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Evaluation of the toxicological effects of the aqueous extract of the kernels of *Tetracarpidium conophorum* (Mull. Arg.) & Dalz in laboratory animals

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Abstract

The main aim of this study was to assess the toxicological effects of the aqueous extract of *Tetracarpidium conophorum* kernels in rodents. To assess the acute toxicity, mice were given the aqueous extract of *Tetracarpidium conophorum* kernels (5000 mg/kg) orally for 14 days. Subacute toxicity of aqueous extract of *Tetracarpidium conophorum* kernels (250 and 500 mg/kg) in rats was tested for 28 days. The results of the acute toxicity study showed that oral administration of the aqueous extract of *Tetracarpidium conophorum* kernels (5000 mg/kg) did not alter the general behavior of mice, and did not cause mortality in mice at a dose of 5000 mg/kg. The aqueous extract of *Tetracarpidium conophorum* kernels, at the doses studied during 28 days of treatment in rats, significantly reduced serum transaminase levels (ALAT and ASAT) compared with negative controls. These levels went from: 97.7±2.28; 98.06±2.46 IU/L (negative control) to 69.44±4.09; 70.44±3.51 IU/L ($p < 0.01$), a reduction of 28.26% and 27.62% respectively in rats treated with *Tetracarpidium conophorum*. The aqueous extract of *Tetracarpidium conophorum* kernels in rats significantly increased white and red blood cell levels: 14.93±0.39; 10.96±0.31 (103/mm³) ($p < 0.05$) versus 7.41±0.11 (103/mm³) in the negative control. However, the drop in serum transaminase levels and the increase in blood cells suggest that this extract may have hepato-protective and immunostimulant effects.

Keywords: *Tetracarpidium conophorum*, acute toxicity, subacute toxicity

1. Introduction

The Congo Basin is the world's second largest forest lung, with a rich floral ecosystem and a wide range of medicinal plants. These plants are prized and used in the Congolese pharmacopoeia for the treatment of a number of pathologies. Indeed, the World Health Organization (WHO), in its resolution AFR/RC50 /R3 of August 31, 2000, encourages African countries to develop strategies based on traditional medicine, in order to promote and valorize medicinal plants in the health sector ^[1]. A number of scientific studies have demonstrated the pharmacological and biological potential of medicinal plants compared with conventional drugs, which are becoming increasingly popular ^[2]. In addition, other scientific studies have shown that medicinal plant extracts may contain toxic substances that can cause serious harmful effects such as: kidney and liver damage, diarrhea, constipation, vomiting, rectal bleeding ^[2, 3] and death ^[4-8] following short, medium and long-term administration of medicinal plant extracts. It is therefore essential to control the doses of medicinal plant extracts to be administered in order to avoid other pathologies that may arise. Presumed toxic plants include *Tetracarpidium conophorum*.

Tetracarpidium conophorum is a plant also found in the Republic of Congo, precisely in the Plateaux department (Lekana, Djambala). It is known by its vernacular names (in TEKE Nkah, and in Mbochi Mbenza). *Tetracarpidium conophorum* belongs to the family Euphorbiaceae, and is prized for its aphrodisiac potential. It is used in Congolese pharmacopoeia to treat male infertility. *Tetracarpidium conophorum* has been the subject of a number of research studies, notably in the field of animal nutrition ^[9]; a study on the characterization of the potential of *Tetracarpidium conophorum* kernels ^[10] and the toxicological effects of the aqueous extract of *Tetracarpidium conophorum* nuts on rats have been carried out ^[11]. However, to the best of our knowledge, no studies have been carried out on the acute and sub-acute toxicity of the aqueous extract of *Tetracarpidium conophorum* kernels. With this in mind, the present study was initiated to assess the acute and subacute toxicity of the aqueous extract of *Tetracarpidium conophorum* kernels in laboratory rodents.

2. Materials and methods

2.1 Materials

2.1.1 Plant materials

Tetracarpidium conophorum kernels from Lekana in the Plateaux department (Republic of Congo) were supplied by vendors at the Lekana market in 2023. *Tetracarpidium conophorum* was identified at the Institut National de Recherche en Sciences Exactes et Naturelles (I.R.S.E.N.).

2.1.2 Animal material

To study acute and sub-acute toxicity, three (3)-month-old male and female albino mice weighing between 25 and 30 g and three (3)-month-old male Wistar rats weighing between 200 and 250 g were used. These rodents were reared at the animal house of the Institut National de Recherches en Sciences de la Santé (IRSSA) and fed in the standard way with free access to water and a nocturnal-diurnal (12/12) lighting rhythm.

2.2 Methods

2.2.1 Preparations of aqueous extract of *Tetracarpidium conophorum* kernels

The aqueous extract of *Tetracarpidium conophorum* kernels was prepared by maceration. *Tetracarpidium conophorum* kernels were stripped of their hulls or skins, then air-dried in the laboratory at room temperature (28-30 °C) for 21 days. They were then crushed and ground in a mortar to obtain a homogeneous powder. One hundred (100) grams of powder were mixed with 1000 mL of distilled water. The resulting mixture was then placed under a magnetic stirrer (model L-73) for 48 hours. The resulting macerate was filtered through Whatman n°3 filter paper and absorbent cotton. The filtrate obtained was concentrated in a water bath thermostated at 55 °C for 3 days, yielding 3.5 g of brown-colored dry extract, which was stored at +4 °C in an Appolo Brant brand refrigerator for pharmacological testing.

2.2.2 Evaluation of the acute toxicity of the aqueous extract of *Tetracarpidium conophorum* kernels in mice

The acute toxicity of the aqueous extract of *Tetracarpidium conophorum* kernels in mice was carried out in accordance with OCED guideline number 423 [12-13]. The aim was to determine the lethal dose 50 (LD₅₀) and the extract doses to be used during pharmacological tests. Six albino mice, fasted for 24 hours prior to the experiment, were divided into two lots of 3 mice each, and treated orally as follows:

- **Lot 1:** 0.5 mL distilled water/30 g body weight.
- **Lot 2:** 5000 mg/kg body weight of the aqueous extract of *Tetracarpidium conophorum* kernels.

2.2.2.1 Effect of aqueous extract of *Tetracarpidium conophorum* kernels on general behavior and mortality rate

After administration of all products, parameters (ptosis, stool condition, aggressiveness, reaction to external stimuli, vocalization, vomiting) were observed every 30 minutes for the first 4 hours. Mortality and LD₅₀ were assessed after 48 h.

2.2.2.2 Effect of aqueous extract of *Tetracarpidium conophorum* kernels on weight development

The weight of each animal was measured every other day for fourteen (14) days using a QUIGG® brand balance (capacity 5000 g, accuracy 1g).

2.2.2.3 Effect of aqueous extract of *Tetracarpidium conophorum* kernels on food consumption in mice

The quantity of food consumed was determined by the following formula:

$AFC = AFD - AFR$; where: AFC = Amount of food consumed; AFD = Amount of food distributed; AFR = amount of food refused.

2.2.3 Evaluation of the subacute toxicity of the aqueous extract of *Tetracarpidium conophorum* kernels in rats

The subacute toxicity of the aqueous extract of *Tetracarpidium conophorum* kernels in rats was studied using the method described by the OECD [14]. Animals were divided into three lots of three animals each and treated for 28 days as follows:

- **Lot 1:** 10 mL distilled water/100 g body weight.
- **Lot 2:** 250 mg/kg live weight of the aqueous extract of *Tetracarpidium conophorum* kernels.
- **Lot 3:** 500 mg/kg live weight of aqueous extract of *Tetracarpidium conophorum* kernels.

2.2.3.1 Effect of aqueous extract of *Tetracarpidium conophorum* kernels on weight development

During 28 days of treatment with 250 mg/kg and 500 mg/kg *Tetracarpidium conophorum* aqueous kernel extract, the body weights of the rats were measured every 2 days using a QUIGG® brand balance (capacity 5000 g, sensitivity 1 g).

2.2.3.2 Effect of aqueous extract of *Tetracarpidium conophorum* kernels on vital organ weights

At the end of 28 days of treatment with *Tetracarpidium conophorum* kernel extract (250 mg/kg and 500 mg/kg, po) and after dissection of the lot of rats sacrificed by ethyl ether overdose, the kidneys, liver and heart were carefully removed and their weights measured using a precision balance with a capacity of 120 g and a sensitivity of 0.001 g. The organs were also macroscopically observed for color and size. Macroscopic observation of the color and size of these organs was also carried out.

2.2.3.3 Effect of aqueous extract of *Tetracarpidium conophorum* kernels on haematological and biochemical parameters

After 28 days of treatment with aqueous extract of *Tetracarpidium conophorum* kernels (250 mg/kg and 500 mg/kg), the animals were anesthetized with ethyl ether. For each animal, around 2 mL of blood was collected from the ophthalmic vein in two types of tube: EDTA tubes for analysis of haematological parameters, and dry "Vacutest" tubes for analysis of biochemical parameters. The latter were centrifuged at 2.500 rpm for 30 minutes using a Hospitex Diagnostics SRL Centrifuga C-60 centrifuge. The serum obtained was collected and stored in eppendorff tubes prior to analysis of biochemical parameters. Hematological and biochemical parameters were assayed using conventional methods [15, 16].

2.2.4 Statistical analysis

Statistical analysis of the data collected was carried out using analysis of variance (ANOVA), Student's t-test and Mann-Whitney to compare the "test" and "control" groups. Results are expressed as mean ± standard error, with $p < 0.05$ as the significance threshold.

3. Results

3.1 Effect of aqueous extract of *Tetracarpidium conophorum* kernels on general behavior and mortality in mice

Aqueous extract of *Tetracarpidium conophorum* kernels,

administered orally at a dose of 5000 mg/kg, did not alter the behaviour or general condition of mice up to 4 h after administration, compared with mice given distilled water. Administration of the aqueous extract of *Tetracarpidium*

conophorum kernels per os at the dose studied caused no mortality in mice 48 h after administration and up to the 14th day of treatment; the mortality rate was 0%. The lethal dose (LD₅₀) was therefore greater than 5000 mg/kg (Table 1).

Table 1: General condition and behavior of mice after product administration

Parameters	Treatment	<i>T. Conophorum</i> (5000 mg/kg)
	DW (0.5 ml/ 30 mg/kg)	
Number of animals	3	3
Mobility	N	N
Aggressiveness	A	A
State of stools	C	C
Trembling	A	A
Sleep	A	A
Sleepiness	A	A
Vocalization	A	N
Vigilance	N	N
vomitting	A	N
Ptosis	N	N
Number of animals	0	0

DW: Distilled water; T. C: *Tetracarpidium conophorum*; N: Normal; A: Absent; C: Compact

3.2. Effect of aqueous extract of *Tetracarpidium conophorum* kernels on weight gain in mice

Figure 1 shows the effect of aqueous extract of *Tetracarpidium conophorum* kernels on weight gain in mice. Figure 1 below shows that administration of the aqueous

extract of *Tetracarpidium conophorum* kernels (5000 mg /kg) after gavage in mice for 14 days resulted in a non-significant increase ($p > 0.05$) in the body weight of mice compared with mice treated with distilled water.

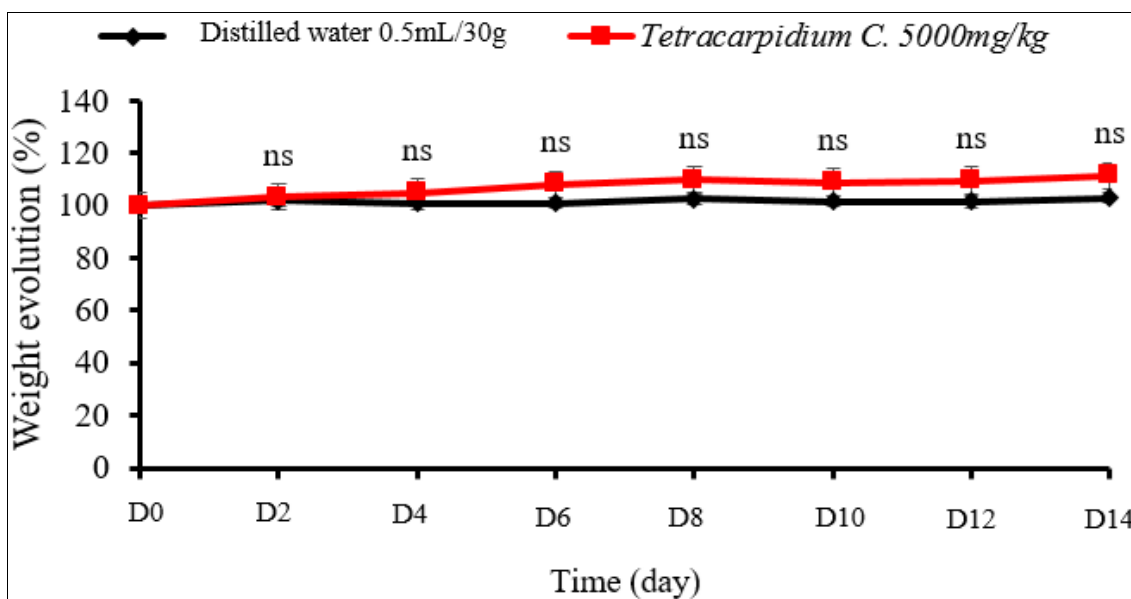


Fig 1: Effect of aqueous extract of *Tetracarpidium conophorum* kernels on weight gain in mice

NS: Non significant compared to control lot (distilled water)
 DW: distilled water, T.C: *Tetracarpidium conophorum*.
 Values are means ± MSE, for a sample of n=3

3.3 Effect of aqueous extract of *Tetracarpidium conophorum* kernels on food consumption in mice

The effect of aqueous extract of *Tetracarpidium conophorum*

kernels on food consumption in mice is shown in figure 2 below. Administration of the aqueous extract of *Tetracarpidium conophorum* kernels to mice showed a significant increase in food consumption compared with control animals treated with distilled water, reflecting good palatability.

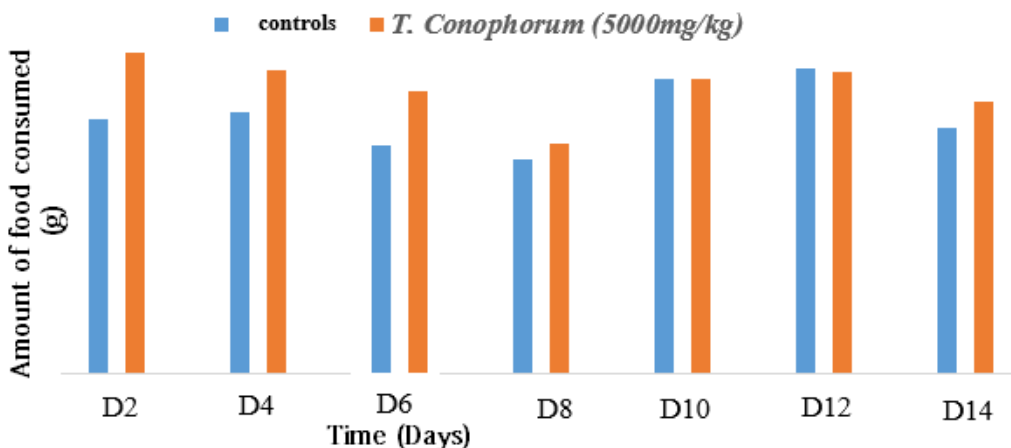


Fig 2: Effect of aqueous extract of *Tetracarpidium conophorum* kernels on food consumption in mice

3.4 Effect of aqueous extract of *Tetracarpidium conophorum* kernels on weight gain in rats

Figure 2 shows the weight development of rats treated with aqueous extract of *Tetracarpidium conophorum* kernels. The figure shows that daily oral administration of aqueous extract of *Tetracarpidium conophorum* kernels (250 and 500 mg/kg bw) for 28 days in rats resulted in a non-significant ($p > 0.05$)

increase in body weight from week 1 to week 3 compared with rats in the control lot treated with distilled water. On the other hand, a significant increase ($p < 0.05$) was observed in rats treated with the aqueous extract of *Tetracarpidium conophorum* kernels at a dose of 500 mg/kg.

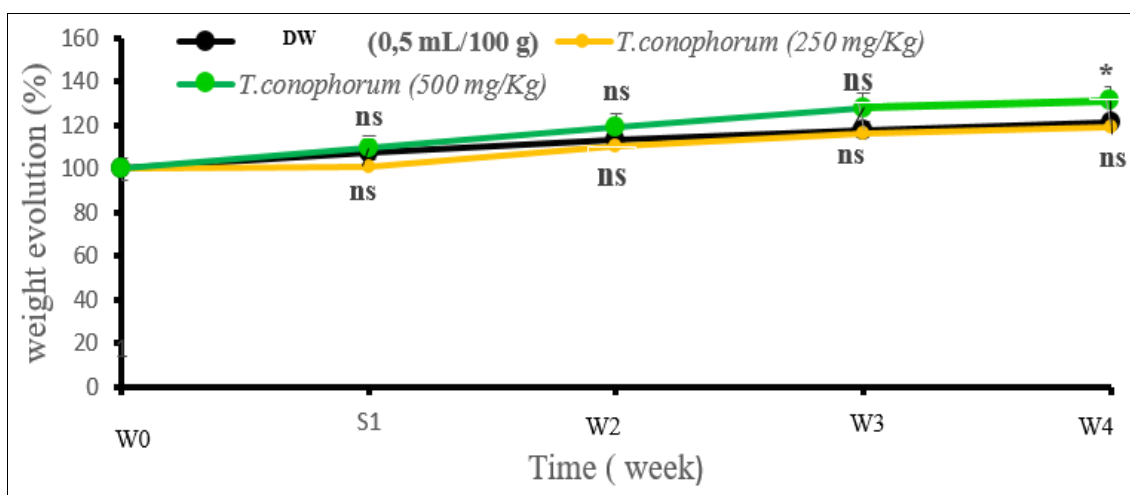


Fig 2: Effect of aqueous extract of *Tetracarpidium conophorum* kernels on weight gain in rats

3.5. Effect of aqueous extract of *Tetracarpidium conophorum* kernels on vital organ weights

Table 2 shows the effect of aqueous extract of *Tetracarpidium conophorum* kernels (250 and 500 mg/kg) administered for 28 days on vital organ weights. It shows that vital organ weights

(heart, liver, kidneys and spleen) did not increase significantly in rats treated with aqueous extract of *Tetracarpidium conophorum* compared with those in the control lot given distilled water.

Table 2: Effect of aqueous extract of *Tetracarpidium conophorum* kernels on vital organ weights

Weight of vital organs (g)	Treatments		
	Distilled water (1 mL /100 g)	<i>Tetracarpidium conophorum</i> (250 mg/kg)	<i>Tetracarpidium conophorum</i> (500 mg/kg)
Heart	0.37±0.05	0.32±0.01ns	0.37±0.01ns
Liver	3.31 ±0.13	3.19±0.26	3.90±0.39ns
Kidneys	0.29±00	0.28±0.02ns	0.28±00ns
Spleen	0.20±0.01	0.20±0.01	0.21±0.02ns

Values are means ± MSE, with n = 3: $p > 0.05$ non-significant difference from control (distilled water). NS: Non-significant difference from control.

3.6 Effects of aqueous extract of *Tetracarpidium conophorum* kernels on haematological parameters

The effect of aqueous extract of *Tetracarpidium conophorum*

kernels on haematological parameters is summarized in Table 3 below. These results show that oral administration of aqueous extract of *Tetracarpidium conophorum* kernels (250

and 500 mg/kg bw) for 28 days in rats produced a significant increase ($p < 0.05$; $p < 0.01$) in white blood cells, monocytes and granulocytes compared with those treated with distilled water.

On the other hand, the concentration of red blood cells was significant ($p < 0.05$) only at a dose of 500 mg/kg of aqueous extract of *Tetracarpidium conophorum* almonds.

Table 3: Effects of aqueous extract of *Tetracarpidium conophorum* kernels on haematological parameters

Hematological Parameters	Traitement		
	Distilled water (1ml/100g)	T.C Extract (250mg/kg)	T.C Extract (500mg/kg)
WBC (103/mm ³)	10.7±0.90	14.93±0.39*	14.06±0.43*
RBC (103/mm ³)	7.41±0.11	9.23±0.11ns	10.96±0.31*
HGB (g/dl)	13.16±0.26	12.76±0.20ns	13.56±0.8.17ns
HCT (%)	46.36±0.32	42.83±0.93ns	46.03±0.93ns
PLA (103/mm ³)	1019.66±110.19	1079±42ns	1106±25.83ns
MCV (µm ³)	64.575±0.149	59.16±0.38ns	57.86±1.25ns
LYM (%)	45.26±6.21	47.16±4.80ns	38.725±0.577ns
MON(%)	4.56±0.40	6/83±0.76 *	7.16±0.66**
GRA (%)	40.16±6.47	47.23±6.52*	48.13±8.72**

Values are means ± MSE, with n = 5, $p^* < 0.05$ and $**$: $p < 0.01$ significant difference from the control (distilled water); ns: non-significant difference from control. WBC: white blood cells; LYM: lymphocytes; MON: monocytes, GRA: granulocytes, RBC: red blood cells; HGB: hemoglobines; MCV: mean corpuscular volume; PLA: blood platelets; MPV: mean platelet volume; HCT: hematocrite, T.C: *Tetracarpidium conophorum*.

3.7. Effect of aqueous extract of *Tetracarpidium conophorum* kernels on biochemical parameters

Table 4 below shows the effect of aqueous extract of *Tetracarpidium conophorum* kernels on biochemical parameters. It shows that the administration of aqueous extract of *Tetracarpidium conophorum* kernels to rats for 28 days resulted in a highly significant ($p < 0.01$) dose-dependent decrease in transaminase (ASAT and ALAT) and triglyceride levels, compared with animals in the control lot given distilled

water. These levels rose from: 97.7±2.28; 98.06±2.46 IU/L, 2.16±0.03 (negative control) to 69.44±4.09; 70.44±3.51 IU/L, a decrease of 28.26% and 27.62% respectively in rats treated with *Tetracarpidium conophorum*. These results also show a significant increase ($p < 0.05$, $p < 0.01$) in HDL, LDL and urea levels in rats treated with the aqueous extract of *Tetracarpidium conophorum* kernels, compared with control rats treated with distilled water.

Table 4: Effect of aqueous extract of *Tetracarpidium conophorum* kernels on biochemical parameters

Biochemical parameters	Treatment		
	Distilled water (1 ml/100g)	T.C Extract (250 mg/kg)	T.C Extract (500 mg/kg)
ALAT (UI/l)	98.06±2.46	44.99±5.31**	37.98±4.93**
ASAT (UI/L)	97.7±2.28	69.44±4.09**	70.44±3.51**
TG (g/l)	2.16±0.03	0.58±0.18**	0.38±0.00**
CREAT (mg/dl)	2.40±0.39	2.11±0.12ns	2.45±0.49ns
GLY (g/l)	0.63±0.11	0.86±0.10ns	0.96±0.05ns
HDL (g/l)	0.34±0.05	0.48±0.00*	0.51±0.06*
URE (g/l)	47.89±0.31	63.29±0.24**	64.44±0.67**
LDL (g/l)	1.40±0.13	2.07±0.1**	2.02±0.07**

Values are means ± MSE, with n = 5. *: $p < 0.05$ et **: $p < 0.01$ significant difference from control (distilled water). NS: non-significant difference from control. ASAT: aspartate amino transaminase; ALAT: alanine amino transaminase; TG: triglycerides; TC: total cholesterol; Creat: creatinemia; (LDL): Low-density lipoprotein; (HDL): High-density lipoprotein, T.C: *Tetracarpidium conophorum*

4. Discussion

4.1. Evaluation of the acute toxicity of the aqueous extract of *Tetracarpidium conophorum* kernels in mice

The results obtained from the acute toxicity study show that oral administration of the aqueous extract of *Tetracarpidium conophorum* kernels at a dose of 5000 mg/kg did not alter the general behavior of mice and did not cause mortality in mice up to 5000 mg/kg. Our results corroborate those of [11] who observed no mortality following oral administration of the aqueous extract of *Tetracarpidium conophorum* nuts in rats at a dose of 3500 mg/kg. These results enable us to classify the toxicity of aqueous extract of *Tetracarpidium conophorum* kernels in category 5 of the Harmonized System of Classification of Chemical Substances, with an $LD_{50} > 5000$ mg/kg, a category characterizing slightly toxic substances [12]. Administration of the aqueous extract of *Tetracarpidium conophorum* kernels (5000 mg/kg) after gavage in mice for 14 days resulted in a non-significant increase in body weight compared with mice treated with distilled water. This increase in body weight observed in animals treated with the aqueous

extract of *Tetracarpidium conophorum* kernels could be explained by a significant food or water intake, suggesting an appetite-stimulating effect of the extract on mice. Our results are similar to those of [11], who noted a significant increase in body gain and food consumption in rats given the aqueous extract of *Tetracarpidium conophorum* nuts at a dose of 3500 mg/kg. Our results are also similar to those obtained by [17], which observed an increase in body gain in mice treated with the aqueous extract of *Strychnos camptoneura* stem bark. These results suggest that the aqueous extract of *Tetracarpidium conophorum* kernels is a material with favourable use in pharmacology.

4.2. Evaluation of the subacute toxicity of the aqueous extract of *Tetracarpidium conophorum* kernels in rats

Administration of aqueous extract of *Tetracarpidium conophorum* kernels (250 and 500 mg/kg bw) to rats for 28 days did not alter the general condition or behavior of the animals, and resulted in no mortality, corroborating the results of the acute toxicity study in mice. Daily oral administration

of the aqueous extract of *Tetracarpidium conophorum* kernels (250 and 500 mg/kg bw) for 28 days in rats produced a non-significant increase in body weight from week 1 to week 3, compared with rats in the control lot treated with distilled water. On the other hand, a significant increase was observed in rats treated with the aqueous extract of *Tetracarpidium conophorum* kernels at a dose of 500 mg/kg (Figure 3). The results in Figure 3 corroborate those obtained by [11] and confirm the acute toxicity results. Increased body weight is an indicator of the anabolic effects of the chemicals consumed by the animal. *Tetracarpidium conophorum* is thought to contain androgenic substances [18], notably proteins [9-11], which are responsible for the anabolic effects observed. This study showed no variation in the weight of vital organs (liver, heart, kidneys and spleen) and corroborates the results of the sub-acute toxicity study carried out by [11].

The hematopoietic system is one of the most sensitive targets of toxic compounds and an important index of the physiological and pathological state of humans and animals [19].

The effect of the aqueous extract of *Tetracarpidium conophorum* kernels on hematological parameters is summarized in Table II. These results show that oral administration of aqueous extract of *Tetracarpidium conophorum* kernels (250 and 500 mg/kg bw) for 28 days in rats produced a significant increase in white blood cells, monocytes and granulocytes compared with those treated with distilled water. On the other hand, the concentration of red blood cells was significant only at a dose of 500 mg/kg of aqueous extract of *Tetracarpidium conophorum* almonds. White blood cells and red blood cells are blood cells involved in the immune system, and the increased levels of these cells in rats treated with aqueous extract of *Tetracarpidium conophorum* suggests that this extract may have immunoprotective potential. The concentration of liver enzymes in the serum is an indicator of hepatic function [20]. High concentration of ASAT and ALAT indicates tissue damage and altered membrane permeability [21]. Administration of the aqueous extract of *Tetracarpidium conophorum* kernels to rats for 28 days resulted in a highly significant dose-dependent decrease in transaminase levels (ASAT and ALAT) compared with the control. Our results corroborate those obtained by [11], which also showed a decrease in the concentration of these two enzymes (ASAT and ALAT). Significant reductions in ASAT and ALAT levels have already been obtained [22-23] respectively with aqueous extracts of *Eleocharis drupifera* and *Artemisia afra* leaves in rats. In fact, the drop in serum transaminase levels, two biochemical markers of liver and muscle damage including the heart, suggests that this extract may have hepatoprotective potential. The significant drop in triglyceride levels observed in this study suggests that the aqueous extract of *Tetracarpidium conophorum* kernels has lipid-lowering potential.

5. Conclusions

These results show that the aqueous extract of *Tetracarpidium conophorum* kernels is a material with a favorable use in pharmacology, and suggest that this extract may have hepatoprotective and immunostimulant effects.

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