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Study of the Subacute Toxicity of Dry Bark of *Albizia ferruginea* (Mimosaceae) (Guill. & Perr.) Berth. in Wistar Albino Rats

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Abbreviations:
ALAT: Alanine aminotransferase;
ASAT: Aspartate aminotransferase;
LD50: Dose lethal to 50% of animals;
OECD: Organisation for Economic Cooperation and Development;

ABSTRACT

This present work aimed to assess the subacute toxicity of the total aqueous extract of the dry bark of *Albizia ferruginea* in rats. Subacute toxicity was done in accordance with 2008 OECD Guideline 407, for oral toxicity at a daily dose for 28 days in rodents. The animals were divided into six groups of 10 rats each (5 males and 5 females). One control group received 10 mL/kg of distilled water, three groups received 200, 400 and 800 mg/kg of extract respectively, one satellite control group and one satellite treated group received 10 mL/kg of distilled water and 800 mg/kg extract respectively. After 28 days of treatment, the satellite groups were left under observation without treatment for an additional 14 days. Behavior, body weight and death rate were monitored during the experimental period. The relative weight of some organs, hematological and biochemical parameters and the histopathological study of the liver, kidneys and lungs were evaluated at the end of the experiment. There were no significant effects on body weight gain and the relative weight of organs investigated. At the 800 mg/kg dose, there was a significant increase in the level of monocytes by 26.53%; the mean corpuscular hemoglobin content (MCHT) of 18.18%; and in the corpuscular hemoglobin concentration (MCHC) of 20.70 %, only in male rats. ALT and ASAT activity were increased significantly in both male and female rats. These increases were not seen in satellite treated rats. The histology of the organs investigated showed no difference when comparing the treated rats to the control rats. The subacute toxicity study of total aqueous extract of the dry bark of *Albizia ferruginea* did not show any signs of significant toxicity for parameters studied in rats.

1. Introduction

Increasing number of people use medicinal plants to heal [1]. It should be emphasized that the traditional use of any plant for therapeutic purposes does not guarantee its safety [2]. If the pharmacological effects of many plants have been proven in various laboratories, their toxicity is generally unknown. Therefore, the assessment of the toxicity of herbal preparations is important in determining the safety of these remedies [3].

Albizia Ferruginea is a kind of plant of the family of the Mimosaceae [4], found in Cameroon, Angola, Benin, Republic of Congo, Nigeria, Senegal, Togo, Uganda among others [5]. This plant has been used for years in traditional medicine for the treatment of several pathologies [6]. Previous pharmacological studies carried out on this plant showed that the ethanol extract of the leaves corrects anemia [5] and the aqueous extract of dry bark reduces inflammation, algia and pyrexia [7] as well as chronic inflammation in rats [8].

The qualitative phytochemical investigations of the dry bark aqueous extract of *A. ferruginea* were performed for alkaloids, flavonoids, saponins, phenols, steroids, glycosides and tannins, by our research team [7, 8]. The study of the acute toxicity of the total aqueous extract of the dry bark of *A. ferruginea* shows that the DL_{50} was greater than 5000 mg/kg [9] and that this extract could be classified according to the classification system generally harmonized of the OECD in category 5 and considered an oral non-toxic substance [9, 10].

However, the long-term daily consumption of this product may present intoxication risks for consumers. The purpose of this work was to study the subacute toxicity of the total aqueous extract of dry bark of *A. ferruginea* in rats.

2. Experimental Methods

2.1 Plant Material

The stem barks of *A. ferruginea* were harvested from Angallé village in the South Region of Cameroon. The plant materials were identified by Dr. Barthélémy TCHIENGUE of the National Herbarium of Cameroon, where a voucher specimen of the plant was deposited under the number 49871.

2.2 Preparation of Plant Extract

Fresh stem barks were air-dried and reduced to a fine powder. The powder (500 g) was macerated with 2.5 L of distilled water for 24 hours. The mixture was filtered with Whatman No.3 filter paper, concentrated under reduced pressure and lyophilized at 50 °C for 48 hours. A dark brown solid (84 g) representing the stem barks aqueous extract of *A. ferruginea* was obtained (yield of 16.8%).

2.3 Experimental Animals

Wistar albino rats (200-250 g) of both sexes were obtained from the animal house unit of the Faculty of Science of the University of Yaoundé I, Cameroon. They were maintained under standard environmental conditions with dark and light circles of 12/12 h. They were fed with standard commercial diet and water was provided ad libitum. Rats were deprived of food but not water prior to administration of the test extracts. The experimental protocol was in conformity with guidelines of the Cameroon National Ethical Committee on the use of laboratory animals for scientific research (CEEC Council 86/609).

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2.4 Oral Subacute Toxicity Test

Subacute toxicity was evaluated in accordance with the 2008 OECD Director No.407, focusing on oral toxicity at a daily dose for 28 days in rodents [11]. The animals were divided into six groups of 10 rats each (5 males and 5 females). One control group received 10 mL/kg of distilled water, three groups received 200, 400 and 800 mg/kg of extract respectively, one satellite control group received 10 mL/kg of distilled water and one satellite treated group received 800 mg/kg of extract. After 28 days of treatment, the satellite groups were left in observation without treatment for 14 additional days. Behavioral reactions were observed especially for 4 hours after treatment and throughout the experimental period to determine any deaths. Observations were focused on symptomatologic disorders observed by the naked eye, including changes in skin, hair, eyes and mucous membranes. Attention was also focused shivers, convulsion, salivation, diarrhea, lethargy, sleep, coma etc. Water and food intakes were measured each day and expressed in weekly intake per animal. The body weight was evaluated 3 times a week on average and allowed the average weight per week. At the end of the experimental period, the rats were switched for 24 hours, then were sacrificed by decapitation and artero-venous blood collected in 2 different tubes: an EDTA tube and dry tube without anticoagulant. Blood from the EDTA tube was used for complete blood count (CBC) using a Coulter counter model s-plus iv impedance machine. The blood from the dry tube made it possible to obtain serum which was stored at -4 °C for the assay of the biochemical parameters. Analysis of the lipid profile (total cholesterol, HDL-cholesterol and triglycerides), liver function (total proteins, bilirubin, alkaline phosphatase, ALAT and ASAT), renal function (creatinine and urea) and blood sugar was performed using kits from Fortress diagnostics (United Kingdom), with procedures based on colorimetric method [12-15]. The liver, kidneys, spleen, lungs and the heart were obtained, rinsed with 0.9% salt solution, then weighed and stored in formol 10% for histological analyzes.

The relative weight of each organ was calculated according to the formula:

$$Pr = Po/Pa \times 100$$

where, Pr: relative weight of the organ (g/100 g); Po: weight of the organ (g) and Pa: rat body weight (g)

The organs, previously stored in 10% concentrated formalin, underwent several liquor baths of increasing degree (80 °C, 90 °C and 100 °C), before passing into toluene and to be included in the liquid paraffin. Paraffin blocks were mounted on a microtome to perform cuts. They were then tempered in aqueous dyes (hematoxylin and eosin) and observed under the microscope.

2.5 Statistics

Values were expressed as Mean±SEM. Data were analysed by one-way ANOVA followed by Dunnett's test using Graph pad prism (5.03) software. P values less than 0.05 were considered statistically significant.

3. Results and Discussion

3.1 Effects of Extract of Albizia ferruginea on Behaviour and Mortality Rate of Rats

During the 28 days of observation after the administration of the unique daily dose extract (200, 400 and 800 mg/kg); no deaths were observed in males and females rats. There was no change in the nature of stool, nor were there changes in the general appearance of rats (hair, skin, eye condition, ears and mouth). Animals did not experienced haematuria, uncoordinated movements nor respiratory distress during the study period. No behavioural change was observed. The same observations were recorded in male and female satellite rats.

3.2 Effects on Weight of the Rats

The administration of single daily dose extract (200; 400 and 800 mg/kg) in male and female rats showed that all subjected animals had a weight gain for the duration of the study. However, the gain was not statistically been different between control and treated groups. The weight of the treated rats was therefore comparable to that of control rats. The same observation was made for the satellite treated groups with respect to the satellite control groups (Fig. 1).

3.3 Effects on the Relative Weight of Bodies of Males and Females Rats

Depending on the dose and sex, no statistically significant differences were found between the control groups and the treated groups at different doses of the extract on the relative weight (g/kg of body weight) for the investigated organs (Heart, liver, kidneys, spleen, lungs). It was also the same for the satellite treated groups compared to the satellite control groups (Fig. 2).

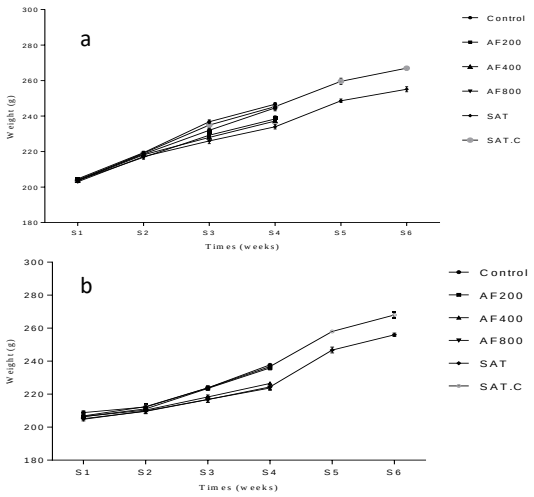

Fig. 1 Effects of total aqueous extract of dry bark of *Albizia ferruginea* on the weight of the male (a) and female (b) rats in subacute toxicity. (*Each point represents the average weight ± ESM, n= 5; AF= aqueous extract from Albizia ferruginea, SAT= satellite, SAT.C = satellite control; ≠ marks the stop of treatment. Satellite: Rats treated with plant extract (800 mg/kg) and left under observation without treatment for 14 days. Satellite control: rats compared to the rats of the satellite group)*

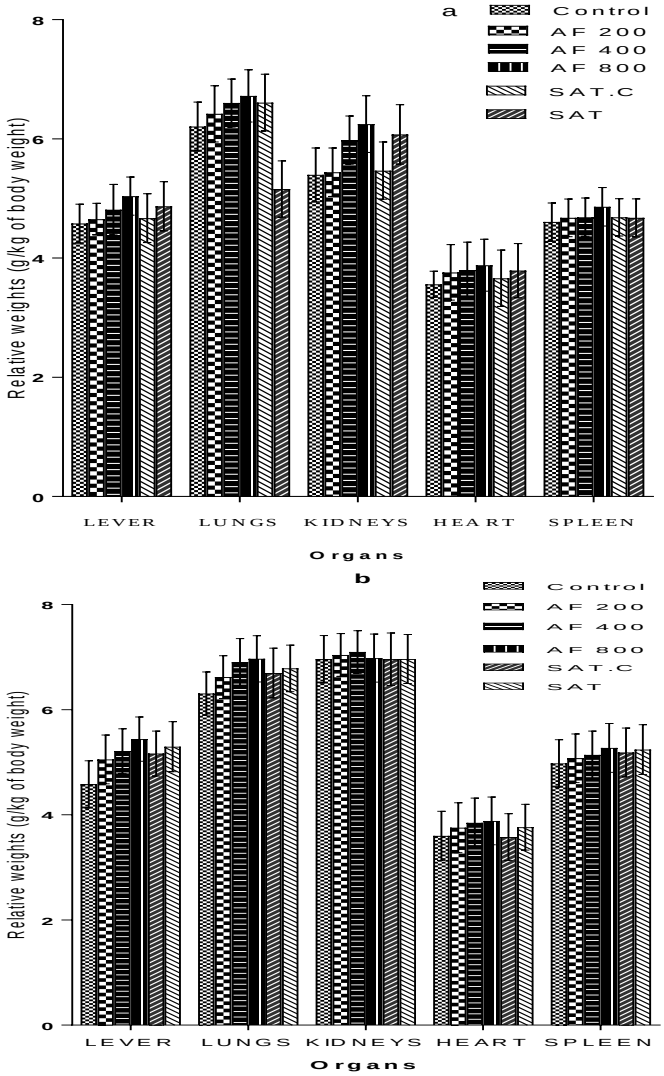

Fig. 2 Effects of total aqueous extract of dry bark of *Albizia ferruginea* on the relative weight of some organs of the male (a) and female (b) rats in the subacute test. (*Each bar represents the average weight± ESM, n= 5; AF= aqueous extract from Albizia ferruginea, SAT= satellite, SAT.C = Satellite control. Satellite: Rats treated with plant extract (800 mg/kg) and left under observation without treatment for 14 days. Satellite control: rats compared to the rats of the satellite group.)*

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Table 1 Effects of total aqueous extract of dry bark of *Albizia ferruginea* on some hematological parameters in males and females rats

	Males					
	Witness	200 mg/Kg	400 mg/Kg	800 mg/Kg	Witness satellite	Treated satellite
White blood cells (10^6/µL)	6.46±0.31	6.50 ± 0.46	6.56 ±0.31	6.62 ±0.54	6.53±0.28	6.60±0.67
Lymphocytes (10^3/µL)	2.41±0.43	2.52±0.33	2.57±0.92	2.69±0.53	2.51±0.51	2.74±0.40
Monocytes (10^3/µL)	0.98±0.02	0.94±0.17	0.96±0.25	1.24±0.29*	1.01±0.18	1.09±0.19
Granulocytes (10^3/µL)	4.93±0.43	5.22±0.59	4.99±0.38	4.98±0.31	4.95±0.59	4.96±0.38
Red blood cells (10^6/µL)	6.67±0.24	6.75±0.23	6.69±0.26	6.83±0.24	6.71±0.30	6.76±0.26
HCT (%)	41.03±0.69	43.23±0.86	40.01±1.36	41.09±0.71	39.90±1.57	40.58±1.07
Hemoglobin (g/dL)	12.38±0.39	12.78±0.24	12.90±0.29	12.77±0.20	12.44±0.28	12.66±0.38
MVC (fL)	52.69±1.16	52.77±1.10	49.95±1.16	50.69±1.08	58.90±7.94	51.30±0.89
MCHT (pg)	16.06±0.37	16.16±0.37	16.71±0.43	18.98±0.62*	16.12±0.76	17.55±0.53
MCHC (g/dL)	30.23±0.88	31.25±0.78	33.44±0.80	36.49±0.72*	32.68±0.95	34.11±0.64
Platelets (10^3/µL)	428.24±12.43	427.23±16.15	427.81±12.59	414.21±29.03	429.24±5.99	420.24±13.01
	Females					
	Witness	200 mg/Kg	400 mg/Kg	800 mg/Kg	Witness satellite	Treated satellite
White blood cells (10^3/µL)	4.85±0.69	5.76±0.35	5.05±0,73	5.09±0.31	4.84±0,38	4.97±0.81
Lymphocytes (10^3/µL)	1.34±0.09	1,46±0,08	1,69±0,07	1.25±0.09	1,39±0,07	1.27±0.08
Monocytes (10^3/µL)	0.83±0.52	0.81±0.74	0.89±0.45	0.88±0.26	0.85±0.13	0.86±0.25
Granulocytes (10^3/µL)	3.86±0.05	3.74±0.03	3.88±0.03	4.07±0.04	3.87±0.02	3.90±0.03
Red blood cells (10^6/µL)	6,85±0,75	7.13±0.11	7.11±0.65	7.23±0.63	6.94±0.54	7.14±0.18
HCT (%)	36.70±1.69	40,1±0,88	42.79±1.09	44.02±0.76	38.00±0.75	42.89±1.17
Hemoglobin (g/dL)	11.96±0.57	12.17±0,62	13.18±0.77	13.21±0.52	12.20±0.65	12.60±0.61
MVC (fL)	54.40±0.75	54.50±0.56	51.40±0.83	53.60±0.84	53.30±0.94	52.40±0.43
MCHT (pg)	17.82±0.65	17.91±0.17	18.08±0.34	19.24±0.23	21.20±0.71	19.14±0.47
MCHC (g/dL)	30.79±0.75	30.88±0.47	31.89±0.56	31.78±0.53	31.90±0.55	36.58±0.82
Platelets (10^3/µL)	464.64±16.38	467.61±49.19	461.83±11.7	455.23±58.21	468.42±34.24	462.26±87.12

*Values represent mean±MSE; n=5, *p<0.05 indicates increasing significance compared to the control group. HCT=hematocrit; MVC=mean corpuscular volume; MCHT=mean corpuscular haemoglobin content; MCHC=mean corpuscular haemoglobin concentration*

Table 2 Effects of total aqueous extract of dry bark of *Albizia ferruginea* one some biochemical parameters of males and females rats in subacute test

	Males					
	Control	200 mg/kg	400 mg/kg	800 mg/kg	Satellite control	Satellite
ALAT (U/L)	47.48±1.08	48.12±1.16	49.66±0.93	56.24±0.97*	47.92±1.14	49.88±1.77
ASAT (U/L)	53.72±3.25	61.01±0.61	61.55±2.82	65.89±1.33*	57.23±1.96	62.81±2.71
Total bilirubin (mg/dL)	1.79±0.08	1.86±0.14	1.88±0.21	1,90±0,03	1.80±0.05	1.87±0.34
Alkaline phosphate (U/L)	18.59±0.12	20.27±2.41	20.64±0.02	20.71±0.63	18.71±6.80	20,34±0,46
Total cholestérol (mg/dL)	71.11±2.67	65.90±2.21	68.32±2.82	69.27±2.14	77.20±2.57	65.82±2.33
HDL-cholestérol (mg/dL)	29.66±1.29	25.27±1.02	21.79±0.91	29.86±1.97	50,74±1,28	24.96±1.53
Triglycerides (mg/dL)	83.89±2.45	79.94±2.05	76.04±2.59	76.54±2.83	80,27±2,77	78.22±2.66
Total proteins (mg/dL)	10.75±1.34	11.01±5.60	11.02±0.26	10.86±1.15	11.89±0.32	10.89±0.29
Blood sugar (mg/dL)	85.13±2.12	88.06±2.17	88.04±2.65	88.11±2.31	86.44±2.53	86.62±2.58
Urea (mg/dL)	193.68±8.63	189.22±6.70	188.88±4.92	188.68±3.58	191.68±4.62	188.95±3.95
Creatinine (mg/dL)	0.81±0.06	1.01±0.10	0.96±0.04	1.05±0.09	0.92±0.07	1.01±0.06
	Females					
	Control	200 mg/kg	400 mg/kg	800 mg/kg	Satellite control	Satellite
ALAT (U/L)	51.64±1.21	53.12±1.62	52.24±1.49	59.79±1.81*	52.58±1.71	57.71±0.98
ASAT (U/L)	57.89±2.35	53.6±1.60	62.03±0.69	64.59±2.16*	56.67±1.82	62.19±2.35
Total bilirubin (mg/dL)	1.72±0.07	1.74±0.30	1.76±0.16	1.78±0.12	1.72±0.16	1.74±0.05
AlKaline phosphatase (U/L)	15,65±0,81	15,86±0,60	15,81±0,74	15.97±0.91	15,76±4,9	15,89±0,56
Total cholesterol (mg/dL)	67.85±4.83	65.48±3.18	64.38±2.82	65.20±6.69	65.98±2.70	64.55±4.92
HDL-cholesterol (mg/dL)	26.64±1.18	25.98±1.16	23.23±1.38	26.28±1.11	27.85±1.52	26.99±1.77
Triglycerides (mg/dL)	74.59±2.81	79.28±2.59	79.26±2.72	79.70±2.51	77.12±1.96	78.74±7.23
Total proteins (mg/dL)	9.71±0.82	9.63±0.85	9.57±0.99	9.46±1.05	9.75±0.91	9.56±1.23
Blood sugar (mg/dL)	73.26±2.56	74.65±1.86	74.46±2.27	74.52±2.25	73.65±1.68	74.38±1.98
Urea (mg/dL)	200.11±2.91	200.21±0.90	198.18±4.28	196.48±6.99	203.03±3.88	198.10±5.52
Creatinine (mg/dL)	0.71±0.09	0.80±0.10	0.81±0.01	0.84±0.13	0.73±0.02	0.82±0.05

*Values represent mean ± MSE; n=5, *p<0.05 indicates increasing significance compared to controls*

3.4 Effects on Hematological Parameters in Male and Female Rats

In male rats treated at doses of 200 and 400 mg/kg, there was no significant variation of investigated haematological parameters, in comparison to male control rats. At the dose of 800 mg/kg, was a significant increase in the percentage of monocytes of 26.53%, the 18.18% hemoglobin (TCMH), medium content of 18.18% and hemoglobin corpuscular concentration (CCMH) of 20.70% in male rats as compared to the male controls.

These different investigated hematological parameters did not undergo any significant changes in the satellite male rats treated at this same dose of 800 mg/kg as compared to male rats of the satellite control group (Table 1). In female treated rats, there was no significant variation of investigated hematological parameters as compared to control female rats, regardless of the extract.

The same observation was made in the satellite treated female rats at the 800 mg/kg dose compared to the female satellite control group rats (Table 1).

3.5 Effects on Biochemical Parameters in Male and Female Rats

The effects of the extract on the biochemical parameters of the male and female rats did not show any statistically significant difference between the treated groups and control groups at different doses of the extract, for total bilirubin, alkaline phosphatase, total cholesterol, HDL-cholesterol, triglycerides, total proteins, blood sugar, urea and creatinine. Meanwhile, after 28 days of daily administration at a dose of 800 mg/kg, the extract induced a significant increase in the ALAT and ASAT activity in male and female rats as compared to the control rats. Two weeks after treatment termination, transaminase activity in the treated satellite group was comparable to that of the control satellite group regardless the sex (Table 2).

3.6 Effects on Histology of Liver, Kidney and Lung in Male and Female Rats

The histological sections of the investigated organs (liver, kidneys and lungs) of the rats treated at different doses of the extract were comparable

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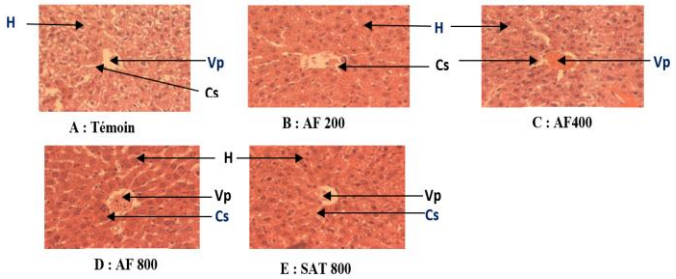
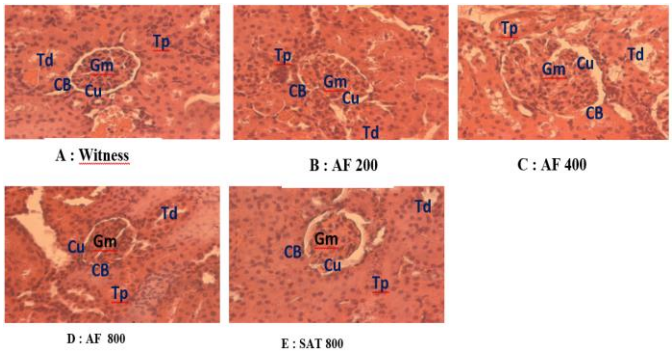
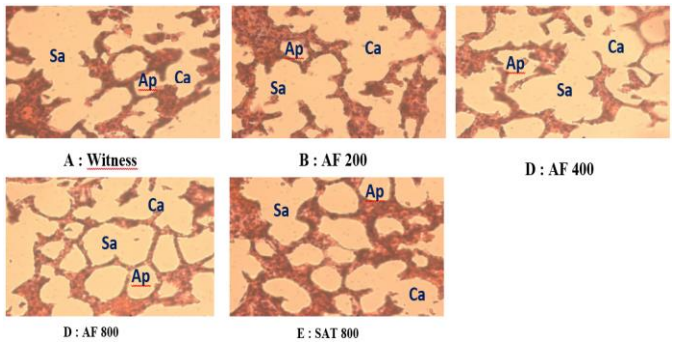
to those of the control group rats. The same observation was made in the rats of the satellite treated groups as compared to the satellite controls. Indeed, normal hepatic architecture has been observed with a hepatic parenchyma consisting of a portal vein and hepatocytes arranged in span and separated from each other by sinusoid capillary and the centro-lobular vein (Fig. 3a); a renal architecture having a normal proximal and distal tube, a glomerulus surrounded by the Bowman capsule, and a very visible urinary space (Fig. 3b) and a lung architecture showing normal pulmonary alveoli (Ap), alveolar bags (Sa) and normal looking ducks (Ca) (Fig. 3c) for treated rats as control rats.



a) Liver/ Cs, : sinusoid capillary, H :hepatocytes, Vp: portal vein



(b) Kidney/ Tp: proximal tube, Td: distal tube, Gm: Glomerulus, CB: Bowman's Capsule, Eu: urinary space



(c) Lung/ Ap: pulmonary alveoli, Sa: alveolar bags, and Ca: normal looking ducks. (HEx400). AF: *Albizia ferruginea* and SAT: Treated satellite.

Fig. 3 Histological section. (a): Liver, (b): Kidney and (c): Lung, in subacute test of the total aqueous extract of the dry bark of *Albizia ferruginea*. Rat witness (A); Rat treated with aqueous extract of *A. ferruginea* at a dose of 200 mg/kg (B), 400 mg/kg (C), 800 mg/kg (D) and treated satellite rat (E)

3.7 Discussion

Although medicinal plants have many biological activities, people are very familiar with the toxic potential of bioactive substances [16]. *A. ferruginea* is a widely available plant in West and Central Africa including Cameroon [17]. In the regions of the Center, Coast and South of Cameroon, *A. ferruginea* is traditionally used for the treatment of several pathologies [6]. Indeed, previous pharmacological studies carried out on this plant have shown that the ethanol extract of *A. ferruginea* leaves corrects anemia [5] and the total aqueous extract of dry bark of *A. ferruginea* was able to reduce inflammation, pain and pyrexia [7]. A previous study on acute toxicity indicated that the DL_{50} of the total aqueous extract of dry bark of *A. ferruginea* would be greater than 5000 mg/kg [9] and this extract could be classified in category 5 of acute toxicity substances relatively low depending on the globally harmonized classification system (GHS) [10]. An additional study was conducted to contribute to the study of the toxicity of this total aqueous extract of *A. ferruginea* dry bark during long-term consumption. We thus, studied the subacute toxicity of this extract during a 28 days experimentation in rats. The subacute toxicity test showed that, regardless of the dose of administered extract, no deaths were recorded and no behavioral changes were observed for 28 days. The same observations were made for the rats of the satellite treated groups compared to satellite control groups. These results were truly expected because the doses administered (200, 400 and 800 mg/kg) on the basis of the therapeutic dose indicated by the therapists were all below the DL_{50} which was greater than 5000 mg/kg [9].

Changes in body weight have been used as an indicator of adverse effects of drugs, chemicals and bioactive substances [18, 19]. Since no significant change in corporal weight has was observed in the male and female rats of the treated groups with respect to the male and female rats of the controls groups after a daily treatment for 28 days, as well as the satellite treated and control groups, one could suggest that the oral and subacute administration of our extract has no effect on the normal growth of rats.

Similarly, no significant change was observed in the weight of the investigated organs (liver, lungs, kidneys and heart), suggesting that the daily administration of our extract for 28 days at doses studied, had no effect on their normal growth. The relative weight of the organs is considered to be a relatively sensitive indicator in the toxicity study [20].

The analysis of the blood parameters is relevant because it gives information on the hematopoietic function (assessment of cells of the myeloid lineage), on the appearance of allergies (studies of white blood cells) and on intravascular effects such as hemolysis [21]. The hematological assessment showed no significant difference between treated rats and controls rats.

The hepatocytes have the role of the neutralization of toxins, whether they come from within or from outside the body (detoxification), while the kidneys have the role of blood purification and disposal of waste [22]. The function of the liver and kidneys is therefore very important in assessing the toxicity of drugs and plant extracts as they are necessary for the survival of an organism [23]. Therefore, hematological and biochemical analyzes were carried out to assess any alterations of the hepatic and renal functions caused by the ingestion of our extract. The significant increase in the levels of ALT and ASAT in male and female rats, treated at the 800 mg/kg dose could be due to their release following the damage of liver cells [24, 25]. This lesion of liver cells would be transitory especially as this significant increase in the levels of ALT and ASAT was not observed in rats of the satellite treated groups at the same dose. In addition, the histological study showed no alteration of the liver structure. Renal dysfunction can be evaluated by simultaneous measurements of urea, creatinine and uric acid [18, 26]. In this study, there were no changes in plasma levels of urea and creatinine of treated rats compared to controls rats. This could also support the absence of alteration of renal function especially as the histological study showed no alteration of the renal structure.

4. Conclusion

The subacute toxicity study of the total aqueous extract of dry bark of *A. ferruginea* in rats did not show signs of notorious subacute toxicity at the doses administered for parameters studied in rats. However, it would be wise to study the chronic toxicity of this extract at higher doses in order to confirm safety of this plant.

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