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Research Article

Acute and Subchronic Toxicity of *Gmelina arborea* Roxb, (Verbenaceae) in Wistar Rat

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ABSTRACT

Gmelina arborea is a plant used in the traditional treatment of many diseases. However, only few pharmaco-toxicological studies are available on this plant. The aim of this study is to investigate the acute and subchronic toxicity of the aqueous extract of *Gmelina arborea* leaves. Materials and Method: acute and subchronic toxicity study has been performed in wistar rats using an aqueous extract of *Gmelina arborea* leaves. In the acute toxicity test, a single dose of 2000 mg/kg of body weight was administered to rats and they were observed during 14 days. The subchronic toxicity study was carried out using three doses of 31.25 mg/kg, 125 mg/kg and 500 mg/kg of body weight, administrated to rats (5 male and 5 female) for 28-days. Physiological behaviour, diet consumption, and body weight were evaluated. Biochemical, haematological and histological studies were realized at the end of the study. Results: There was neither mortality, nor physiological behaviour changes. The body weight and diet consumption of the rats were not modified. As for blood parameters, a dose dependent increase in Cholesterol and transaminases levels and decrease in blood glucose were observed. There was also an increased level of creatinine in male rats and urea in female rats. Histology of the treated rats' liver shows in the centrolobular area lipid inclusions in hepatocytes almost at 500 mg/kg. In kidneys, a thickening of the glomerular interstitium was observed. Conclusion: These results show that the aqueous extract of *Gmelina arborea* is probably hepato- and nephro-toxic.

Keywords: *Gmelina arborea*, wistar rat, toxicity

INTRODUCTION

Gmelina arborea Roxb, Verbenaceae, is a tropical fast growing tree. It originated in an area of South and Southeast Asia from Pakistan and Sri Lanka to Myanmar and widely introduced in many African countries (Nigeria, Sierra Leone, Côte d'Ivoire, Mali, Gambia, Benin, Senegal, Burkina Faso, and Zambia) and American countries (Brasilia, Venezuela, Honduras and Cuba)[1]. In many African countries, *Gmelina arborea* is used for the treatment of arterial hypertension[2] and has been reported to possess vasodilating activity[3]. Many other usages of the plant in the traditional medicine are known. It is used in Nigeria to treat diarrhoea and in Guinea traditional medicine[4]; it serves for the treatment of leucorrhoea. The root bark is used for the treatment of pile. Indians people use the stem bark for the treatment of fractures and scorpions sting[3,5]. Many ayurvedic preparations attribute several therapeutic properties to the plant among which anti-inflammatory and anti-pyretic action of the leaves, stomachic action of the roots, Detoxicant and regulator action of the hepatobiliary function and against rash. It is also used as a post-partum diet for the mother's recovery and to reinforce the baby's health[6,7]. The fruit is used as astringent, diuretic and tonic. The flowers are used against blood parameters troubles and leprosy. The root is anthelmintic, laxative, stomach burning fever, hallucinations, piles and urinary discharges[8]. Beyond that usage in traditional medicine, *Gmelina arborea* also serve in wood industry mostly in sawmills.

Many studies have shown an antibacterial activity of its stem bark and leaves[9]. Cardio-protective and antioxidant activity of the leaves have also been described[10].

Despite the various uses over long periods, there is a lack of toxicological information regarding the safety of repeated exposure to the plant. Except the work of *Kulkarni et al*, 2010 conducted in India on toxicological studies of the stem bark of *Gmelina arborea* in rodents[11], no toxicological data is available on *Gmelina arborea* leaves. Thus as a part of a safety evaluation of *G. arborea*, acute and subchronic oral dose toxicity studies were carried out to investigate the potential toxicity after single and 28-days repeated oral administration of the aqueous extract of *G. arborea* on Wistar rats.

MATERIAL AND METHODS

Material

Wistar albinos rats weighing 200 g ± 20 g were used. They were maintained in standard environmental conditions (22 to 25°C, 12 h dark/light cycle, frequent air change) and had

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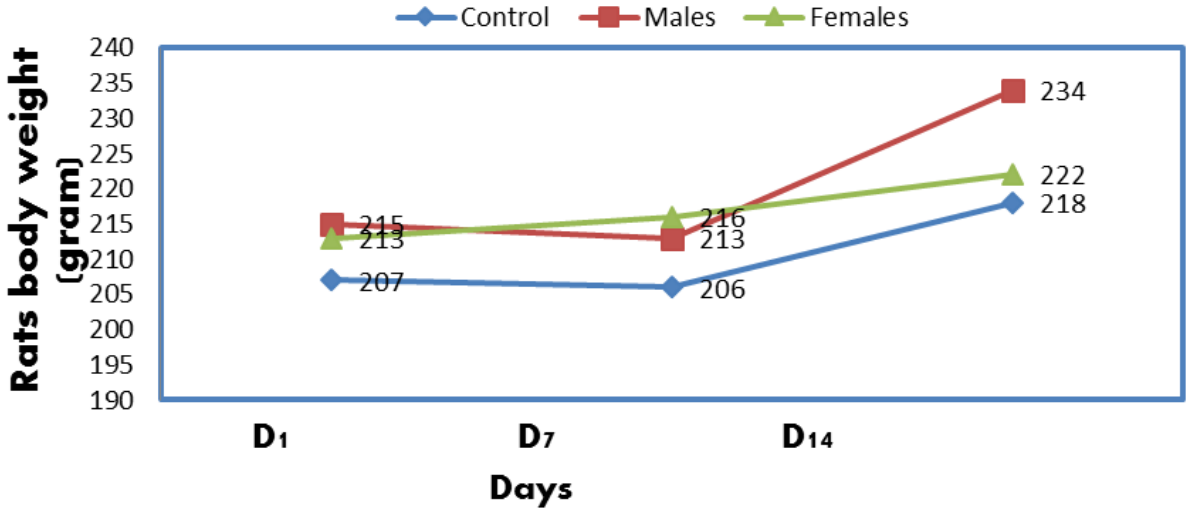

Fig. 1: Evolution of rat body weight during the acute toxicity test period. Each point represents mean. (n= 5).

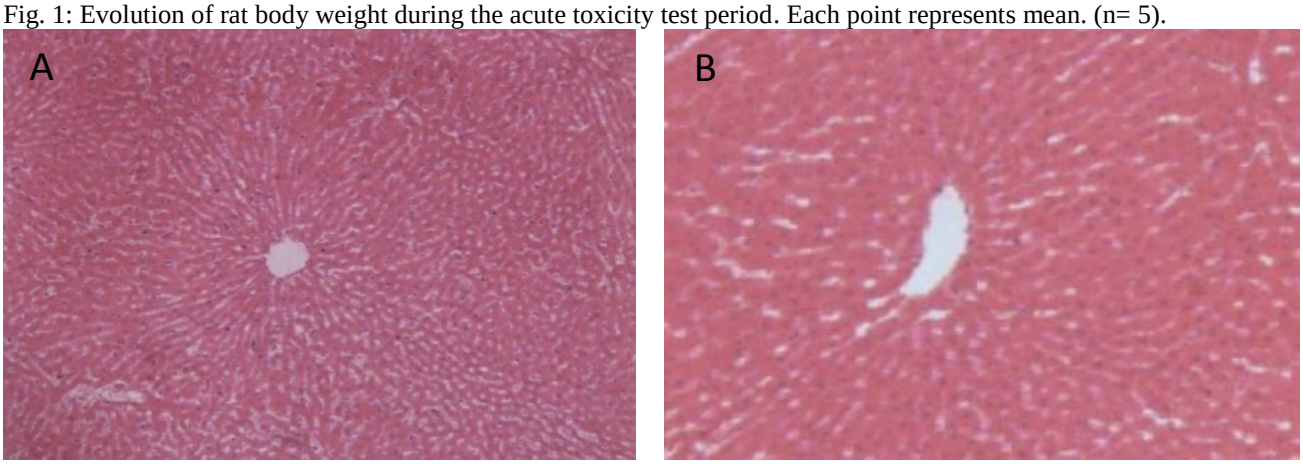

Figure 2: Histopathology of liver from control (A) and treated rats (B) showing hepatic lobules
A: Hepatocytes are disposed radially around a centro-lobular vein (HE x 10); B: Liver of a rat treated with *Gmelina arborea* extract at 2000 mg/kg (HE x 10), global architecture of the liver is conserved

free access to tap water and food. They were separated by gender and housed five per cage.

The plant material consisted in leaves of *Gmelina arborea* Roxb (Verbenaceae) collected in July 2013 at Zè (Southern Benin). The leaves were identified and authenticated at the National Herbarium of Benin (N° AA 6337). The leaves were dried under the lee of sun between 20-25°C during ten days and ground into powder. A decoction was made from 200 g of the powder with distilled water. The decoction was filtered on Whattman N°1 paper and evaporated with a rotavapor type RE-300 at 80°C. The dried extract obtained was stored at 4°C.

Acute toxicity test

The acute toxicity test was carried out based on OECD 423 directive adopted in 2001[12]. Rats were preliminarily acclimatized during five days in the laboratory and were starved 12 hours before the experimentation. Two groups of 6 rats (3 males and 3 females) were force-fed with a single dose of 2000 mg/kg of the aqueous extract. The control group was treated with distilled water. The animals were observed quietly and continuously for eight hours just after the administration and on daily basis up to 14 days. The monitoring was based on general behaviour changes, body weight evolution, food and water consumption, mortality and any toxicity signs. Histological examinations were carried out on liver and kidney at the end of the experimentation.

Sub-chronic toxicity test

It consists in a repetitive administration of the *Gmelina arborea* leaves aqueous extract to three groups of 10 rats (5 males and 5 females). The treatment consisted of a daily gavage of 500 mg/kg, 125 mg/kg and 31.25 mg/kg respectively during 28 days. The control lot received distilled water. Individually, animals were clinically monitored quietly before the first exposure. Observations were focused on changes in the skin and fur, eyes, mucous, respiratory system, autonomic and central nervous systems as well as somatomotor activity and behavioural patterns. During the fourth week of exposition, rat observation was more particularly focused on their sensorial and auditive stimuli reactions [13]. Body weight as well as food consumption were recorded every week[14, 15]. At the end, rats were starved overnight (12 hours) but with free access to tap water. They were then anesthetized with thiopental

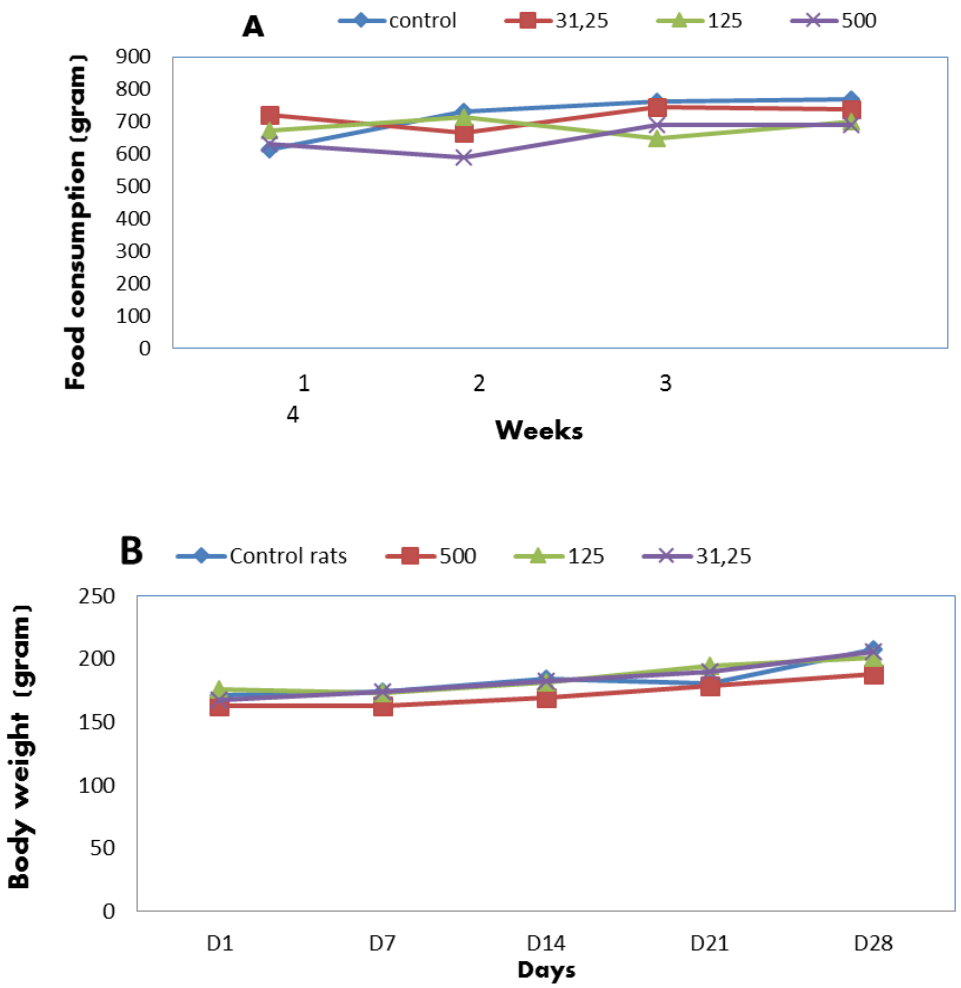

Figure 3: Body weight and food consumption of rats during subchronic toxicity test.
A: Food consumption of control and treated rats respectively at 31.25; 125 and 500 mg/kg body weight; B: Body weight of control and treated rats respectively at 31.25; 125 and 500 mg/kg of body weight

by intraperitonial injection and blood samples were collected for biochemical and haematological determinations. Rats were euthanized by lethal dose of thiopental then liver and kidney of three rats per group were removed for histological examinations. Biochemical parameters including serum concentrations of glucose, total cholesterol, urea, creatinine, total proteins, potassium, chloride, sodium, alanine aminotransferase, and aspartate aminotransferase were performed using an automatic analyzer (MTN-658F) with specific kits. For haematological analysis, haematocrit (HCT), haemoglobin (HB), Mean corpuscular haemoglobin concentration (MCHC), red blood count (RBC), leukocyte count, mean corpuscular volume differential (MCV), mean corpuscular haemoglobin (MCH), platelet count (PLT), white blood count (WBC) were performed on blood using Sysmex K x 21 automated haematology analyzer.

Statistical analysis

The results shown are expressed as means ± standard error of mean (S.E.M.). Body weights and food consumption values were compared by student T test while biological parameters data were analyzed by one way ANOVA followed by LSD (Least Significant Difference) post hoc with SPSS 19. Results were considered significant for a p-value less than 5% ($p < 0.05$).

RESULTS

Acute toxicity

No animal mortality was induced by a single dose of 2000 mg/kg of the *Gmelina arborea* leaves aqueous extract. However, it was recorded that animals scratched themselves excessively during ten minutes just after being fed. No other toxicity sign was observed. The extract did not cause any negative effect on the rats body weight (Figure 1). Besides, neither the kidney nor the liver histological structures were affected (Figure 2).

Sub-chronic toxicity

Rats behaviour

Gmelina arborea aqueous extract, administered at 500 mg/kg, 125mg/kg and 31,25mg/kg to Wistar rats did not result in mortality. During the study, alteration of general aspect, diarrhoea, haematuria, autonomic or central systems movements were not observed. However the excessive skin scratching just after feeding occurred even

Table 1: Biochemical parameters of male rats during subchronic test

Parameters	Control Rats (n=5)	Treated rats at 31.25mg/kg; (n=5)	Treated rats at 125mg/kg (n=5)	Treated rats at 500mg/kg (n=4)
Glucose (g/L)	2.16±0.07	1.78±0.28*	1.23±0,38*	0.91±0.47*
Urea (g/L)	0.5±0.07	0.42±0.08	0.41±0.08	0.41 ±0.11
Creatinine (mg/L)	11.5±0,70	3.75±0.50*	9.8±0.57	10.25±1.70
Total cholesterol (g/L)	0.92±0.04	0.78±0.12	0.95±0.12	1.00±0.08
	157.5±3.53	134±6.57*	236.25±3.69*	360.75±32.94
ASAT (UI/L)				
ALAT (UI/L)	89.5±13.53	148±27.80	168±12.36*	266.75±15.65
Sodium (mEq/L)	140±4.46	140±6	140.5±4.93	136±4.20
Potassium (mEq /L)	5.2±0.03	6.2±0. 09*	4.52±2.08	7.90±3.01
Chloride (mEq /L)	81.5±14.94	73.5±13.07	81.0±13.42	90 ± 11.10
Total Proteins (g/L)	63.5±6.35	58±13.72	51.3±17.4	65±7.67

Values represent Means ± SEM. ASAT: Aspartate Amino-Transferase, ALAT: Alanine Amino Transferase. * $p<0.05$: Significantly different from the control group.

Table 2: Biochemical parameters of female rats during subchronic test.

Parameters	Control Rats (n=5)	Treated rats at 31,25 mg/kg (n=4)	Treated rats at 125 mg/kg (n=5)	Treated rats at 500 mg/kg (n=5)
Glucose (g/L)	2.53 ±0.32	2.33±0.34	1.59±0.40*	1.56±0.44*
Urea (g/L)	0.33±0.04	0.36±0.05	0.42±0.09	0.51±0.09*
Creatinine (mg/L)	15.5±2.12	12.75±4.50	15.75±0.97	16.43±2.65
Total cholesterol (g/L)	1.47±0.64	1.45±0.15	1.54±0.15	1.53±0.04
ASAT (UI/L)	141.5±52.83	134.5±46.6	158±22.73	170±41.07
ALAT (UI/L)	67±7.07	55.25±10.8	88±8*	78.66±8.73
Sodium (mEq/L)	142.5±0.70	141.25±2.7	138.75±0.95*	141.66±2.51
Potassium (mEq/L)	6.1 ± 1.32	8.2±0.51*	7.4±1.17	6.7±1.81
Chloride (mEq/L)	99.5±0.70	98±2.44	100.5±10	101±20
Total proteins (g/L)	72.5±0.70	78±6.87	74.75±7.54	74±2

Values represent Means ± SEM. ASAT: Aspartate Amino-Transferase,
ALAT: Alanine Amino Transferase. * $p<0.05$: Significantly different from the control group.

at the lowest dose of 31, 25 mg/kg.

Rat food consumption and body weight

As shown in figure 3, administration of *Gmelina arborea* aqueous extract did not significantly affect food consumption and the body weight of rats. However, up to the end of the test, an increase in rat body weight was observed but there were no significant difference between treated rats and rats of the control group.

Biochemical and haematological parameters of rats.

Globally, administration of *Gmelina arborea* aqueous extract did not cause major changes in biological parameters values.

However, changes in glucose, transaminases, creatinine and urea levels have been induced by *Gmelina arborea* aqueous extract administration. As shown in tables 1 and 2, an increased level of transaminases (male and female), creatinine (male), and urea (female) was observed. A dose dependent increase in Cholesterol level, in both male and female rats, was also observed although the difference is not statistically significant. In contrast to these parameters, administration of *Gmelina arborea* induced a dose dependent decrease of blood glucose level.

As shown in Table 3 (male) and 4 (female), significant changes in rat haematological parameters were induced by *Gmelina arborea* administration. Thus, values of erythrocytes, haemoglobin, MGV and lymphocytes of males treated rats almost at 500 mg/kg are higher than those of the control group. In female rats, the main significant change observed was a dose dependent decrease of leucocyte count.

Histopathological examination

Histopathological examination of the liver (fig 6) and kidneys (fig 7) revealed a dose dependent toxicity of *Gmelina arborea* in treated rats. Indeed, histology of the treated rat liver showed in the centrolobular area, lipid inclusions in hepatocytes almost at 500 mg/kg. In kidneys of treated rats, histology revealed a progressive thickening of the glomerular interstitium.

DISCUSSION

Gmelina arborea is reported by many authors to possess several pharmacological effects in traditional medicine[1,2]. As only a few studies have been dedicated to its pharmaco-toxicological properties, our work is the first one to investigate the acute and subchronic toxicity of *Gmelina* arborea leaves aqueous extract.

In our study, no clinical or histopathological sign of toxicity was induced by a single dose of 2000 mg/kg of *Gmelina arborea* suggesting that the LD_{50} of *Gmelina arborea* leaves in Wistar rats is higher than 2000 mg/kg. The hyper-reactivity observed just after feeding could be explained by a normal physiological reaction of rats. These results are in agreement with those obtained by *Kulkarni et al*, 2010 in India conducted on toxicological studies of the

Table 3: Haematological parameters of male rats during subchronic test.

Parameters	Control Rats (n=5)	Treated rats at 31,25 (n=5)	Treated rats at 125 (n=5)	Treated rats at 500 (n=4)
ed blood cell (T/L)	7.38±0.42	6.93±1.85	7.25±1.51	8.44±0.70*
Leucocytes (G/L)	6.75±1.06	6.6±1.48	7.25±2.62	7.17±1.24
Platelets (10^3/µL)	592±1	592±11	477±35	669±69.74
Haemoglobin (g/dl)	13.05±0.77	11.3±3.91	13.3±2.59	16±1.27*
Haematocrit (%)	47.5±2.94	29.25±9.85	38.77±7.57	47.15±8.02
MGV (fL)	64±2.82	59.15±6.72	53.62±0.95*	55.82±2.42*
MCH (Pg)	17.50±0.7	18.25±1.10	18.90±0.49	18.87±0.20
MCHC (%)	27.50±0.7	31.20±3.7	34.25±0.45*	33.97±1.39*
Neutrophils (%)	31.50±9.46	30.50±10.6	34.25±5.85	32.00±7.68
Eosinophils (%)	0.20±0,4	0	0	0
Lymphocytes (%)	65.60± 10.31	69.00±7.61	64.75±10.24	6 7±7.09
Monocytes (%)	2.5 ±2.12	0.25±0.5	0.45±0.96	1.05±1.26

Values represent Means ± SEM. MGV: Mean globular volume, MCH: Mean Concentration Haemoglobin, MCHC: Mean Corpuscular haemoglobin Concentration, *p<0.05: Significantly different from the control group.

stem bark of *Gmelina arborea* in rodents[11]. It is known that there is no real correlation between acute dose of LD_{50} and prediction of adverse effects of a dose chronically administrated. In addition, the LD_{50} in animals does not predict the lethal dose of a drug in humans or the symptomatology of acute poisoning after overdose[16]. Nevertheless, the acute dose study provides a guideline for selecting doses for the chronic (or sub-chronic) lower dose study, which may be more clinically relevant.

During the sub-chronic toxicity study, rats were submitted on doses of 31, 25 mg/kg, 125 mg/kg and 500 mg/kg of the aqueous extract of *Gmelina arborea*. 28-days administration of *Gmelina arborea* leaves aqueous extract did not produce any death, abnormality or clinical signs of toxicity, any changes in animal behaviour, food consumption and body weight evolution. This suggests that the aqueous extract of the plant does not affect the general aspect of rats at those doses during that period. Likewise, general biological parameters studied did not show very marked differences in relation to the control group. Nevertheless, a significant difference was observed between treated rats and rats of the control group for glycaemia, transaminases. Glycaemia of the rats were abnormally high although they have been starved overnight. This elevation of glycaemia could be due to intrinsic properties of the rats. The dose dependent decrease of blood glucose observed suggests a hypoglycaemic activity of *Gmelina arborea* aqueous extract. Indeed, it has been reported that *Gmelina arborea* was used for the treatment of diabetes mellitus [2,17]. In addition to changes in blood glucose, a dose dependent increase in blood transaminases was also induced by the aqueous extract administration. These changes, almost at 500 mg/kg, could be associated with liver lesion or dysfunction. These results contrast with those of *Vijay et al*, in 2011 who demonstrated that the ethanol extract of *Gmelina arborea* decreases transaminases of doxorubicin treated rats[10]. These differences could be explained by the type of the organic extract used (alcohol versus water), the duration of extract administration and the dose used. The histological examination of hepatic tissue shows the presence of lipid vacuoles in the cytoplasm of hepatic cells. This could be a consequence of lipids peroxidation and suggests that the extract would contain oxygen reactive species. Nevertheless, many studies have reported antioxidant properties of *Gmelina arborea* [9,10,17,18]. As for

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Table 4: Haematological parameters of female rats during subchronic test.

Parameters	Control rats (n=5)	Treated rats at 31,25 (n=4)	Treated rats at 125 (n=5)	Treated rats at 500 (n=5)
Red blood cell (T/L)	8.02±1.62	7.83±0.55	6,94±1,01	7,31±0,40
Leucocytes (G/L)	13.4±1.18	7,3±4,07	5,40±1,8*	5,75±2,8*
Platelets (10^3/µL)	762±32	846±12	745±34	689±98
Haemoglobin (g/dl)	12.1±2.12	12.82±0.95	10.97±1.54	12.31±0.97
Haematocrit (%)	53±11,31	46.5±2.64	40.29±8.09	47±2
MGV (fL)	65.5±0.70	65.5±2.08	57.56±5.567	64.66±1.52
MHC (Pg)	16.5±0.7	17±0.81	15.6±1.4	17±1
MCHC (%)	25.5±2.1	27.75±0.9*	24.5±2	26.93±1.1
Neutrophils (%)	30±2.6	29±9.4	28.1±1.7	28±4
Eosinophils (%)	1.5±2.1	0.5±1.10	1.8±1.4	1,1±1.17
Lymphocytes (%)	65.5±6.3	69±13.3	69.1±12.4	66.3±2.3
Monocytes (%)	3±1.1	1.5±0.5	3 ±2.3	2.66±1,5

Values represent Means ± SEM. MGV: Mean globular volume, MCH: Mean Concentration Haemoglobin, MCHC: Mean Corpuscular Haemoglobin Concentration. * p<0.05: Significantly different from the control group.

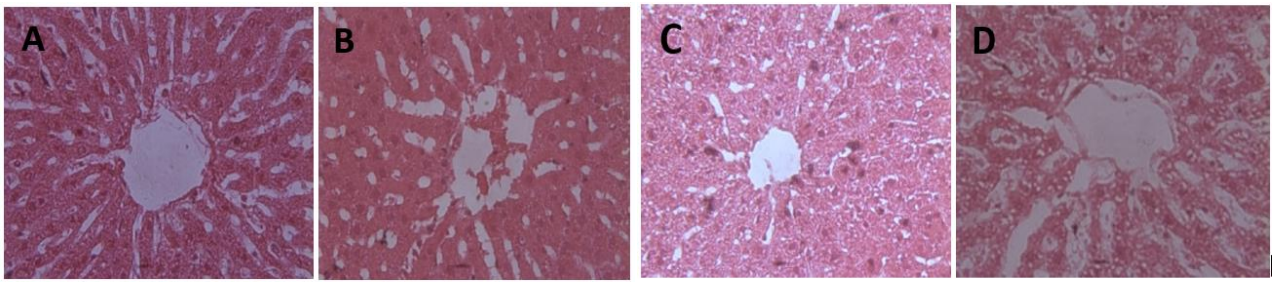

Figure 4 : (HEX40) liver of a control rat (A), treated rats with the aqueous extract of *Gmelina arborea* at 31,25 mg/kg (B), 125 mg/kg (C) and 500 mg/kg (D).)

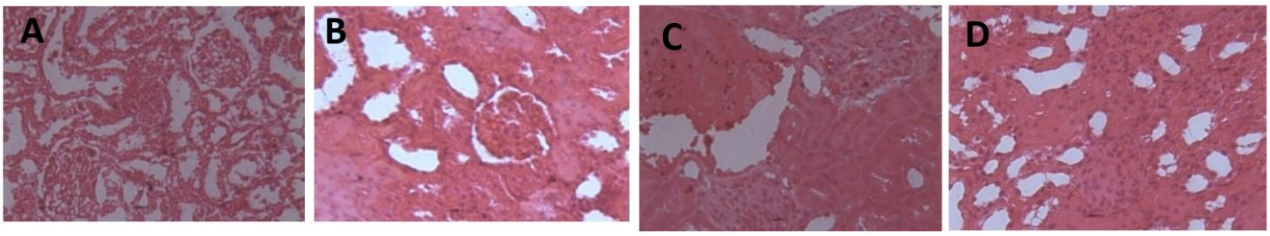

Figure 5 : (HE x 40) Kidney of a control rat (A) and rats treated with the aqueous extract of *Gmelina arborea* at 31,25 mg/kg (B), 125 mg/kg (C) and 500 mg/kg (D)

kidneys, a dose-dependent thickening of the glomerular interstitium has been found at histological examination. This could be a consequence of the inability of this organ to assure properly their function of filtration resulting in an accumulation of substances at basal membrane level. But as blood creatinine values of treated rats are within normal range, the residual function seems sufficient to maintain a normal glomerular filtration rate. Administration of *Gmelina arborea* aqueous extract for more than 28 days could therefore lead to marked kidney dysfunction. The haematological values such as erythrocytes, haemoglobin, lymphocytes, and MGV of male are higher than those of control rats. In female rats, only leucocytes decreased significantly and MCHC in both sexes. But those variations are not considered as pathologically significant. It could be thought that those variations bring a beneficial effect for blood cells and justify why the plant is used for its antifungal, antibacterial and antioxidant properties [18,19].

CONCLUSION

This study shows that single dose of *Gmelina arborea* aqueous extract is without toxicity in rat but 28-days administration of the extract affects blood biochemical and haematological parameters and induces kidney and liver structure disturbance. Long term administration of could be thus cause of toxicity in animals and humans. Further studies are necessary to investigate the mechanism of the observed disorders and to determine conditions of safe use of *Gmelina arborea*

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