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Original Research

Acute and sub-chronic oral toxicity assessment of the aqueous extract leaves of *Ficus glumosa* Del. (Moraceae) in rodents

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ABSTRACT

Background: *Ficus glumosa* Del (Moraceae), a plant used in traditional medicine in Cameroon, Senegal, and East Africa for the treatment of edema, hemorrhoid, cardiovascular diseases especially hypertension. **Aim:** The present study evaluated the potential toxicity of the aqueous extract of the leaves of *F.glumosa* in acute and sub-chronic administration in rodents. **Methods:** Acute toxicity was evaluated on 3 months old mice of both sexes and weighing 20-30 g. A single dose (2-12 g/kg) of *F. glumosa* was administered orally to mice. Animal behavior, adverse effects, and mortality were determined for 14 days. In sub-chronic toxicity studied in both sexes of 9 weeks old rats and weighing 100-120 g at the start of the experiment, animals were treated orally with a daily dose of 300, 600 and 1200 mg/kg of the aqueous extract of the leaves of *F. glumosa* for 6 weeks. The body weight change, food, and water consumption, were determined throughout the experimental period, while the relative organ weights, the hematological and biochemical parameters of blood and urine, as well as the histology of tissues kidney and liver, were recorded at the end of the experiment. **Results:** For acute treatment, no dose used induced critical behavioral changes or death. In sub-chronic treatment, daily oral administration of *F. glumosa* at the dose of 300, 600, and 1200 mg/kg resulted in a significant increase in body weight relative to food and water consumption in the last week of treatment. The relative organ weights were not affected by treatment. No hematological changes were observed except the significant increase in platelets. Aspartate aminotransferase, alanine transaminase, alkaline phosphatase, total protein, increased while the total cholesterol, triacylglycerol, conjugated bilirubin, and total bilirubin significantly decreased. Index of renal function showed a decrease of creatinine, urea, uric acid and Na^+, Cl^- and Ca^{2+}, and inorganic phosphate. The histology of liver and kidney showed no significant alteration of tissue. **Conclusion:** These observations support the traditional use of *F. glumosa* in the treatment of hypertension. These results have shown that *F. glumosa* has a safety margin for therapeutic use.

KEY WORDS: Acute toxicity, *Ficus glumosa,* histopathology, leaf aqueous extract, sub-chronic toxicity

INTRODUCTION

Efforts of scientists and traditional therapists are growing in the direction of improvement and enhancement of the use of medicinal plants, to elucidate the pharmacological properties of these plants and possibly to extract active ingredients. Even when effective, preparations have to undergo toxicological tests. So far, population show no concern for the simple reason that they believe the preparation is free of toxicity. Many medicinal plants showed relative toxicity or were not toxic when administered in acute or subacute treatment in experimental animals. For instance *Ficus exasperata* (Moraceae) used in the treatment of asthma, bronchitis, and tuberculosis [1], *Celtis durandii* (Ulmaceae) used as effective antihypertensive plant [2,3], Ojeok-san used in the treatment of gastrointestinal diseases and fatigue [4], or *Erythrina senegalensis* (Fabaceae) used in the treatment of liver diseases, jaundice [5,6], and in the treatment of gastrointestinal diseases, malaria, infections were found to be moderately or non-toxic [7].

The toxicological evaluation of any medicinal plant preparation is important to ensure the safety of these phyto-medicines. *Ficus glumosa* Del (Moraceae) is a plant used in pharmacopeia of Cameroon, Senegal, and East Africa for the treatment of edema, hemorrhoid, cardiovascular diseases, especially hypertension. Originally from Ethiopia, it grows in many parts of tropical Africa and is typically found in dry country in the meadow and wooded bush [8,9]. *F. glumosa* grows on rocky outcrops, where it splits rocks; it could also be found along dried river beds. It reaches its maximum size (10 m) in the valleys. This species can also be found in the fringe forest, in the savannah, especially in the swamp forest in coastal areas. A decoction of the bark is used as a stimulant for milk production, for both women and animals [10,11]. The leaves are used in East Africa, Cameroon and Senegal for the treatment of skin diseases and diabetes [12]. Recently, acute toxicity of methanol extract of leaves of *F. glumosa* were carried out [9]. Phytochemical analysis of *F. glumosa* phytochemicals revealed the presence of flavonoids, saponins, carbohydrate, tannins, and triterpenes [9]. Effects of ethanol leaf extract of *F. glumosa* on fasting blood glucose and serum lipid profile in diabetic rats were also carried out [8]. The purpose of this study was to assess the acute and subacute toxicity of *F. glumosa* aqueous extract in rodents.

MATERIALS AND METHODS

Plant Material and Preparation of the Extract

The leaves of *F. glumosa* were harvested from Ngaoundéré, Adamawa region of Cameroon. Then, we proceeded to the identification by comparing the harvested plant to specimen N^0 60695/HNC deposited at the National Herbarium of Cameroon.

One thousand grams of fresh leaves of *F. glumosa* was steeped in 1 L of distilled water for 12 h at room temperature. The macerate was filtered through Whatman filter paper No. 3, and the filtrate concentrated in a rotary evaporator at 40°C for 24 h. This process repeated several times and yielded 112 g of concentrated of crude extract in the form of an oily paste. The extract was stored at −20°C.

Animals

Acute toxicity was evaluated on 3 months old mice (*Mus musculus*) of both sexes and weighing 20-30 g. Wistar rats of both sexes, of 9 weeks old and weighing 100-120 g at the start of the experiment were used to evaluate the subacute toxicity. Strains of animals were from Center Pasteur in Yaoundé. They were reared in the Department of Biological Sciences, Faculty of Sciences (University of Ngaoundéré). The animals were housed under controlled temperature (24 ± 2°C) and relative humidity (45 ± 10%). Moreover, they had free access to food (pellets from LANAVET [Laboratory NVS]) and filtered 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.

Acute Toxicity

Mice were divided into 6 groups of 10 each. Animals in each group were housed separately in Plexiglass cages. Mice were acclimatized in the laboratory environment 7 days before the start of the experiment. The mice were fasted for 12 h prior to the experiment with free access to water. Mice were orally administered; a single dose of *F. glumosa* aqueous extract (2-12 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 2 h after administration of the extract and were supplied with food. Mortality was recorded after 24 h. Food and water intake and body weight of surviving animals were evaluated after 7 days. Dead animals were autopsied for macroscopic observation of internal organs [3].

Subacute Toxicity

Rats were divided into 4 groups of 10 each (5 males and 5 females). The control group was treated with distilled water, and the other 3 groups were administered the plant extract at the dose of 300, 600 and 1200 mg/kg. The doses were selected from the literature as appropriate doses to evaluate the hepato-protective activity [13,6]. The extract was administered by oral route once daily for 6 weeks. 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°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 rpm for 20 min. The collected plasma was stored at −20°C for biochemical analyzes. Liver, kidney, and

heart were removed, cleared of fat material, weighed and stored at −20°C for biochemical analyzes and a portion preserved in formalin for histological analysis.

Analysis

Urinary and plasma electrolyte concentrations were determined using a flame photometer (JENWAY PFP 7, Japan) according to standard methods described before [14]. 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, Germany). Hematological and biochemical analyzes were performed by means of an automatic device type Toshiba 200 FR NEO (TOSHIBA Co., Japan). For hematological analysis, parameters like red blood cell, mean corpuscular volume, etc., were measured as described by Lahlou *et al*. [15]. Alanine transaminase (ALT), aspartate transaminase and alkaline phosphatase (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 hematoxylin and eosin staining.

Statistical Analyses

The results expressed are the mean ± standard error of the mean. Comparison of means was made using the Student's *t*-test and one-way ANOVA of Origin Graph software (Microcal Origin 6.0, Microcal, MA USA) software version 6.0. The difference was considered significant when $P < 0.05$.

RESULTS

Acute Toxicity Study

The extract at a dose 8000 mg/kg in single administration caused no death in mice during the 14 days of observation. But there were, however, a slight decrease in locomotion, aggression, sensitivity to noise and touch and a slight decrease in respiratory movement 2 h after administration of the extract of *F. glumosa*. The examination of organs did not show any signs of major pathology. The median lethal dose 50 (LD_{50}) of the *F. glumosa* aqueous extract should be above 12 g/kg. Generally, at this dose, the mice gain all their capacities within 48 h after administration of the extract. Animals that received the extract at this dose showed diarrhea. No animal had a convulsion after administration of the extract. Necropsy of sacrificed animals showed a digestive tract brownish aspect, probably due to the color of the extract. The extract had no negative impact on food and water consumption, mice showed a body weight gain [Table 1].

Subacute Toxicity

A single administration of *F. glumosa* aqueous extract (300, 600, and 1200 mg/kg) was able to provoke 24 h later a significant increase ($P < 0.05$) and dose-dependent volume of urinary excretion. Urine volume increased from 22.38 ± 3.13 ml/100 g/24 h in controls (distilled water) to 38.53 ± 4.17 ml/100 g/24 h at the dose of 300 mg/kg that represents an increase of 72.16%. With the dose of 600 mg/kg, urine volume increased to 46.81 ± 2.14 ml/kg/24 h representing an increase of 109.15%. For the highest dose (1200 mg/kg), the volume of urinary excretion went from 22.38 ± 3.13 in controls ml/100 g/24 h to 59.80 ± 2.65 to ml/100 g/24 h in the treated group [Figure 1], which represents an increase of 167.20%. The pH values of urine of animals treated with the extract of *F. glumosa* at the dose 300 mg/kg showed no significant change. The dose of 1200 mg/kg showed a nonsignificant ($P > 0.05$) pH values (7.12 ± 0.17). The pH value of the urine of animals treated with the extract at dose of 600 mg/kg was reduced (6.35 ± 0.67) than that of the control group [Figure 1].

Effect of F. glumosa on the relative organ weights

The aqueous extract of *F. glumosa* had no significant effect ($P < 0.05$) on the heart. However, the dose of 1200 mg/kg, increased significantly ($P < 0.05$) the relative weight of liver, kidney, testis, and epididymis in males whereas, in females, the weight of kidney, uterine, and ovarian was significantly increased 6 weeks after administration of a daily dose of the *F. glumosa* extract [Table 2].

Effect of F. glumosa on body weight change

The body weight of rats was not affected by the administration of a daily dose of the aqueous extract of *F. glumosa* for

Table 1: Effects of the aqueous extract of *F. glumosa* on animals behavior

Dose (g/kg)	% Mortality	Latency	Symptoms	% Weight change (g)	% Food consumption (g)	% Water consumption (mL)
0	0/10	-	None	16.88±12	14.51±11	27.00±03
2	0/10	-	None	24.67±11*	29.61±06*	12.50±02
4	0/10	-	None	28.98±07*	30.25±10*	21.59±06
6	0/10	-	None	20.44±09*	25.36±11*	25.45±10
8	0/10	>2h<4h	Light reduction in locomotion, aggressiveness, noise and touched sensitivity and respiratory movement	21.84±12*	36.29±06*	28.94±08
10	0/10	>2h<8h	Light reduction in locomotion, aggressiveness, noise and touched sensitivity and respiratory movement	16.55±13	17.50±12*	27.00±07
12	0/10	>2h<3h	Reduction in locomotion, aggressiveness, noise and touched sensitivity and respiratory movement	14.25±14	15.88±13	17.23±11

Values are means±SEM, $n=10$, $*P<0.05$, a significant difference compared to the control. SEM: standard error of mean, *F. glumosa: Ficus glumosa*

Table 2: Effects of the aqueous extract of *F. glumosa* on the relative organ weights

Organs	Male treatment (mg/kg)				Females treatment (mg/kg)			
	Control	300	600	1200	Control	300	600	1200
Liver	3.38±0.02	3.53±0.03	3.68±0.12	3.76±0.22*	3.12±0.02	3.15±0.01	3.13±0.02	3.24±0.11
Kidneys	0.71±0.04	0.72±0.02	0.73±0.02	0.75±0.04*	0.69±0.01	0.69±0.02	0.67±0.04	0.72±0.04*
Heart	0.30±0.01	0.31±0.02	0.31±0.02	0.32±0.04	0.34±0.02	0.35±0.03	0.35±0.03	0.36±0.04
Lung	0.72±0.01	0.73±0.04	0.75±0.02	0.74±0.03	0.70±0.03	0.71±0.04	0.75±0.02	0.73±0.03
Spleen	0.31±0.03	0.31±0.02	0.35±0.01	0.31±0.03	0.29±0.02	0.30±0.01	0.29±0.01	0.31±0.02
Testis	0.62±0.03	0.62±0.02	0.64±0.01	0.66±0.03*				
Epididymis	0.25±0.01	0.27±0.02	0.29±0.01	0.30±0.02*				
Uterus					0.27±0.03	0.31±0.02	0.35±0.01	0.38±0.03*
Ovary					0.031±0.003	0.032±0.002	0.035±0.001	0.037±0.003*

Values are means±SEM, n=5, *P<0.05, a significant difference compared to the control. SEM: Standard error of mean, *F. glumosa: Ficus glumosa*

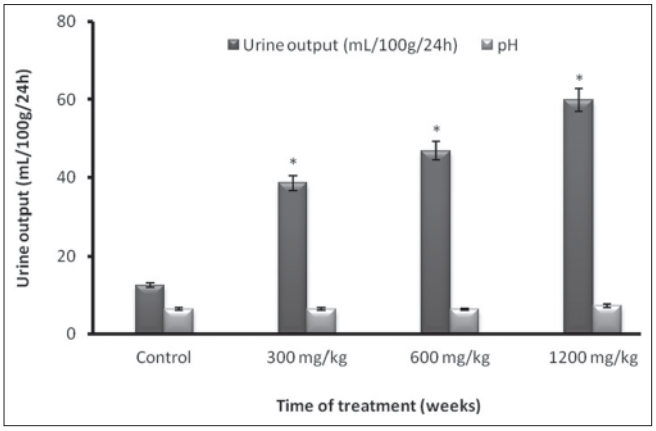

Figure 1: Effects of the aqueous extract of *Ficus glumosa* on the urinary excretion and pH for 100 g of body weight. Values are means ± standard error of mean, n = 5, *P < 0.05, significant difference compared to the control

6 weeks. At the doses of 300, 600, and 1200 mg/kg, the body weight of male rats varied, respectively, from 94.69 ± 0.85%, 87.87 ± 0.78%, and 79.12 ± 1.23% in week 6 of treatment, whereas in females the body weight change was from 83.12 ± 0.39%, 85.56 ± 0.58%, and 76.35 ± 1.28%, respectively, at the doses 300, 600 and 1200 mg/kg in week 6 of treatment. The body weight decreased in both male and female rats treated with the extract at the dose of 1200 mg/kg [Figure 2].

Effects of extract of F. glumosa on food and water intake

An increase of water consumption was observed in all groups. In animals treated with distilled water, the average water consumption increased by 83.12 ± 2.11% at week 6 of the experiment compared to week 1. In animals treated with the extract at dose of 300, 600, and 1200 mg/kg, consumption increased by 94.69 ± 2.68%, 89.87 ± 3.20%, and 74.12 ± 2.22% in males at week 6, respectively. The water consumption followed the same trend in females with increase of 90.69 ± 3.14%, 87.87 ± 3.11%, and 74.52 ± 4.18%, respectively, at doses of 300, 600, and 1200 mg/kg [Figure 3]. The oral administration of a daily dosage of the aqueous extract *F. glumosa* did not have effects in food consumption across treatments. However, there was an increase in food intake from week 1 to week 6 [Figure 4].

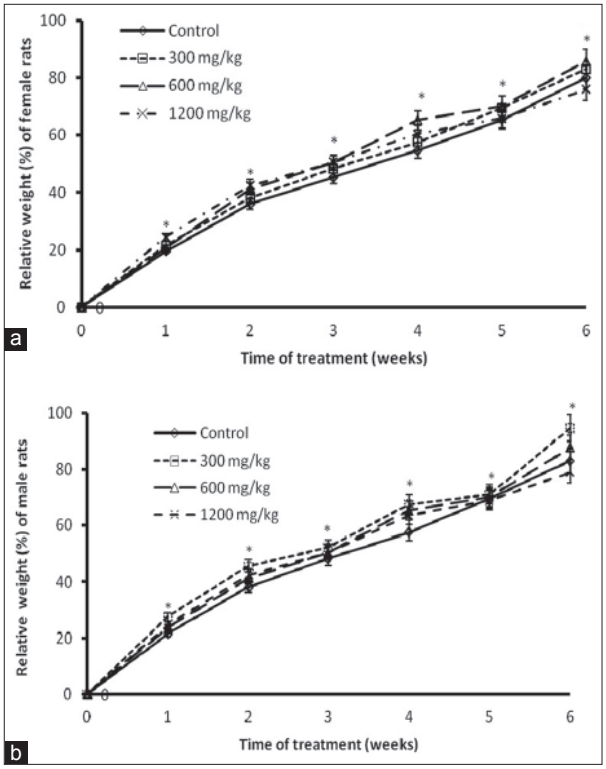

Figure 2: Effects of the aqueous extract of *Ficus glumosa* on body weight change in (a) females (b) males, 6 weeks after administration of a daily dose of extract. Values are means ± standard error of mean, n = 5, *P < 0.05, significant difference compared to the control

Effect of F. glumosa on hematological and biochemical parameters

Daily administration of *F. glumosa* aqueous extract for 6 weeks did not cause significant change in hematological parameters except the platelets which had been increased significantly by 67.79%, 65.97%, and 70.17%, respectively, at the doses of 300, 600, and 1200 mg/kg in males and 120.67%, 122.54%, and 126.85%, respectively, at doses 300 600 and 1200 mg/kg in females (P < 0.05). There were also a nonsignificant decrease in the percentage of basophiles, hematocrit, and a non-significant increase in the percentage of eosinophiles and hemoglobin in males as in females [Table 3].

The effect of the extract was evaluated in the index of liver function. It is clear that cholesterol decreased by 5.15%;

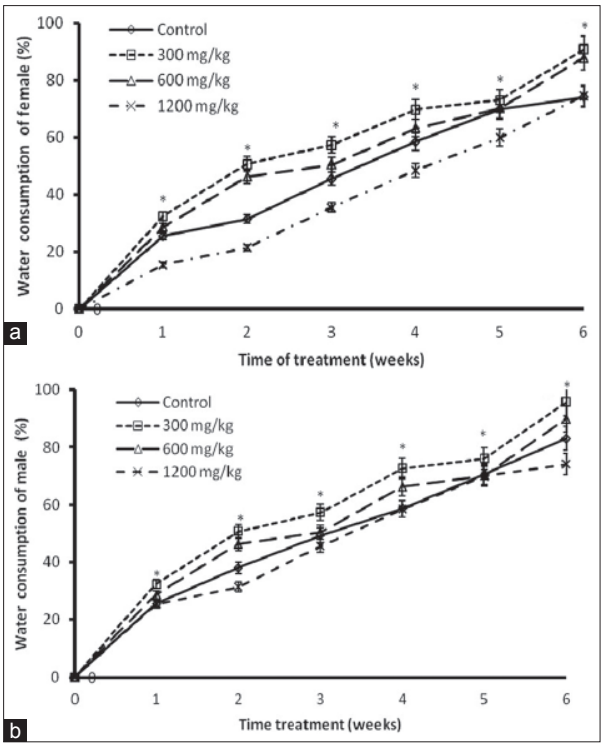

Figure 3: Effects of the aqueous extract of *Ficus glumosa* on water consumption in a) females, b) males, 6 weeks after administration of a daily dose of extract. Values are means ± standard error of mean, $n = 5$, $^*P < 0.05$, significant difference compared to the control

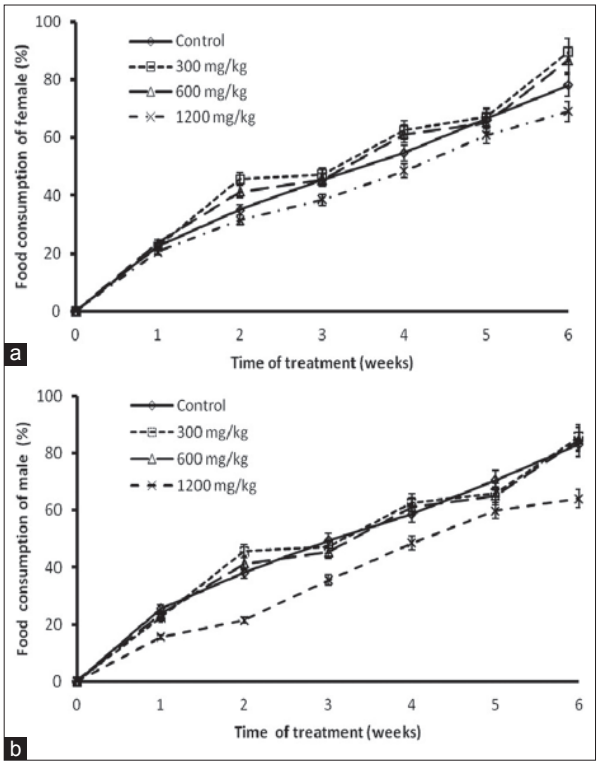

Figure 4: Effects of the aqueous extract of *Ficus glumosa* on food consumption in a) females, b) males, 6 weeks after administration of a daily dose of extract. Values are means ± standard error of mean, $n = 5$, $^*P < 0.05$, significant difference compared to the control

Table 3: Effects of the aqueous extract of *F. glumosa* on hematological parameters

Organs	Normal range	Male treatment				Females treatment			
		Control	300	600	1200	Control	300	600	1200
RBC ($\times 10^6/\mu L$)	5-10	9.12±0.12	9.13±0.23	9.11±0.12	8.76±0.22	8.12±0.22	8.15±0.21	8.43±0.12	8.24±0.11
WBC ($\times 10^3/\mu L$)	1-5	11.71±0.04	12.72±0.02	10.73±0.02	11.25±0.04	8.45±0.1	8.34±0.2	8.67±0.4	8.11±0.4
Platelets ($\times 10^3/\mu L$)	600-1100	456.30±56.61	765.61±86.52*	757.31±45.32*	776.52±34.44*	357.84±12.72	789.65±43.33*	796.35±81.43*	811.76±34.34*
Hemoglobin (g/dL)	11-19	11.22±0.41	11.73±0.54	11.79±0.62	12.74±0.73	11.70±0.53	11.71±0.44	12.75±0.72	11.73±0.63
Hematocrit (%)	35-57	38.31±2.13	41.31±2.32	39.35±2.11	42.31±2.13	36.29±2.08	41.30±2.11	43.29±2.07	41.31±2.22
RDW (%)	12-18	15.42±0.43	15.53±0.54	15.72±0.42	14.84±0.63	15.60±0.43	15.75±0.43	15.65±0.52	14.83±0.60
MCV (fL)	46-65	51.62±0.53	53.67±0.42	54.55±0.44	56.66±0.76	52.45±0.33	51.65±0.22	54.74±0.51	53.56±0.63
MCH (pg)	18-23	17.25±0.51	17.27±0.32	17.49±0.17	17.30±0.02	18.12±0.43	18.34±0.32	18.54±0.41	18.47±0.33
MCHC (g/dL)	31-40	32.12±0.3	32.22±0.2	32.14±0.1	32.26±0.3	33.11±0.3	33.12±0.2	33.24±0.1	33.16±0.3
Neutrophil (%)	2-20	18.62±2.13	19.56±4.22	20.68±3.44	18.56±3.57	19.27±2.33	20.36±3.52	20.85±3.31	19.38±4.43
Basophil (%)	0-7	1.62±0.13	0.92±0.12	0.94±0.11	0.96±0.13	0.83±0.13	0.7±0.12	0.6±0.11	0.7±0.13
Eosinophil (%)	0-1	1.62±0.23	2.22±0.12	2.34±0.24	1.69±0.03	1.60±0.21	2.02±0.32	3.14±0.21	1.78±0.23
Lymphocyte (%)	65-94	67.42±2.23	68.65±1.33	67.69±2.45	69.68±2.43	68.31±2.23	71.42±0.02	72.64±2.43	67.46±2.53
Monocyte (%)	0-6	4.82±0.63	5.61±0.22	6.54±0.43	4.36±0.63	4.77±0.33	6.62±0.32	6.14±0.41	5.16±0.46

Values are means±SEM, $n=5$, $^*P<0.05$, a significant difference compared to the control. SEM: Standard error of mean, *F. glumosa: Ficus glumosa*

10.16%; and 22.41%, respectively, at the doses of 300, 600, and 1200 mg/kg for male and 5.77%, 12.57%, and 21.14%, respectively, at the same doses in females. There was also a decrease in low-density lipoprotein and increase high-density lipoprotein in males and females. The extract did not cause variation in levels of blood glucose and albumin [Table 4].

The index of kidney function was also determined through the blood tests. It appeared from the analyzes that blood levels of creatinine, urea, uric acid, Cl^-, Na^+, K^+, inorganic phosphate, and Ca^{2+} significantly decreased when compared to the control ($P < 0.05$). Only the concentration of Mg^{2+} was significantly higher than that of the control ($P < 0.05$) [Table 5].

Histopathology

The examination of the histopathological cuts of liver, heart, and kidneys of animals treated with aqueous extract of the leaves of *F. glumosa* showed no abnormality.

DISCUSSION

The use of pharmacological properties of this plant in traditional medicine makes this toxicity studies fundamental. Oral administration of aqueous extract of *F. glumosa* in mice did not cause alteration in behavioral responses. No death occurred in any group. These results showed that a single dose of *F. glumosa* had no acute toxic effects, indicating that the medium LD_{50} is higher than 12 g/kg for mice. Therefore, oral administration of *F. glumosa* aqueous leaves extract is safe in mice. However, the aqueous extract of *F. glumosa* in the acute treatment caused at the dose 12 g/kg, depression resulting in a decrease in locomotion, sensitivity to noise and touch and movement and breathing. Acute diarrhea, which preceded the administration of the extract, could be attributed to a volume effect of the aqueous extract of the leaves of *F. glumosa* on intestines [9,16].

No deaths or no clinical signs of toxicity were recorded after daily administration of *F. glumosa* leaf extract for 6 weeks. The extract of *F. glumosa* did not have a significant effect on the heart of rats. However, the dose of 1200 mg/kg increased the relative weight of liver, kidney, testis, and epididymis in males significantly ($P < 0.05$). Whereas, in females, kidney, uterine, and ovarian weights were significantly increased 6 weeks after the treatment. This increase may be attributed to an adaptive response (inflammation or hyperactivity) to the accumulation of the extract or its metabolites within their body. Such results have been reported by Jimoh *et al.* [17], who found an increase in relative kidney weight and liver following subacute administration extract *Arctotis*

Table 4: Effects of the aqueous extract of *F. glumosa* on index of liver function

Organs	Normal range	Male treatment				Females treatment			
		Control	300	600	1200	Control	300	600	1200
Glucose (mg/dL)	70-119	87.53±2.97	89.23±2.11	88.83±2.01	89.35±2.34	90.12±3.39	91.58±2.3*	93.14±2.17*	93.56±3.21
ALT (IU/L)	10-50	39.15±3.9	41.25±2.5*	42.35±3.11*	43.02±3.15*	36.45±2.71	37.8±2.46*	39.49±2.94*	40.87±2.53*
AST (IU/L)	68-135	45.23±3.1	47.25±2.31*	48.35±2.49*	50.12±4.2*	39.27±2.64	40.1±2.65*	42.37±3.15*	43.52±2.17*
ALP (IU/L)	30-90	31.54±4.5	32.67±2.16*	34.26±4.56*	35.97±2.56*	26.31±2.15	27.34±3.14*	29.3±3.27*	30.97±4.26*
TP (g/dL)	4.8-9.2	6.49±0.26	6.98±0.22*	7.03±0.24*	7.12±0.28*	7.63±0.31	7.86±0.37*	8.07±0.36*	8.16±0.34*
Albumin	1.2-6	5.94±0.45	6.02±0.4	6.14±0.41	6.19±0.37	6.17±0.32	6.35±0.26	6.43±0.25	6.45±0.38
TB (mg/dL)	0-0.5	1.3±0.31	1.1±0.23	0.9±0.13*	0.7±0.15*	0.8±0.2	0.7±0.17	0.6±0.11*	0.4±0.09*
CB (mg/dL	0-1	1.15±0.21	1.79±0.11	1.9±0.22*	1.7±0.15*	1.8±0.31	1.7±0.14	1.6±0.21*	1.4±0.11*
TC (mg/dL)	38-96	61.35±3.14	58.34±2.16*	55.69±4.05*	50.12±3.62*	70.21±4.11	66.38±3.16*	62.37±3.6*	57.96±2.54*
TG (mg/dL)	60-140	87.35±3.54	90.01±3.14*	93.24±3.39*	94.21±3.26*	95.12±2.16	97.85±2.67*	99.6±2.64*	102.3±4.18*
LDL (mg/dL)	10-30	17.23±2.31	15.62±3.17*	14.11±3.29*	11.29±2.56*	22.03±3.14	19.36±2.54*	16.64±2.57*	13.89±3.27*
HDL (mg/dL)	15-35	21.35±1.37	22.01±2.04*	22.95±2.03*	23.15±3.01*	19.76±3.2	20.34±1.25*	20.96±2.17*	21.09±1.62*

Values are means±SEM, n=5, *P<0.05, a significant difference compared to the control. SEM: Standard error of the mean, *F. glumosa: Ficus glumosa*, ALT: Alanine transaminase, AST: Aspartate aminotransferase, ALP: Alkaline phosphatase, TP: Total protein, TB: Total bilirubin, CB: Conjugated bilirubin, TC: Total cholesterol, TG: Triacylglycerol, LDL: Low-density lipoprotein, HDL: High-density lipoprotein

Table 5: Effects of the aqueous extract of *F. glumosa* on index of kidney function

Organs	Male treatment				Females treatment			
	Control	300	600	1200	Control	300	600	1200
Creatinine (mg/L)	8.53±2.97	8.23±2.11*	7.83±3.01*	6.35±2.34*	8.12±2.39	8.58±2.3*	7.14±2.17*	6.56±3.21*
Urea (mg/L)	0.55±0.01	0.45±0.01*	0.35±0.02*	0.22±0.03*	0.45±0.01	0.41±0.02*	0.46±0.04*	0.38±0.03*
Uric acid (mg/L)	45.21±3.11	37.25±2.33*	28.35±2.42*	25.12±1.2*	42.20±2.64	40.1±2.65*	37.39±2.15*	26.32±1.16*
Cl^- (mEquiv./L)	83.53±4.31	72.65±2.26*	64.26±4.46*	57.93±2.56*	88.31±2.15	75.34±3.24*	69.3±3.22*	58.97±4.36*
Na^+ (mEquiv./L)	146.44±0.26	137.68±0.22*	141.03±0.24*	145.17±0.28*	142.62±0.71	145.56±0.57*	156.17±0.37*	162.36±0.64*
K^+ (mEquiv./L)	5.44±0.05	5.67±0.04*	5.76±0.01*	5.89±0.03*	5.24±0.02	5.44±0.03*	5.56±0.05*	5.89±0.03*
Ca^{2+} (mg/L)	81.32±0.31	77.11±0.43*	68.29±0.43*	63.71±0.45*	77.28±0.29	73.70±0.37*	68.62±0.31*	61.96±0.39*
Mg^{2+} (mg/L)	15.14±0.15	16.37±0.24*	20.16±0.31*	17.39±0.23*	15. 54±0.22	16.44±0.23*	18.56±0.25*	17.49±0.43*
Pi (mg/L)	31.35±0.24	28.34±0.36*	30.69±0.35*	28.32±0.62*	30.26±0.11	32.34±0.16*	29.37±0.22*	27.96±0.34*

Values are means±SEM, n=5, *P<0.05, significant difference compared to the control, mEquiv./L: Milli equivalent/L, SEM: Standard error of mean, *F. glumosa: Ficus glumosa*

arctotoides. A daily administration of a dose of *F. glumosa* aqueous extract did not affect the body weight after 6 weeks of treatment. The body weight of rats treated with the plant extract at the dose of 1200 mg/kg was, however, decreased in both males and females.

The hematological profile of treated rats showed no significant differences with the control group, except that platelets significantly ($P < 0.05$) increased by 67.79%; 65.97%, and 70.17%, respectively, at doses 300, 600, and 1200 mg/kg in males and 120.67%; 122.54%, and 126.85%, respectively, at doses 300, 600, and 1200 mg/kg in females. Analysis of blood parameters is relevant to assess the effect of plant extract on the bone narrow [18]. The increase of leukocytes may indicate strength of the defense mechanism of an organism [19,20] or an unknown subchronic inflammation. In addition, there were no inclusions in the red cells or white cells were observed from the cell morphology that supports the safety nature of the plant extract.

Total bilirubin was significantly increased ($P < 0.05$) in treated animals suggesting an increase of hemolysis. Biochemical analysis showed that daily administration of aqueous extract in subacute toxicity caused a significant increase ($P < 0.05$) in serum activity of aspartate aminotransferase (AST), ALP, and ALT in rats treated with an extract at doses of 300, 600, and 1200 mg/kg. The increases in AST and ALT may explain hepatocytes attack [21]. This toxic effect could be attributed to various secondary metabolites such as saponins, tannins, and flavonoids present in *F. glumosa* aqueous extract as suggested by Agbaje *et al*. [22] when studying the subacute toxicity of *Syzigium aromaticum* in rats.

The decrease in creatinine and cholesterol levels in rats treated with plant extract suggests beneficial effects of the extract on the kidney and liver [23]. The creatinine and urea levels increased in animals with renal dysfunction, particularly when the glomerular filtration rate is reduced. High cholesterol levels could be explained by the stimulation of lipid anabolism hepatocyte under the action of the extract or an exogenous supply of fatty compounds contained in the extract [24,25].

CONCLUSION

In conclusion, oral acute administration of *Ficus glumosa* aqueous extract produced no signs of toxicity in mice. No mortality was recorded in treated mice after 24 h. The autopsy of organs after 14 days of treatment showed no pathological abnormality in the internal organs. The LD_{50} was above of 12000 mg/kg. Therefore, oral acute administration of *F. glumosa* aqueous extract is safe in mice. Daily administration of the doses of 300, 600, and 1200 mg/kg of the aqueous extract of leaves of *F. glumosa* for 6 weeks in treatment was well-tolerated and did not cause lethal or toxic clinical symptoms in the rat of both sexes.

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