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Original Article

Acute Toxicity Studies of the Stem Bark Extract of *Zanthoxylum heitzii* A. & P. (Rutaceae) on Haematological Parameters, and Body Temperature

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ABSTRACT

Introduction: Zanthoxylum heitzii is a medicinal plant used in an empirical way in Cameroun and Chad to treat various diseases such as the headaches, sterility, the diarrheas, cancer, syphilis, paludism, cardiovascular diseases and the urogenital affections. **Aim of the study:** The present study aims to evaluate the use limits of the aqueous extract of the stem bark extract of Z heitzii in acute treatment in rat. **Materials and methods:** Acute toxicity was evaluated on the rats of two sexes, 3 months old and weighing 250 ± 10 g. A single dose (3-18 g/kg) of Z heitzii was administered by oral way to the rats.The behavior of the animals, the harmful effects and mortality were determined during 14 days.The ponderal evolution, hydrous and food consumption, the relative weight of organ and the rectal temperature were determined throughout the experimental period, while the hematologic and biochemical parameters of blood and the urine, were evaluated at the end of the experiment.
Results: The animals treated with the high doses presented behavioral deteriorations. The DL_{50} determined by calculation were 11,7 g/kg. The maximum tolerated dose was 6 g/kg and DL_{100} were 18g/kg. The biochemical analysis of plasma revealed that the aqueous extract of Z heitzii caused, dose-dependent, a significant reduction of ASAT and ALAT.The males and females rats, treated with the doses 12-15 g/kg saw their rectal temperatures increased on the first six hours before decreasing 24h later. The general reduction in values of these hematologic parameters can be due to the direct destruction of the cells in circulation or of the loss of mature cells in circulation by haemorrhage or by escape through the capillaries or even by reduction of the production of the cells.
Conclusion: In conclusion, although the present study indicates that Z heitzii, has medicinal values, its capacity to produce damage on liver with high doses in rats suggests that the human exposure to this plant for a long time must be narrowly supervised.
Keywords: Zanthoxylum heitzii, Aqueous extract, Acute Toxicity, Rectal Temperature.

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1. INTRODUCTION

Nowadays the medicinal plants are used more and more by the poor layers of the African population for the medicinal aims.Although the dose of the majority of the botanical products administered were often below the normal, some are however known to be toxic with the increased doses, whereas others have the potential for the unfavourable side effects[1]. The use of the medicinal plants relieve certainly the diseases, but therapeutic proportioning and toxicity are not often determined. Thus, very produced biologically active is likely to involve toxic effects. Consequently, the toxicity of a biological substance must be evaluated with precision before all scientific studies in order to determine the operational limit doses[2]. *Z heitzii* is a medicinal plant belonging to the family of Rutacées used in Tandjilé region (Chad) and present since the south of Cameroon, of Central Africa to Gabon and the province of Low-Congo in R.D. Congo.*Z heitzii* is a medicinal plant used empirically in Cameroun and Chad to treat various diseases such as the headaches, sterility, the diarrheas, cancer, syphilis, paludism, the diseases cardiovascular and the urogenital affections[3,4]. The phytochimic analyses showed that *Z heitzii* presents many components of which the amides, the lignanes[5], alkaloids, steroids and terpene[6,7].It is with an aim of promoting and to develop the medicinal plants of Chad in order to facilitate the access of the populations to the drugs to lower cost than we want to check the use limits of *Z heitzii* in acute treatment.

2. MATERIALS AND METHODS

2.1. Plant Material

The bark of *Z. heitzii* (Rutaceae) was collected in January 2013, period of flowering and of fructification, in a rice zone of Tandjilé, Tandjilé Division, Far North Region. The plant was authenticated by comparing the harvested plant to specimen N^0 60695/HNC deposited at the National Herbarium of Cameroon. The barks were dried and crushed into powder.

2.2. Preparation of stem bark aqueous extract of Z. heitzii

The extraction of the plant was made by taking account phytotherapeutists methods of preparation.The powder obtained was used to prepare the aqueous extract. Thus, 1 kg of powder was macerated in 1 litre of distilled water during 12 hours.The macerate was filtered through Whatman filter paper N^o 3, and the filtrate concentrated in a rotary evaporator at 40 ^{0}C for 24 hours. This process repeated several times yielded 10.04 g of concentrated of crude extract in the form of an oily paste. The extract was stored at -20 ^{o}C.

2.3. Animals

Wistar rats (250 ± 10 g) of both sexes were used in all experiments. Strain of animals was from Centre Pasteur in Yaoundé. They were reared in the Laboratory of the Medicinal Plants, Health and Galenic Formulation of Department of Biological Sciences, University of Ngaoundéré. The animals were housed under controlled temperature (24 ± 2 ^{0}C) and relative humidity (45% ± 10 %). Moreover, they had free access to food (pellets from LANAVET (Laboratory NVS)) and tap water. The animal handling was under the control of the veterinary surgeon of the Science Veterinary surgeon and medical school of the university Ngaoundéré. Experimental protocols and procedures were approved by the institutional Animals Care and Use Committee and the research was approved by the Animal Ethics Committee of the University of Ngaoundéré.

2.4. Animals

Rats were divided into 7 groups of 10 each. Animals in each group were housed separately in Plexiglass cages. Rats were acclimatized in the laboratory environment seven days before the start of the experiment. The mice were fasted for 12 hours prior to the experiment with

free access to water. Rats were orally administered; a single dose of *Z. heitzii* aqueous extract (3-18 g/kg) or distilled water for the control group. Animals from the same batch received the same dose of extract once daily. The animals were observed during the first two hours after administration of the extract and were supplied with food. Mortality was recorded after 24 hours. Food and water intake and body weight of surviving animals were evaluated after 14 days. Dead animals were autopsied for macroscopic observation of internal organs[8]. During this period the behavior of the animals was observed and recorded. The weight, water and food consumption were monitored at the end of each week. The last day of treatment, the animals were placed individually in metabolic cages for 24 h. Urine were collected, the pH was evaluated and stored at -20 ^{o}C for biochemical analyzes. The survivors were anesthetized with chloroform and sacrificed. The arterio-venous blood was collected in heparinized tubes and centrifuged at 4900 rev/min for 20 min. The collected plasma was stored at -20 ^{o}C for biochemical analyzes. Liver, kidney, and heart were removed, cleared of fat material, weighed and stored at -20 ^{o}C for biochemical analyzes and a portion preserved in formalin for histological analysis.

2.5. Analysis

Urinary and plasma electrolyte concentrations were determined using a flame photometer (JENWAY PFP 7) according to standard methods described by Henry[9]. Concentrations of creatinine, urea, glucose, albumin and electrolytes in the plasma and urine samples were evaluated using a two-way digital spectrophotometer (SECOMAM, RS 232C). Hematological and biochemical analyzes were performed by means of an automatic device type Toshiba 200 FR NEO (TOSHIBA Co., Japan). For hematological analysis, parameters such as RBC, MCV etc. were measured as described by Lahlou et al[10]. For biochemical tests, ALT, ASP and ALP were evaluated in serum and urine. Kidney functioning index was assessed by determination of the concentration of creatinine, urea, uric acid, Na^{+}, K^{+} and Cl^{-}. The kidneys, liver and heart were dissected out and fixed in 10% formalin fluid for haematoxylin and eosin staining.

2.6. Phytochemical study

Analytical tests for the identification of different families of metabolites in crude extracts of the leaves were made at IMPM (Institute of Medicinal Plants for Medicinal research) Cameroon. The procedures described by Treases and Evans[11] were used for the detection of various chemical groups. In view of the identification of the chemical structure of the compounds responsible for potential biological activity, preliminary tests of the phytochemical study were conducted.

2.7. Statistical Analyses

The results expressed are the mean ± SEM (n = 5). Comparison of means was made using the Student t test and one-way ANOVA of Origin Graph software (Microcal Origin 6.0 Microcal software version 6.0, Inc., One roundhouse plaza, Northampton, MA 01060 USA.). The difference was considered significant when $P < 0.05$.

3. RESULTS

3.1. Phytochemical study

Phytochemical screening performed on crude stem bark extract of *Z. heitzii* revealed the presence of several primary and secondary metabolites such as fatty acids, flavonoids, alkaloids, sterols, triterpenes, saponins, tannins, coumarins and phenolic compounds.

3.2. Acute toxicity

The behavioral reactions of the animals are consigned in table 1.It is deduced from this table that during the first two hours, the sensitivity to the touch, with the noise, the aggressiveness and the locomotion of the animals having received the extract with the doses (12-

18 g/kg) strongly decreased in way dependent amounts (Table 1).

The saddles of aspect liquidate were observed with doses 15 and 18 g/kg. 48 hours after administration the surviving animals find little by little their aptitudes.The died animals, treated with the extract with the doses (15-18 g/kg) presented convulsions, jumps disordered and suffocated. The autopsy of the dead animals showed a digestive tract having a color chestnut, probably due to the extract.The ponderal evolution was evaluated during the 14 days of the experimentation.

In the rats having received distilled water, the body weight passed from 252.81±21.79g the first week to 271.58±23.09g the second week, with a significant increase of 12.28%.To the dose of 3g/kg, the body weight passed from 255.86±47.97g the first week to 266.59±47.84g the second week, with an average increase in 10.73±0.13 g. This increase was noted in the animals treated with the dose 6g/kg. It passed from 272.89±8.76g the first week to 259.69±8.91g the second week at those treated with the dose of 6g/kg, that is to say an average increase in 13.20±0.15g (Table 1). On the other hand in the animals treated with extract at the dose of 9g/kg, the body weight decreased significantly (P < 0,05), the reduction was 7.22% the second week.This reduction was respectively of 8.12% and 11.12% with the doses 12g/kg and 15g/kg the second week. The DL_{50} was determined by calculation is equal to 11.7 g/kg, the tolerated maximum dose is 6 g/kg and DL_{100} = 18g/kg.

3.2.1. Effects of Z. heitzii extract on food intake

In the animals treated with distilled water, food consumption passed from 276.85±5.65g/week/rat the first week to 276.51±3.54 g/week/rat the second week, with a non significant difference (P<0.05) (Figure 1).Animals treated with the extract at the dose of 3g/kg, food consumption passed from 227.92±6.54 g/week/rat the first week to 225.05±1.99 g/week/rat the second week, with an average and significant reduction (P<0,05) in 2.87 ± 4.55 g/week/rat. With the dose 6g/kg, the food consumption of the rats shows a significant increase (P<0.05) average in 1.19±0.33 g/week/rat.The food consumption of the animals treated with the dose of 9g/kg passed from 298.62±4.58 g/week/rat the first week to 297.43±4.87 g/week/rat the second week, with an average reduction in 1.19±0.29 g/week/rat. With the dose 12g/kg and 15g/kg, the average food consumption of each rat decreased respectively by 5.90% and 5.07% the second week (Figure 1).

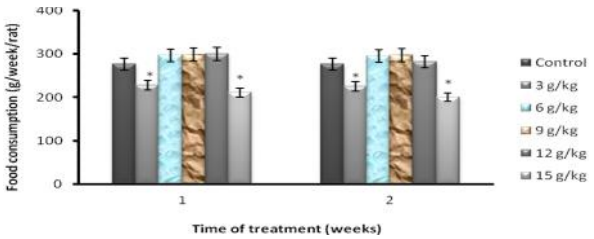

Fig 1: Food consumption (g/week/rat)

Values are means ± S.E.M., n = 10, *p < 0.05, significant difference compared to the control.

3.2.2. Effects of Z. heitzii extract on water consumption

In the animals treated with distilled water, average water consumption increased by 26,89% at the second week of the experimentation. With the doses (6-15g/kg) average water consumption decreased significantly (P<0.05) by 12.07%, 44.57%, 47.05%, 53.94% compared to the witness at the first week of experimentation. At the second week, it rather increased by 17.44%, 46.45%, 53.28% and 63.99% respectively with the doses (6-15g/kg) compared to the first week (Figure 2).

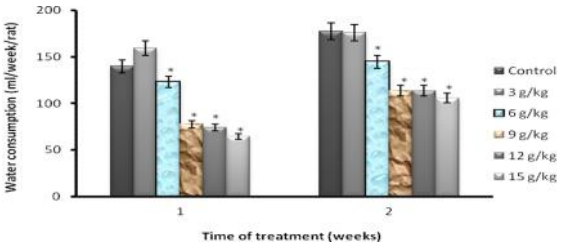

Fig 2: Effects of *Z. heitzii* on water consumption

Values are means ± S.E.M., n = 10, *p < 0.05, significant difference compared to the control.

3.2.3. Effects of the extract of Z heitzii on organs weight

effect (P<0.05) on the heart and the lung as well at the male as in the females.On the other hand with the doses 9-15 g/kg, *Z heitzii* significantly increased (P<0.05) the relative weight of the liver (8.92%;14.76%, and 17.23%), of the kidney (5.48%), the testis (3.77%) and the epididymis (22.72%) at the males (Table 2).Whereas in the females the relative weight of the liver (6.06%;7.80%, and 9.53%), of the kidney (4.05%).The weight of the uterus and the ovary did not know significant modification 14 days after administration of a daily dose of the extract of *Z heitzii* (Table 3).

3.3.Biochemical analysis

3.3.1. hematological Parameters in the males

Table 4 shows the various hematological parameters after 14 days of the treatment. The rate of haemoglobin passed from 18.06±0.7 g/dl to 19.12±0.39 g/dl with a significant increase (P<0.05) of 5.87% in the males with the dose 3g/kg. The rate of hématocrite increased by 0.4%. the rate of the red blood cells (RBC) decreases significantly (P<0.05), of 0.32% in the males which received the smallest dose (3g/kg) compared to control. As for the three other parameters:haemoglobin, the hématocrite and Mean corpuscular volume (MCV), we noted a significant increase (P<0.05) concentrations.That is to say a significant increase (P<0.05) of 5.87% in the males.Hématocrite are a significantly increase, (P<0.05) in the males (0.85%).MCV showed a significant difference (P<0.05) of 0.24% This increase in these three hematological parameters took place in the first two doses (3-6g/kg).For the doses 9, 12 and 15g/kg, it observes a fall of value on all the levels.Mean corpuscular hemoglobin (MCH), Plaquettes, White Blood Cells (WBC) and Neutrophiles present an increase of 1.82% and 7.21% respectively for Neutrophiles and MCH with doses 3 and 6g/kg. At the dose 3g/kg, the WBC decreased 2.09 % in the males at the dose 9g/kg. The WBC passed from 7.15±1.23k/µl to 6.87±1.12 k/µl in the males, that is to say a significant reduction (P<0,05) of 3,92%.We notice an increase in Eosinophile, Basophile, Lymphocyte, in the blood of the rats males At the dose 3g/kg, the values passed from 1.46±0.42% to 1.51±0.34 % at the males, that is to say a significant increase (P<0,05) in 3.42% for the eosinophile, 22.5% for the basophile, 2.93% for the lymphocytes (Table 4). Starting from the dose 12g/kg, we noticed a reduction in the concentration in lymphocyte, basophilic, and eosinophilic.As for the monocytes, their rate decreases dose- dependent during all the administration, it passed from 3.1±0.67% to 2.64±0.82% at the males, that is to say a significant fall (P<0.05) of 14.84% (Table 4).

3.3.2. Hematologic parameters at the females

The rate of haemoglobin increased by 1.47%. The rate of hématocrite of 0.39% at the dose 3g/kg. RBC A decreases significantly (P<0.05), of 1.35%. As for the three other parameters:haemoglobin, the hématocrite and Mean Corpuscular Volume (MCV), we noted a significant increase (P<0.05) concentrations.It passed from 18,06 ± 0,7g/dl to 19,12±0,39g/dl in the males and from 17.63±0.34g/dl to 17.89±0.52g/dl in the females for haemoglobin.showing a significant increase (P<0.05) of 1.47%. Hematocrite were increased by 0.86%. The MCV increased by 1.03%.This increase in these three hematologic parameters took place in the first two doses (3 and 6g/kg).For doses 9, 12 and 15g/kg, we observes a fall of value on all the levels.The MCH, WBC and Neutrophiles show an increase at the doses 3 and 6g/kg and decrease dose-dependent with the doses 9, 12 and 15g/kg. It noted that the MCH significantly increased (P<0.05) 0.99 % and Neutrophiles of 13.24%. As for the reduction, the value passed from 21.15±1.12(pg/red

cell) in the rat control to 20.11±1.01(pg/red cell) in the rat treated with 9g/kg, showing a reduction of 2.3% respectively. The WBC passed from 4.71±0.84k/µl to 4.53±0.96k/µl, showing a significant reduction (P<0.05) in 3.82 %. We notice an increase in Eosinophilic in (2.68%), Basophile (3.25%), Lymphocyte (0.61%) dose 3 g/kg.Starting from the dose 12g/kg, we noticed a reduction in the concentration in lymphocyte, basophilic, monocytes and eosinophilic (Table 5).

3.3.4. Effects Z heitzii on the index of function of the liver at the males

The rate of enzymes AST, ALT, ALP increased significantly (P<0,05) and dose dependent in the rats blood.At the dose 3g/kg, the AST passed from 61.5±2.62 (U/l) at the control to 61.52±1.76 (U/l), showing an increase of 0.03%.The ALAT increased significantly (P<0.05) by 0.52% compared to the control.The ALP passed from 37.79±1.96 (U/l) at the control to 38.11±2.03 (U/l) with the rats treated with extract, that is to say a significant increase (P<0.05) in 0.85%.The glucose rate increased significant (P<0.05) by 2.21 compared to the control. The TP, TB, TC, Albumine increased respectively and dose-dependent. The dose 3g/kg showed an increasing of 5.41%, 5.56%, 0.21%, and by 1.43% respectively for TP, TB, TC, and Albumine. The TG, LDL, HDL also increased with the dose 3g/kg. the TG pass from 83.24±2.19 (mg/dl) at the control to 83,45±1,74 (mg/dl) at the males treated with the dose 3g/kg. It notes that LDL increased significantly (P<0,05) by 3.85% and HDL of 1.12% (Table 6).

3.3.5. Effects Z heitzii on the index of function of the liver at the females

In the females, the rate of enzymes AST, ALT, ALP also increased significantly (P<0,05) at the dose 3g/kg. The ASAT passed from 46.2±2.1 (U/l) to the control to 46.29±3.27 (U/l), showing an increase of 0.19%.The ALT increased significantly (P<0.05) by 1.23% compared to the control.The ALP passed from 28.91±2.3 (U/l) to 29.13±1.93 (U/l), showing a significant increase (P<0.05) of 0.76%.The rate of glucose is also dose-dependent At the dose 3 g/kg, the rate of glucose showed a significant increase (P<0.05) by 0.76% compared to the control (Table 7).

At the dose 3g/kg, the TP passed from 7.45±0.4 at the control (g/dl) to 7.5±0.73 (g/dl) in the females treated with the extract, showing a significant increase (P<0,05) in 0.67%.Albumin passed from 5.02±0.39 (g/dl) at the control to 5.03±0.41 (g/dl) in the females treated with the extract, showing a significant increase (P<0,05) in 0.2%.TB increased significant (P<0.05) by 4.28% and the TC of 1.99%. The TG, LDL, HDL increased respectively by 0.31%, 0.11% and of 0.43% (Table 7).

3.3.6. Effects of the extract of Z heitzii on the index of function of the kidney in the males

The index of function of the kidney was given at the males through the biochemical analyses blood. It comes out from these analyses that the blood concentrations of uric acid, Cl^-, Na^+, and $Ca2^+$ significantly (P<0,05) decreased by comparison with the control. Only the creatinin concentration, urea, $Mg2^+$, K+ and inorganic phosphate, significantly (P<0,05) increased (Table 8).

3.3.7. Effects of the extract of Z heitzii on the index of function of the kidney in the females

In the females the ' index of function of the kidney was also given through the biochemical analyses blood.Blood concentrations of the uric acid Cl^-, inorganic phosphate, and $Ca2^+$ significantly (P<0,05) decreased by comparison with the control. On the other hand the creatinine concentrations, urea, $Mg2^+$, K^+, by Na^+ significantly (P<0,05) increased by comparison with the control (Table 9).

3.3.8. Effects of the extract of Z heitzii on the Temperature body

The rats males and females, treated with the doses 12 and 15 g/kg saw their temperatures advanced the first six hours before decreasing 24h later.At the dose 15 g/kg the temperature passed from 36.35 ± 0.11 ^{0} C to 39.16 ± 0.19 ^{0} C, showing an increase of 7.73% at the males as in the females, as of first hour of the administration of the extract. The animals treated with the doses 3-9 g/kg did not present significant modifications of temperature as well at the males as in the females (Table 10).

4. DISCUSSION

The study of the acute toxicity of the aqueous extract of *Z heitzii* revealed that the administration of a single dose involves in the follow hours a deterioration of the behavioral reactions for the doses higher or equal to 9 g/kg.The animals presented a reduction in aggressiveness, locomotion, sensitivity to the noise and the touch. These behavioral deteriorations are comparable with those observed by Kanjanapothi et al.[12] at the time of the study of the acute toxicity of *Kaempferia galanga* in rabbits. The animals died following the administration of a single dose of the aqueous extract of *Z heitzii* presented convulsions and the ultimate stage was disordered jumps followed by a suffocation. These results show that the aqueous extract of *Z heitzii* would have a depressive action on the central nervous system. The convulsions observed in the animals would be due to the increase in the exitability of the neurons[13]. The administration by oral way of a single dose of the aqueous extract of *Z heitzii* does not involve any death with dose lower or equal to 9g/kg.Beyond this concentration, mortality increases with the dose until a total lethality 18 g/kg.The DL_{50} determined by calculation and graphically was respectively, of 11,7 g/kg and 11,75 g/kg. By admitting that the values of DL_{50} lower than 5 g/kg correspond to highly toxic substances and values of DL_{50} higher than 5 g/kg with the substances slightly toxic[14,15], The results show that the aqueous extract of *Z heitzii* has a relatively low toxicity, but considerable. The tolerated maximum dose (6g/kg) represents approximately 250 times the therapeutic dose 475 mg/kg, dose roughly prescribed by the tradipratician. The aqueous extract of *Z heitzii* in treatment acute caused as of dose 9 g/kg, a depressive state dose-dependent on the rat, resulting in a reduction in the locomotion, sensitivity and aggressiveness.The extract could act like a myorelaxant or a tranquillizing, by action on the nerve central[13].

These observations confirm the traditional use of the extracts of this plant in the treatment of the painful rules, the migraines and the epilepsy. The acute diarrheas, which precede death of the rat could be allotted to a stimulative action of the aqueous extract of *Z heitzii* on gastro-intestinal motricity.The extract could contain substances able to act like laxative. The observation of the diarrheal saddles two hours after administration of *Z heitzii* could be explained by admitting that the extract contains substances able to cause an acceleration of the intestinal transit. This acceleration would be due to a direct action of the extract on the smooth musculature intestinal[8].

Rats treated with the aqueous extract of the stem bark of *Z heitzii* (9-15 g/kg) significantly presented a loss of body weight per comparison at the pilot rats.The results of this study also showed a reduction in the food consumption in the rats treated with the aqueous extract of *Z heitzii* to the dose 9-15 g/kg.Thus, the loss of body weight could be probably explained by the reduction in the food consumption due to an action of the extract on the appetite[16].However, the reduction in the profit of weight observed in these rats (9-15 g/kg) would undoubtedly be due to the presence in the plant, of the chemical substances like the tanins.Such results

were reported by Ntchapda et al.[8], on acute toxicity in the mouse.The deceleration of the growth would be the consequence of a metabolic disorder or a disorder of the appetite caused by the extract of the plant which involves a reduction of the food catch as well as water.

It was observed significant modifications of the organs weight of detoxication (kidney, liver) to the doses 9-15 g/kg.Creatinine and the urea are the two markers of the renal function.These metabolites generally have, a constant concentration under the normal conditions[17].The urea rate increased with the amount of 12-15g/kg. This increase would mark a renal beginning of affection, because according to Rock et al.[17], the urea and creatinine rate increases at the individuals presenting a renal dysfunction and particularly when glomerular filtration is disturbed.

The increase in the creatininemy could be explained by a renal insufficiency, resulting from a nephrons deterioration[18,19]. Serum and hepatic cholesterol increase dose-dependent.The hypercholesterolemy observed with the higher doses could be explained by the stimulation of the lipidic anabolism hepatic under the action of the extract[18] or by an exogenic contribution of fatty compounds contained in the extract.

The biochemical analysis of plasma revealed that the aqueous extract of *Z heitzii* caused a reduction significant and dose-dependent on the serum protein rates.This dose-dependent decrease of the proteinemy is correlated in this study by a significant increase in the rates of tissue protein hepatic. Indeed, it is known that the derease of proteinemy results from a mobilization of plasmatic proteins in tissue when those are low in proteins.

It is obvious that hepatic deterioration is due to a cellular escape of the enzymes in plasma.When the plasmic membranes of the hepatocytes are damaged, a variety of enzymes normally localised in the cytosol, are released in blood.Their estimates in the serum are used like markers to measure the damage of the hepatocytes.The serums analysed in clinic make it possible to appreciate the existence and the intensity of the hepatic cytolysis which are transaminases (ASAT and ALAT).The administration of the aqueous extract of *Z heitzii* caused a significant increase in the serum activity of ASAT starting from the dose of 12 g/kg compared with the control. In the same way, it was observed a significant rise in the activity of ALAT to the dose of 12-15 g/kg compared with the control.These increases would translate an attack hepatic[20, 21].This toxic action could be allotted to different secondary metabolites such as saponins, the tanins and the flavonoïdes, all present in the extract of the plant.These results were in conformity with those observed by Benhamou et al.,[21] at the time of the study of acute toxicity and subaigüe of *Syzigium aromaticum* on the rats.The results showed a significant increase in the serum cholesterol level what to suggest an increased synthetic activity of the liver.

The rats males and females, treated with the doses 12 and 15 g/kg saw their temperatures advanced the first six hours before decreasing 24h later.To the dose 15 g/kg the temperature passed from 36,35 ± 0,11 ^{0}C to 39,16 ± 0,19 ^{0}C, showing an increase of 7,73% at the males as in the females, as of the first hour of the administration of the extract. The animals treated with the dose 3-9 g/kg did not present significant modifications of temperature as well at the males as in the females.These results suggest that *Z heitzii* does not remove hypothermia and does not heat the body.The administration of a single dose of the aqueous extract of *Z heitzii* during 14 days showed a reduction in the RBC, haemoglobin and hématocrite with the doses 12-15 g/kg.This reduction in the RBC makes it possible to suggest that the repeated administration of *Z heitzii* can cause in subacute treatment or chronicle a heavy

bleeding[22]. The general reduction in values of these hematologic parameters can be due to the direct destruction of the cells in circulation or of the loss of mature cells in circulation by haemorrhage or escape has through the capillaries or even by reduction of the production of the cells. [23]

Table 1: Effects of the aqueous extract of stem bark of *Z Heitzii* on the behavior of the animals

	% Mortality	Latency	Symptoms	Ponderal evolution (g)	
				First week	Second week
0	0/10	-	none	252.81±3.79	271.58±3.09*a
3	0/10	-	none	255.86±4.97	266.59±4.84*a
6	0/10		none	259.69±8.91	272.89±2.76*a
9	3/10	>4h<8h	light reduction in locomotion, aggressiveness, noise and touched sensitivity and respiratory movement	250.46±1.47*b	230.92±2.90
12	5/10	>2h<8h	reduction in locomotion, aggressiveness, noise and touched sensitivity and respiratory movement	252.42±4.7*b	231.92±3.76
15	8/10	>2h<6h	Reduction marked in the locomotion, aggressiveness, the sensitivity to the noise and with touched and jerked respiratory movement, in the convulsions, the jumps disordered followed by death	259.65±1.88*b	238.55±4.46
18	10/10	>0h<1h	Reduction marked in the locomotion, aggressiveness, the sensitivity to the noise and with touched and jerked respiratory movement, in the convulsions, the jumps disordered followed by death		

Values are means ± S.E.M., n = 10,
[a]* P < 0.05, significant difference compared to the first week
[b]* P < 0.05, significant difference compared to the first week

Table 2: Effects of the aqueous extract of *Z heitzii* on the males organs weight

	Doses (mg/kg)					
Organs	**Control**	**3**	**6**	**9**	**12**	**15**
Liver	3.23±0.23	3.25±0.22	3.39±0.14	3.54±0.21*	3.73±0.22*	3.79±0.21*
Kidneys	0.73±0.11	0.74±0.22	0.75±0.12	0.76±0.33*	0.77±0.22*	0.77±0.13*
Heart	0.36±0.22	0.36±0.14	0.37±0.25	0.36±0.18	0.37±0.28	0.36±0.21
Lung	0.76±0.31	0.75±0.12	0.76±0.31	0.76±0.13	0.77±0.32	0.76±0.23
Spleen	0.32±0.23	0.31±0.32	0.33±0.11	0.32±0.23	0.33±0.22	0.33±0.21
Testis	0.53±0.23	0.53±0.22	0.54±0.11	0.55±0.23	0.55±0.22	0.55±0.11*
Epididymis	0.22±0.26	0.24±0.25	0.26±0.21	0.27±0.12	0.26±0.21	0.27±0.12*

Values are means ± S.E.M., n = 5, *p < 0.05, significant difference compared to the control**.**

Table 3: Effects of the aqueous extract of *Z heitzii* on the females organs weight chez les

	Doses (mg/kg)					
Organs	**control**	**3**	**6**	**9**	**12**	**15**
Liver	3.46±0.23	3.47±0.30	3.48±0.34	3.67±0.25*	3.73±0.22*	3.79±0.23*
Kidneys	0.74±0.26	0.74±0.25	0.75±0.23	0.76±0.13*	0.77±0.12*	0.77±0.23*
Heart	0.37±0.33	0.37±0.25	0.37±0.26	0.39±0.13	0.38±0.22	0.39±0.31
Lung	0.75±0.21	0.75±0.12	0.76±0.21	0.76±0.23	0.77±0.42	0.77±0.33
Spleen	0.33±0.09	0.32±0.12	0.34±0.11	0.34±0.10	0.34±0.32	0.34±0.31
Uterus	0.27±0.13	0.29±0.12	0.28±0.23	0.29±0.12	0.27±0.43	0.28±0.32
Ovary	0.032±0.013	0.032±0.022	0.030±0.013	0.031±0.012	0.030±0.023	0.032±0.012

Values are means ± S.E.M., n = 5, *p < 0.05, significant difference compared to the control

Table 4: Hematologic parameters at the males

	Doses en (g/kg)						
	Normal range	**0**	**3**	**6**	**9**	**12**	**15**
RBC (x 10^6/µL)	5-10	9.52±0.46	8.49±0.39	7.45±0.71*	7.36±0.34*	6.33±0.28*	6.25±0.27*
WBC (x 10^3/µL)	1-5	7.15±1.23	6.87±1.12	6.39±1.17*	6.25±1.53*	5.89±1.37*	5.64±1.05*
Plaquettes (x 10^3/µL)	600-1100	1017.09±0.32	968.84±7.86	987.13±8.11*	982.31±6.29*	964.28±5.13*	1023.14±7,03
Hémoglobine (g/dL)	11-19	19.06±0.7	18.12±0.39	18.31±0.41*	17.64±0.23*	17.58±0.62*	16.44±0.29*
Hématocrite (%)	35-57	47.85±1.13	46.25±1.22	46.15±1.19*	45.09±2.01*	44.39±2.16*	43.82±1.78*
RDW (%)	12-18	13.16±0.17	14.15±0.29	14.34±0.31*	12.63±0.21	12.53±0.63	13.41±0.29*

MCV (fL) (fl/red cell)	46-65	53.14±2.8	53.27±1.73	54.44±1.35*	52.52±2.15	50.33±1.38	50.04±2.33
MCH (pg)	18-23	18.2±0.98	18.53±1.03	19.07±1.1	17.83±0.95	17.54±1.03*	1.14±0.92*
Neutrophile (%)	2-20	12.9±1.5	13.83±1.26	14.02±1.6	12.28±1.49*	12.11±1.59*	12.08±1.72*
Basophile (%)	0-7	3.2±0.67	2.48±0.35	1.21±0.45*	1.15±0.48*	2.13±0.43*	2.42±0.61*
Eosinophile (%)	0-1	1.46±0.42	1.51±0.34	1.54±0.59*	1.51±0.81*	1.43±0.43	1.37±0.56
Lymphocytes (%)	65-94	78.05±3.25	80.34±4.02	82.17±4.11*	79.23±2.39*	77.14±3.16	76.85±3.26
Monocytes (%)	0-6	3.1±0.67	2.64±0.82	2.38±0.46*	2.05±0.53*	1.89±0.34*	1.95±0.41*

Values are means ± S.E.M., n = 5, *p < 0.05, significant difference compared to the control. k/µl : x 10^3/µL

Table 5: Hematologic parameters at the males females

Organes	**Doses en (g/kg)**						
	Normal range	**0**	**3**	**6**	**9**	**12**	**15**
RBC (x 10^6/µL)	5-10	9.12±0.37	8.01±0.78	7.97±0.29*	7.87±0.38*	7.73±0.19*	7.65±0.54*
WBC (x 10^3/µL)	1-5	4.71±0.84	4.53±0.96	4.06±0.75*	3.97±0.63*	3.92±0.87*	3.85±0.68*
Plaquettes (x 10^3/µL)	600-1100	936.18±6.14	925.24±9.12	919.16±5.07*	867.53±6.72*	859.24±8.02*	952.15±9.85
Hémoglobine (g/dL)	11-19	17.63±0.34	17.89±0.52	16.2±0.21*	15.05±0.32*	14.84±0.37	12.09±0.44*
Hématocrite (%)	35-57	47.24±2.7	45.63±2.1	44.32±1.72*	43.21±1.24*	43.07±1.11*	40.91±1.39*
RDW (%)	12-18	14.44±0.24	14.29±0.32	15.12±0.23*	15.15±0.12*	13.14±0.27	15.19±0.24*
MCV (fL) (fl/red cell)	46-65	57.09±1.7	57.68±2.82	58.28±2.25*	57.84±1.63*	57.15±2.05	55.81±1.56
MCH ((pg/red cell)	18-23	21.15±1.12	21.36±0.99	21.47±0.97	20.11±1.01*	19.82±0.93*	19.53±1.2*
Neutrophile (%)	2-20	17.15±2.3	19.42±2.27	19.57±2.13	17.08±1.56*	16.61±1.59*	16.43±2.14*
Basophile (%)	0-7	1.23±0.34	1.27±0.29*	1.32±0.44*	1.2±0.37	1,09±0.24	0.98±0.32
Eosinophile (%)	0-1	1.49±0.36	1.53±0.82*	1.58±0.58*	1.54±0.54*	1.52±0.39*	1.48±0.46
Lymphocytes (%)	65-94	74.89±4.26	75.35±5.03*	76.24±4.36*	75.63±3.18*	74.02±3.07	73.68±2.71
Monocytes (%)	0-6	5.6±2.44	5.51±1.46*	4.37±1.85*	4.44±1.43*	3.97±1.62*	3.85±2.13*

Values are means ± S.E.M., n = 5, *p < 0.05, significant difference compared to the control. k/µl : x 10^3/µL

Table 6: Effects *Z heitzii* on the index of function of the liver at the males

	Doses en (g/kg)						
	Normal range	**0**	**3**	**6**	**9**	**12**	**15**
Glucose (mg/dL)	70-119	90.1±2.3	92.09±3.02*	92.61±3.56*	94.5±1.93*	95.2±3.05*	97.04±2.16*
ALT (IU/L)	10-50	54.15±3.2	54.43±2.16	54.89±1.95*	57.11±2.6*	59.3±2.1*	62.14±.19*
AST (IU/L)	68-135	61.5±2.62	61.52±1.76	63.1±3.2*	65.78±3.17*	68.34±3.17*	70.68±2.14*
ALP (IU/L)	30-90	37.79±1.96	38.11±2.03*	38.85±1.94*	40.61±3.11*	42.56±2.3*	45.09±2.61*
TP (g/dL)	4.8-9.2	7.02±0.37	7.4±0.8*	7.51±0.39*	7.89±0.64*	8.06±0.42*	8.23±0.68*
Albumine	1.2-6	4.2±0.25	4.26±0.31	4.35±0.44*	4.51±0.6*	4.75±0.36*	5.03±0,52*
TB (bilirubine total)(mg/dL)	0-0.5	0.9±0.08	0.95±0.11	1.0±0.20*	1.1±0.13*	1.3±0.10*	1.4±0.17*
TC(mg/dL)	38-96	61.2±1.96	61.33±3.15*	61.52±2.14*	63.1±2.61*	65.47±2.19*	66.72±1.95*
TG(mg/dL)	60-140	83.24±2.19	83.45±1.74	84.02±3.4*	87.4±3.17*	88.07±4.09*	90.1±2.51*
LDL(mg/dL)	10-30	16.62±2.15	15.98±2.02	16.45±2.15	17.83±3.1*	19.36±1.79*	22.04±2.64*
HDL(mg/dL)	15-35	20.47±3.16	20.7±1.59	21.04±2.34*	23.14±2.56*	26.34±3.12*	28.57±2.61*

Values are means ± S.E.M., n = 5, *p < 0.05, significant difference compared to the control**.**

Table 7: Effects *Z heitzii* on the index of function of the liver at the females

	Doses en (g/kg)						
	Normal range	**0**	**3**	**6**	**9**	**12**	**15**
Glucose (mg/dL)	70-119	87.68±3.4	88.35±2.83*	88.35±1.27*	91.3±3.4*	94.6±1.64*	95.73±1.98*
ALT (IU/L)	10-50	41.52±3.4	42.03±3.01*	42.85±2.56*	44.5±3.1*	46.18±2.6*	48.17±3.05*
AST (IU/L)	68-135	46.,2±2.1	46.29±3.27	46.97±2.46*	49.12±1.69*	54.5±3.16*	59.35±3.16*
ALP (IU/L)	30-90	28.91±2,3	29.13±1.93*	29.76±3.2*	31.65±2.19*	34.41±2.16*	37.14±2.36*
TP (g/dL)	4.8-9.2	7.45±0.40	7.50±0.73	7.58±0.43*	8.01±0.63*	8.31±0.54*	8.67±0.46*

Albumine	1.2-6	5.02±0.39	5.03±0.41	5.07±0.27	5.09±0.5	5.26±0.34*	5.34±0.43*
TB (bilirubine total)(mg/dL)	0-0.5	0.70±0.19	0.73±0.11*	0.75±0.09*	0.86±0.12*	0.9±0.16*	1.0±0.20*
TC(mg/dL)	38-96	67.4±2.5	68.74±3.16*	68.94±3.08*	70.13±1.96*	73.16±2.59*	75.68±3.01*
TG(mg/dL)	60-140	79.85±3.12	80.1±2.16*	80.52±1.96*	82.46±2.13*	85.7±2.6*	87.11±2.53*
LDL(mg/dL)	10-30	20.35±2.53	20.53±2.29	21.06±3.14*	23.4±3.6*	25.15±2.64*	26.78±2.05*
HDL(mg/dL)	15-35	18.6±2.20	18.68±3.20	19.03±2.52*	21.25±2.86*	23.17±2.03*	24.75±1.68*

Values are means ± S.E.M., n = 5, *p < 0.05, significant difference compared to the control.

Table 8: Effects of the extract of *Z heitzii* on the index of function of the kidney in the males

	Doses en (g/kg)					
	0	**3**	**6**	**9**	**12**	**15**
Creatinine (mg/L)	6.13±3.01	6.73±2.11	7.53±2.97*	7.73±3.01*	8.23±1.14*	9.33±2.27*
Urée (mg/L)	0.55±0.32	0.59±0.21	0.60±0.19*	0.63±0.26*	0.65±0.15*	0.64±0.11*
Acide urique (mg/L)	46.25±2.11	43.15±2.03*	42.38±2.12*	39.11±3.33*	37.45±2.13*	28.65±3.52*
Cl^- (mEquiv./L)	92. 35±3.32	87.65±2.26	74.26±4.46*	66.73±4.31*	64.85±2.26*	59.24±4.46*
Na^+ (mEquiv./L)	146.54±0.26	147.28±0.12	146.23±0.14	146.44±0.34	137.58±0.63*	143.23±0.42*
K^+ (mEquiv./L)	5.49±0.45	5.87±0.24	5.56±0.31	5.64±0.45*	6.57±0.24*	6.86±0.31*
Ca^{2+} (mg/L)	81.32±0.31	78.11±0.43*	74.29±0.43*	69.36±0.15*	67.12±0.23*	67.24±0.43*
Mg^{2+} (mg/L)	15.14±0.15	16.37±0.24*	20.16±0.31*	19.14±0.15	21.47±0.23*	22.18±0.32*
Pi (mg/L)	31.35±0.24	28.34±0.36*	30.69±0.35*	31.47±0.63	32.32±0.33*	33.19±0.15*

Values are means ± S.E.M., n = 5, *p < 0.05, significant difference compared to the control.

Table 9: Effects of the extract of *Z heitzii* on the index of function of the kidney in the females

	Doses en (g/kg)					
	0	**3**	**6**	**9**	**12**	**15**
Creatinine (mg/L)	5.14±1.17	5.58±2.37	6.54±2.13*	7. 4±2.17*	8.08±2.32*	8.10±1.19*
Urée (mg/L)	0.37±0.24	0.38±0.12*	0.42±0.21 *	0.46±0.34*	0.51±0.12*	0.55±0.31*
Acide urique (mg/L)	52.21±2.14	50.12±2.15*	47.37±1.15*	42.22±2.34*	40.21±2.45*	37.35±1.35*
Cl^- (mEquiv./L)	88.21±2.35	75.34±2.54*	69.3±1.12*	68.11±1.15*	65.14±3.24*	59.3±3.22*
Na^+ (mEquiv./L)	142.62±0.71	145.56±0.57*	156.17±0.37*	155.22±1.71*	155.56±1.55*	159.27±1.32*
K^+ (mEquiv./L)	5.24±0.02	5.44±0.03*	5.56±0.05*	5.58±0.02*	6.14±0.03*	6.56±0.05*
Ca^{2+} (mg/L)	77.11±0.21	73.70±0.32*	68.62±0.31*	67.21±0.29*	54.20±0.17*	55.62±0.21*
Mg^{2+} (mg/L)	15. 34±0.20	16.44±0.22*	18.26±0.25*	20. 54±0.21*	21.40±0.23*	22.46±0.27*
Pi (mg/L)	30.16±0.10	32.34±0.16*	29.37±0.22*	28.26±0.11*	27.34±0.13*	27.11±0.12*

Values are means ± S.E.M., n = 5, *p < 0.05, significant difference compared to the control.

Table 10: Effects of the extract of *Z heitzii* on the Temperature body

		Doses en (g/kg)				
Time (h)	**Control**	**3**	**6**	**9**	**12**	**15**
1	36.35 ± 0.11	35.31 ± 0.11	36.37 ± 0.14	37.24 ± 0.13	39.33 ± 0.16*	39.16 ± 0.19*
2	37.14 ± 0.15	36.42 ± 0.12	37.34 ± 0.16	37.35 ± 0.19	39.22 ± 0.23*	39.19 ± 0.14*
3	36.34 ± 0.14	35.27 ± 0.17	35.41 ± 0.15	37.62 ± 0.23	39.44 ± 0.17*	39.14 ± 0.21*
4	37.23 ± 0.17	36.46 ± 0.16	37.45 ± 0.16	36.72 ± 0.24	39.37 ± 0.18*	39.24 ± 0.23*
5	37.24 ± 0.11	37.44 ± 0.14	36.34 ± 0.11	36.62 ± 0.17	38.18 ± 0.19*	39.35 ± 0.17*
6	36.31 ± 0.24	35.45 ± 0.21	35.37 ± 0.17	36.45 ± 0.38	38.34 ± 0.18*	38.64 ± 0.16*
7	36.16 ± 0.14	36.59 ± 0.19	35.21 ± 0.12	36.36 ± 0.17	37.19 ± 0.17	37.44 ± 0.22
24	37.24 ± 0.14	36.35 ± 0.14	36.45 ± 0.15	36.38 ± 0.35	36.24 ± 0.21	36.72 ± 0.16

Values are means ± S.E.M., n = 10, *p < 0.05, significant difference compared to the control.

5. CONCLUSION

In conclusion thus, although the present study indicates that *Z heitzii*, has medicinal values, its capacity has to produce damage on the level of the liver to dosed raised in rats suggests that the human exposure has this plant for a long time must be narrowly supervised.

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