each week (*$p < 0.05$).

Figure 3. Effects of EHAT on LDH activity as a function of time.

795 ± 86.9 (S4) ($p < 0.05$) (Figure 3). Which corresponded to variations of −19.96%; −15.74%; −12.86% and −15.42% decrease.

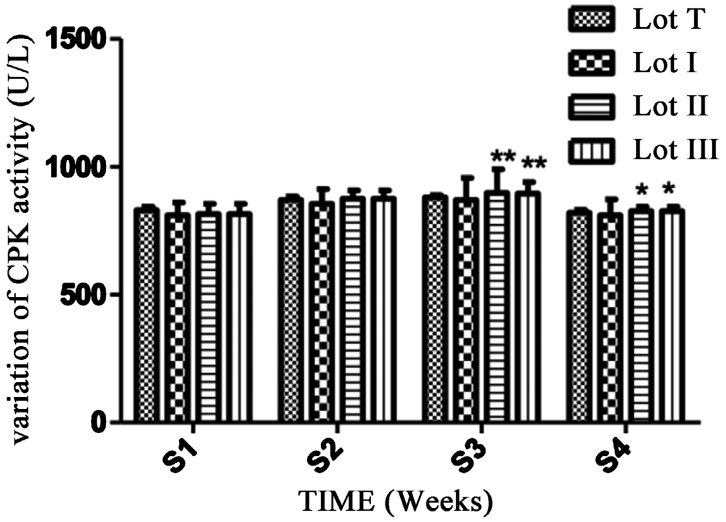
Creatine Phosphokinase (CPK)

Figure 4 and Table 2 show the influence of (HAEBTM) on CPK activity. CPK activity increases from 810 ± 50 (S1) to 898 ± 92 (S3). This increase is significant in animals from Batch II from 815 ± 40 (S1) to 898 ± 92 (S3) and from Batch III from 815 ± 40 (S1) to 895 ± 46 (S3) ($p < 0.01$) with $p < 0.01$). Likewise, a significant variation in CPK is observed in animals from batch II from 898 ± 92 (S3) to

827 ± 17 (S4) and from batch III from 875 ± 33.23 (S3) to 835 ± 19.9 (S4) with ($p < 0.05$) (Figure 4). Which corresponded to variations of +9.80% and +10.70% increase.

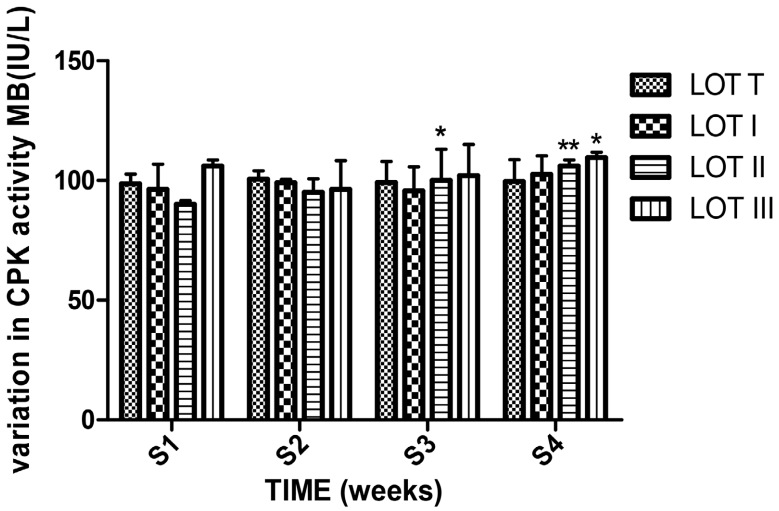
Creatine Phosphokinase CPK MB

Figure 5 and Table 2 show the influence of (HAEBTM) on CPK MB activity. CPK MB activity increased significantly in treated animals from batch II from 90 ± 1.53 (S1) to 106 ± 25 (S4) ($p < 0.05$) and from 95 ± 5.66 (S2) to 106 ± 25 (S4)



Each bar represents the mean ± standard, n = 10 with Lot T = control; Lot I = 150 mg/kg; Lot II = 300 mg/kg; Lot III = 600 mg/kg of body weight of animal S1; S2; S3; S4: weeks of study; the asterisk indicates the significant differences of each group of animals treated according to the time of each week (*$p < 0.05$; **$p < 0.01$).

Figure 4. Effect of EHAT on CPK activity according to the time.



Each bar represents the mean ± standard, n = 10 with Lot T = control; Lot I = 150 mg/kg; Lot II = 300 mg/kg; Lot III = 600 mg/kg of body weight of the animal; S1; S2; S3; S4: weeks of study; the asterisk indicates the significant differences of each group of animals treated according to the time of each week (*$p < 0.05$; **$p < 0.01$).

Figure 5. Effect of EHAT on CPK MB activity as a function of time.

Table 2. Effect of HAEBTM on biochemical activity according to the time.

Biochemistry parameters	Concentration of HAEBTM (mg/kg of the body weight)	Weeks (S1)	Weeks (S2)	Weeks (S3)	Weeks (S4)
ALAT (UI/L)	0	35.33 ± 461	34.50 ± 2.12	35 ± 5	35.50 ± 0.70
	150	35.30 ± 2.5	33 ± 3	33.33 ± 1.52	34.50 ± 6.36
	300	35.40 ± 10.39	33.5 ± 6.36	31.67 ± 6.35**	33.60 ± 12
	600	35.67 ± 10.79	34 ± 7.07	33 ± 3.4	32.50 ± 2.82*
ASAT (UI/L)	0	218 ± 28.30	217 ± 88.14	200 ± 45	210 ± 38
	150	214 ± 48.3	212 ± 10	198 ± 13	209 ± 39.6
	300	212 ± 83	215 ± 38	197 ± 19.6	206 ± 25
	600	210 ± 37	214 ± 55.20	188 ± 39*	205 ± 26*
LDH (UI/L)	0	820 ± 64.84	850 ± 30	821 ± 35*	818 ± 83*
	150	821 ± 73.7	852 ± 62.23	810 ± 66.7	800 ± 14.14
	300	869 ± 70.60	862 ± 29	809 ± 83.77	790 ± 32
	600	874 ± 52.12	870 ± 52.12	796 ± 46	795 ± 86.97
CPK (UI/L)	0	830 ± 10.60	870 ± 10	880 ± 6	820 ± 8.18
	150	810 ± 50	855 ± 58	870 ± 86.7	810 ± 62.9
	300	815 ± 40	850 ± 45.25	898 ± 92**	827 ± 17*
	600	815 ± 40	875 ± 33.23	895 ± 46**	835 ± 19.9*
CPKmb (UI/L)	0	98.67 ± 4.04	100.5 ± 3.5	99.20 ± 8.7	99.50 ± 4.95
	150	96.33 ± 10.50	99 ± 1.41	95.67 ± 10.07	102.50 ± 7.77
	300	90 ± 1.52	95 ± 5.65	100 ± 13.11*	106 ± 25**
	600	106 ± 25	96 ± 12.02	102 ± 23	109.50 ± 27.28*

Results are presented as Mean ± S.D. p value is significant: *$p < 0.05$; **$p < 0.01$.

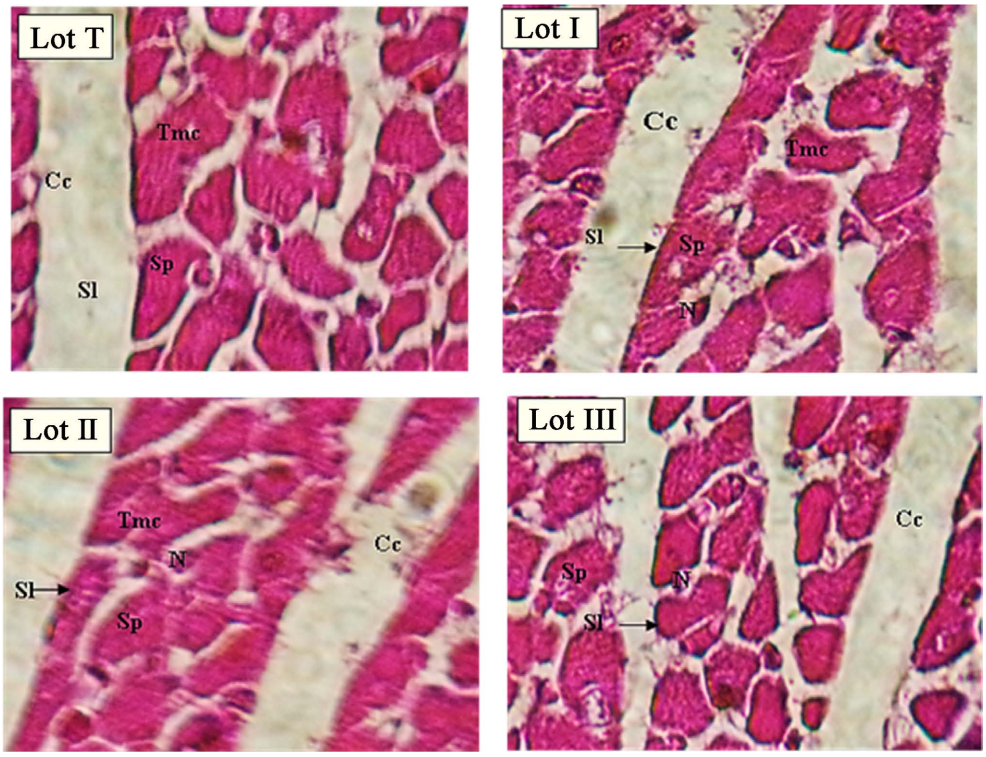
($p < 0.01$); of batch III from 90 ± 12 (S2) to 109 ± 27.28 (S4) ($p < 0.05$). Which corresponded to variations of +26.35%; +20.30% and +21.15% increase (include the variation table in the results).

3.2. Heart Histology Study

Figure 6 shows histological sections of the heart in animals. These sections show an almost identical normal anatomical structure in the hearts of rats from Lot T to Lot III. The myocardial fibers have bifurcations at their ends and are connected together by the collagen network contained in the connective tissue. The cardiac cells are clearly distinct, and the integrity of the tissue seems preserved.

4. Discussion

The heart plays a vital role in general circulation and is therefore the likely target



Magnification: ×400. Tmc: Heart muscle tissue; Cc: Heart cavity, Sp: sarcoplasma, Sl: sarcolemma, N: nucleus.

Figure 6. Section of rat heart with detailed view of muscle fibers.

of substances released into general circulation [19]. Exogenous substances which have an effect on the heart act either on its function by influencing its contractility, or on its integrity by disrupting its tissue structure. Changes in cardiac markers have often proven to be an important aid in diagnosing certain diseases and determining patient prognosis. [20]. This is why the effects of *Terminalia mantaly* on cardiac integrity and function as well as on cardiovascular risk factors were evaluated by measuring markers such as: CPK, CPK-MB, AST, ALT and LDH [20] [21]. Myocardial infarction is a multifactorial disease caused by numerous cardiovascular risk factors, including exposure to xenobiotics [22]. Indeed, CPK is an enzyme found mainly in muscles, and which is involved in storing energy through a mechanism called creatine phosphorylation. Among the signs defining myocardial infarction, one of the most constant is the significant increase in CPK, especially in the MB fraction. The determination of the CPK-MB isoenzyme is particularly interesting for the detection of myocardial infarction, due to their cardiospecificity, the precocity of their variation [23] [24]. On the other hand, LDH is mainly found in plasma. It constitutes an indicator of a disturbance in the energy balance of the cell leading to the accumulation of LDH followed by cell death [25]. The activities of these enzymes evolved differently during this study. Transaminases (AST) and LDH activities decreased while those of CPK and CPK-MB increased slightly briefly in the third week and in the fourth week in the time-dependent groups. This reduction in enzyme ac-

tivity reflects the protective effect of the heart by (HAEBTM). These results corroborate with those obtained from *Tail et al.* [26] who obtained a significant reduction in vascular congestion in mice treated with (HAEBTM) compared to the untreated control.

These results are contrary to those of *Coulibaly et al.* [27] who showed that the aqueous extract of Phyllanthus amarus reduced the CPK level over time and induced a cardioprotective effect. The activities of transaminases (AST) and LDH decreased, while that of CPK-MB increased in the groups treated at the dose of 600 mg/kg body weight over time. High concentrations of *Terminalia mantaly* would have a significant effect on the activities of these enzymes. However, despite the increase in the enzymatic activity of CPK-MB induced by this high dose, the range of mean values of the activities of these enzymes is within the range of the mean values of control rats and that of normal values. found in rats[28]. Therefore, the extract would not cause damage to heart muscle cells. The histopathological study revealed a normal structure of the heart in all groups (control and experimental groups). There were no features showing cellular damage such as myocyte necrosis, nuclear pyknosis, vascular proliferation, inflammatory cell infiltration, fibrosis and myocyte hypertrophy [29]. These results indicate that the hydroalcoholic extract of the bark of *Terminalia mantaly* (HAEBTM) used at doses varying from 150 to 600 mg/kg of body weight would not have harmed cardiac tissue. These results are similar to those of *Yapo et al.* [30] which showed that the aqueous extract of Parkia biglobosa leaves does not present any toxicity on the heart observed by *Koudou et al.* [18] who also showed that the ethyl acetate extract from the leaves of Holarrhena floribunda did not cause functional disorders or cardiac lesions in rats.

5. Conclusion

Our study showed that *Terminalia mantaly* hydroalcoholic bark extract (HAEBTM) is generally well tolerated by the body when used at doses ranging from 150 to 600 mg/kg body weight. It does not induce functional disorders or cardiac lesions in rats. It would be important to continue work to establish the bioactive compounds of the extract involved in mediating these biological effects, to isolate the active principles from the plant extract and to present them in an acceptable galenic form that would be recommended to the public.

Acknowledgements

We express gratitude to the Department of Biochemistry of Université Félix Houphouet-Boigny of Abidjan (Ivory Coast), Institute Pasteur de Côte d'Ivoire, and to the authorities of the Superior Normal School of Abidjan for providing the facilities in conducting this research.

Conflicts of Interest

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

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