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Lipid profiles, hematological parameters and histopathological analysis of CCl_4-intoxicated wistar albino rats treated with n-butanol extract of *Ficus glumosa* leaves

MICHAEL SUNDAY ABU[1,♥], OJOCHENEMI EJEH YAKUBU[1], JOB ITANYI ONUCHE[1], OCHE OKPE[2]
[1]Department of Biochemistry, Faculty of Pure and Applied Sciences, Federal University Wukari. PMB 1020, Katsina Ala Rd, Wukari, Nigeria. Tel./fax. +23-480-000-0000, ♥email: abulex77@yahoo.com
[2]Department of Biochemistry, Federal University of Agriculture. PMB 2373, Makurdi, Benue State, Nigeria

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Abstract. *Abu MS, Yakubu OE, Onuche JI, Okpe O. 2022. Lipid profiles, hematological parameters and histopathological analysis of CCl_4-intoxicated wistar albino rats treated with n-butanol extract of* Ficus glumosa *leaves. Cell Biol Dev 6: 6-12.* This research critically assessed the effect of the n-butanol fraction of methanol extract of *Ficus glumosa* Delile leaves on serum lipid profile, hematological parameters, and some organ architecture of experimental albino rats intoxicated with carbon tetrachloride. The crude methanol extract was re-dissolved in 300 mL of distilled water and repeatedly partitioned in a separating funnel with 400 mL of n-hexane with vigorous shaking. This process was repeated using other solvents (ethyl acetate, n-butanol, and distilled water), and the n-butanol was selected based on antioxidant potency. A total of 35 albino rats were used. The rats were divided into 7 groups of 5 animals each. Lipid profile, hematological indices, and histopathological analysis were carried out. With the administration of the extract, triacylglycerol and total cholesterol levels in the Carbon tetrachloride-induced but treated rats were significantly ($P<0.05$) reduced compared to the normal levels, 1.84±0.27 mmol/L, and 0.54±0.11 mmol/L, respectively. In contrast, high-density lipoprotein was relatively increased compared to the normal level, 1.44±0.43 mg/dL. Similarly, packed cell volume, hemoglobin, and white blood cell levels were significantly ($P<0.05$) reversed to near normal in the extract-treated rats. On the other hand, the histopathological examinations of a liver section of the normal control group showed normal hepatocellular architecture with distinct hepatic cells with a well-conserved central vein. Carbo tetrachloride-induced control group liver showed intense hepatic necrosis with vascular congestion, kupffer cells hyperplasia, vacuolation, and degeneration of normal hepatic cells (hepatic necrosis). However, the induced but treated groups almost normalized the hepatic cells (moderate hepatic necrosis). The findings showed that the n-butanol fraction of *F. glumosa* could reverse the deleterious effects of CCl_4 on lipid profile and hematological parameters with the restoration of the architectural integrities of the liver and kidney of the treated rats.

Keywords: *Ficus glumosa,* hematological parameters, histopathology, lipid profile, n-butanol fraction

INTRODUCTION

Ficus glumosa Delile is commonly known as the fig tree or African rock fig (a sacred Fig tree of religious importance in ancient times documented in holy books such as the Bible and Qur'an). In Nigeria, it is more distributed in the southern region. It is referred to as "Kawuri" in the Hausa language (Paul 2013), "Obata" in Yoruba, "Obadan" in the Edo language (Aigbokhan 2014), "Akpuru" in the Igbo language, and "okoklodu" in the Idoma language (tribe found in the southern part of Benue state in Nigeria). *Ficus glumosa* is indigenous to tropical and sub-tropical Africa, including Nigeria, with few species being found in south Asia and the Mediterranean zone, where they usually inhabit dried river beds, fringe forests, savannah areas, and swamp forests in the coastal regions (Umar et al. 2013). In Cote d'Ivoire, the Central Africa Republic, and Zimbabwe, the latex is used to ameliorate pains from sprains and treat diarrhea and sore eyes, whereas in Central Africa, Senegal, East Africa, and Tanzania, the stem bark is used as mouthwash agents to alleviate toothache, to prevent conjunctivitis, treatment of jaundice, dysentery, typhoid fever and stomach disorders (Kwazo et al. 2015). In addition, this plant is used in traditional medicine in East Africa, Cameroon, and Senegal to treat edema, hypertension, diabetes, hemorrhoids, rheumatism, skin diseases, and stomatitis (Orwa et al. 2009).

Lipids have been noted to perform important bodily functions but may cause various health problems if present in excess amounts (Ankur et al. 2012). Hyperlipidemia is a medical condition characterized by elevated lipid/lipoproteins levels in the body, including high cholesterol and triglyceride levels (Guo et al. 2011; Braamskamp et al. 2012; Bassam 2013). Lipids are considered "fats" in the bloodstream, commonly divided into cholesterol and triglycerides. Cholesterol circulates in the bloodstream and is involved in the structure and function of cells, whereas triglycerides are either used immediately or stored in the fat cells (Lughetti et al. 2010). High cholesterol levels in the body have been considered a modifiable risk factor which is evident by the fact that plasma cholesterol at levels >200 mg/dL causes 4.4 million deaths in a year (Brouwers et al. 2012; Gosh and Gosh

2012). Various types of cholesterol have been reported that include total cholesterol (TC), consisting of all the cholesterols combined; HDL cholesterol, often referred to as good cholesterol that carries cholesterol from the peripheral cells to the liver; and LDL cholesterol often called bad cholesterol that carries cholesterol from the liver to the peripheral cells (Sacks and Katan 2002; Priskila et al. 2008; Siri-Tarino et al. 2010). The abnormal lipid levels result from an alteration in lipid metabolism, an unhealthy lifestyle, including a high-fat diet, and other lifestyle factors like being overweight, heavy alcohol use, and lack of exercise (Bassam 2013).

Carbon tetrachloride (CCl_4) is one of the rats' most used experimental models for hepatic and renal toxicity induction (Tsuchiya et al. 2007). Within the body, CCl_4 is metabolized by the liver enzyme CYTP450 to produce highly toxic trichloromethyl free radical ($CCl_3^{\cdot}$), which in turn reacts with oxygen to generate trichloromethyl peroxyl ($CCl_3O_2^{\cdot}$) free radicals that cause damage to hepatocytes and renal cells (Knockaert et al. 2012). Trichloromethyl and its peroxy radical can bind to proteins or lipids or abstract a hydrogen atom from an unsaturated lipid, initiating lipid peroxidation and, consequently, liver and kidney damage (Mariam et al. 2015). Treatment of carbon tetrachloride-induced hepatotoxicity in experimental rats with methanol leaves extract of *Jatropha tanjorensis* significantly ($P<0.05$) reduced the elevated liver function parameters, total cholesterol, triacylglycerol, low-density lipoprotein cholesterol and increased high-density lipoprotein cholesterol in rats (Madubuike et al. 2015). Equally, Saba et al. (2010) demonstrated the hepatoprotective potential of *Cnidoscolus aconitifolius* leaves in rats. They were found to be potent against hepatotoxicity induced by carbon tetrachloride by reversing liver enzymes to a near normal. In order to increase the horizon of traditional therapeutic molecules against chemical intoxicants, this research was designed to assess the effect of the n-butanol fraction of methanol extract of *F. glumosa* leaves on serum lipid profile, hematological parameters and some organs architecture of experimental albino rats intoxicated with carbon tetrachloride.

MATERIALS AND METHODS

Fractionation of crude methanol extract of *F. glumosa* leaves

Exactly 20 g of crude methanol extract was re-dissolved in 300 mL of distilled water and repeatedly partitioned in a separating funnel with 400 mL of n-hexane three times with vigorous shaking (Abu et al. 2020). At each portioning, the mixture was allowed to stand for 30 minutes to separate into distinct layers of hexane and aqueous. The n-hexane fraction was then collected and concentrated using a water bath. Next, the aqueous layer was partitioned with 400 mL of ethyl acetate to obtain an ethyl acetate fraction repeatedly. The above-aqueous layer was then saturated with distilled water and repeatedly partitioned with 400 mL of n-butanol solution. Finally, the n-butanol fraction and the aqueous residue were separated. That was followed by the evaporation of moisture content from the n-butanol fraction using a water bath maintained at 45ºC until the residues were obtained. The residual fraction was kept in a sealed container and refrigerated at 2-4ºC for further use.

Animal grouping

A total of 35 albino rats were used. The rats were divided into 7 groups of 5 animals each, Table 1.

Table 1. Animal grouping

Group	Group description	Treatment
1	Negative control	No treatment
2	Vehicle control	1 mL/kg b.w olive oil
3	Positive control	1 mL/kg b.w 50% carbon tetrachloride (CCl_4) in olive oil
4	100 mg extract	1 mL/kg 50% CCl_4 in olive oil + 100 mg/kg b.w *n*-butanol fraction
5	300 mg extract	1 mL/kg 50% CCl_4 in olive oil + 300 mg/kg b.w *n*-butanol fraction
6	500 mg extract	1 mL/kg 50% CCl_4 in olive oil + 500 mg/kg b.w *n*-butanol fraction.
7	100 mg silymarin	1 m/kg 50% CCl_4 in olive oil + 100 mg/kg b.w silymarin

Figure 1. *Ficus glumosa*

Toxicity and oxidative stress induction using CCl_4 and treatment with the n-butanol fraction of methanol extract of F. glumosa *leaves*

The animals were pre-treated on the first day of the experiment with 1 mL/kg body weight from 50% solution of CCl_4 in olive oil (IP), followed by oral administration of the extract after 24 hours of intoxication with CCl_4. Then, the administration of the *n*-butanol fraction was continued for 21 days with a once-weekly challenge with 1 mL/kg body weight 50% solution of CCl_4. Finally, the animals were fasted for 24 hours after the last administration of the extract and sacrificed at the end of the experiment for sample collection and subsequent analysis (Abu et al. 2020).

Collection and preparation of animal samples

Collection and preparation of sera samples

At the end of 21 days of treatment, the animals were sacrificed by decapitation using chloroform anesthesia. Blood samples were collected from the throat in plain bottles (for biochemical parameters) and EDTA bottles for hematological analysis. The Blood samples collected in plain tubes were allowed to clot, and the sera were separated by centrifugation using Labofuge 300 centrifuge (Heraeus) at 3000 rpm for 10 minutes. The sera collected were then subjected to biochemical analysis.

Collection of liver and kidney for histopathological analysis

After the rats were sacrificed and the blood samples were collected, the liver and the kidneys were quickly excised, trimmed of connective tissues, rinsed with saline to eliminate blood contamination, dried by blotting with filter paper, and weighed (to calculate the relative weight) and were placed in freshly prepared 10% formalin for histopathological studies.

Estimation of some lipid profiles of experimental animals

The total serum cholesterol was quantified by the method described by Stein (1987). Approximately 1000 µL of the cholesterol reagent made up of 4-amino antipyrine, phenol, peroxidase, cholesterol esterase, cholesterol oxidase, and buffer was added into a clean test tube containing 10 µL of serum, mixed, and incubated for 5 minutes at 37ºC. The absorbance was read against the reagent blank at 500nm within 60 minutes.

The concentration of cholesterol in the sample is given by standard:

Conc. of cholesterol (mg/dL) = ΔA_{sample} / $\Delta A_{standard}$ X Conc. of Standard

ΔA_{sample} = Change in absorbance of the sample

$\Delta A_{standard}$ = Change in absorbance of the standard

The serum triacylglycerol level was estimated by the enzymatic method described by Stein (1987). Approximately 1000 µL of the cholesterol reagent comprised of 4-aminophenazone, peroxidase, glycerol kinase, Glycerol-3-phosphate oxidase, and buffer was added into a clean test tube containing 10 µL of serum, mixed, and incubated for 5 minutes at 37ºC. The absorbance was read against the reagent blank at 500nm.

Conc. of triacylglycerol (mg/dL) = ΔA_{sample} / $\Delta A_{standard}$ X Conc. of Standard

ΔA_{sample} = Change in absorbance of the sample

$\Delta A_{standard}$ = Change in absorbance of the standard

The serum levels of HDL-c were determined by the enzymatic method described by Stein (1987). Exactly 0.5 µL of reagent A made up of phosphotungstate and magnesium chloride was added into a clean test tube containing 0.2 mL of serum, mixed thoroughly, and allowed to stand for 10 minutes at room temperature, centrifuged at 4000 rpm for 10 minutes and supernatant was collected. Exactly 0.1 mL of reagent B, made up of 4-amino antipyrine, sodium cholate, and dichlorophenol sulfonate, was added into a clean test tube containing 50 µL of sample supernatant, mixed thoroughly, and incubated for 30 minutes at room temperature. The absorbance was read against the reagent blank at 500 nm within 60 minutes.

HDL-c += ΔA_{sample} / $\Delta A_{standard}$ X Conc. of Standard

ΔA_{sample} = Change in absorbance of the sample

$\Delta A_{standard}$ = Change in absorbance of the standard

Assessment of some hematological parameters of experimental animals

The PCV is the volume of red blood cells (RBC) expressed as a fraction of the total volume of the blood. The microhaematocrit method was used (Cheesbrough 2000). Blood samples from the rats were filled into a heparinized capillary tube, after which one end of the tube was sealed by flaming. It was then centrifuged at a speed of 7,000 rpm for 5 minutes. The PCV was estimated using a microhaematocrit reader and expressed as a percentage of the blood's erythrocytes.

Hemoglobin concentration (Hb) was determined using the cyanmethemoglobin of Alexander and Griffins (1993a,b), respectively.

Sample solutions and standard solutions were prepared as follows.

Blank: Exactly 5000 µL of Drabkin reagent was mixed with 20 µL of distilled water

Standard: Exactly 5000 µL of Drabkin reagent was mixed with 20 µL of a standard hemoglobin solution.

Test sample: Exactly 5000 µL of Drabkin reagent was mixed with 20 µL of blood.

The concentration of hemoglobin was marked with Drabkin's method, with the use of a spectrophotometer. Once the Drabkin reagent was mixed with the blood, the solution was incubated at room temperature for 5 mins, and absorbance was measured at 540 nm against distilled water.

The concentration of hemoglobin was calculated according to the following formula:

$$Hb\ concn.\ \left(\frac{g}{dL}\right) = \frac{absorbance\ of\ tested\ sample}{absorbance\ of\ standard} X concn.\ of\ standard\ \left(\frac{g}{dL}\right)$$

The total white blood count was determined using the counting chamber method. First, exactly 20 µL of the blood sample was added to 0.4 mL of diluting fluid which consists of 2% acetic acid lightly colored with 1% crystal violet (1:21 dilution of the blood). The counter chamber was then filled with the mixture from above and allowed to stand for 3-5 minutes, after which it was placed on a microscope stage and observed using an X25 objective to count the number of cells seen a sufficient number of $1mm^2$ areas to obtain at least 100 cells.

Cell count (/L) = N x (D/D) x 10 x 10^6

Where: N = total number of cell counted; D = dilution of blood; A = total area counted (in mm^2); 10 = factor to convert area to volume (in µL); 10^6 = factor to convert count per µL to litre.

Histological study of the liver and kidney of experimental animals

A portion of the liver and kidneys of the animals were cut into two to three pieces and fixed in 10% formalin (Lillie 1965). The paraffin sections were prepared and stained with hematoxylin and eosin. The thin sections of the liver and kidneys were made into permanent slides and examined under a high (X250) resolution microscope with a photographic facility and photomicrographs.

Statistical analysis

The data were analyzed by the analysis of variance (ANOVA) using the SPSS program (version 20 SPSS Inc., Chicago, IL, USA). In addition, the differences in parameters between the various animal groups were compared using the Bonferroni multiple comparison test (post-hoc test). The results were expressed as mean ± standard deviation (SD). P-value less than 0.05 was considered as significant ($P< 0.05$). Results were presented in tables, charts, and graphs using Microsoft Word and Excel.

RESULTS AND DISCUSSIONS

Effect of *n*-butanol fraction of methanolic leaf extract of *F. glumosa* on lipid profile

The effects of daily oral administration of *n*-butanol fraction of methanolic leaf extract of *F. glumosa* for 21 days on the lipid profile (total cholesterol, TCH, triacylglyceride, TAG, and high-density lipoprotein, HDL) of CCl_4-induced liver damaged rats is represented in Table 2. There was a significant ($P<0.05$) increase in the level of TCH and TAG with a significant ($P<0.05$) decrease in the level of HDL of the CCl_4-induced control group compared with the induced but treated groups. However, there was no significant ($P>0.05$) difference in the HDL and TCH levels of the induced but treated groups compared with the normal control group.

Effect of n-butanol fraction of methanolic leaf extract of *F. glumosa* on hematological parameters

Some hematological parameters (packed cell volume PCV and hemoglobin HB) found in CCl_4-intoxicated rats are presented in Table 3. There was a significant ($P<0.05$) decrease in the level of packed cell volume and hemoglobin of the CCl_4-induced control group compared with the induced but treated groups. However, compared with the normal control group, there was no significant ($P>0.05$) difference in the levels of PCV and HB of the induced but treated groups. There was a significant increase ($P<0.05$) in WBC in the CCl4-induced but not treated group compared to the normal and CCl_4-induced but treated groups.

Histopathological effect of n-butanol fraction of methanol extract of *F. glumosa* leaves on liver and kidney of CCl_4 intoxicated albino rats

The histological section of the liver and kidneys of CCl_4-induced oxidative damage rats treated with an *n*-butanol fraction of methanol of *F. glumosa* leaves extract for 21 days is shown in Figures 2 and 3. The histopathological examinations of a liver section of the normal control group showed normal hepatocellular architecture with distinct hepatic cells with the well-conserved central vein. On the contrary, the CCl_4-induced control group liver showed intense hepatic necrosis with vascular congestion, kupffer cells hyperplasia, vacuolation, and degeneration of normal hepatic cells (hepatic necrosis). However, the induced but treated groups almost normalized the hepatic cells (moderate hepatic necrosis).

Discussion

The lowered levels of high-density lipoprotein (HDLc) and increased total cholesterol (TC) and triacylglyceride (TAG) in the CCl_4-induced untreated group were in agreement with earlier findings by Adejo et al. (2014), where CCl_4 was able to significantly ($P<0.05$) caused similar effects in rats. These observations could indicate metabolic distortion in the liver due to the severity of hepatic injury inflicted by CCl_4 (Abu et al. 2021). However, treatments with the n-butanol fraction of methanol extract of *F. glumosa* leaves and silymarin reversed the status to near normal. This ameliorative effect of the extract could be attributed to its bioactive compounds, possibly increasing lipase activity that hydrolyses TAG (Adejo et al. 2014). Again, the extract may have possibly acted as an inhibitor to hydroxyl-methyl-glutaryl-CoA reductase, a key enzyme in the *de novo* biosynthetic pathway of cholesterol (Gebhardt and Beck, 1996). On the other hand, the extract probably chelated the by-products of CCl_4 metabolism, thereby stabilizing the lipid regulatory roles of the liver (Dawood et al. 2014).

Table 2. Lipid profile of CCl_4-induced liver-damaged albino rats treated orally with an n-butanol fraction of methanolic leaf extract of *F. glumosa*

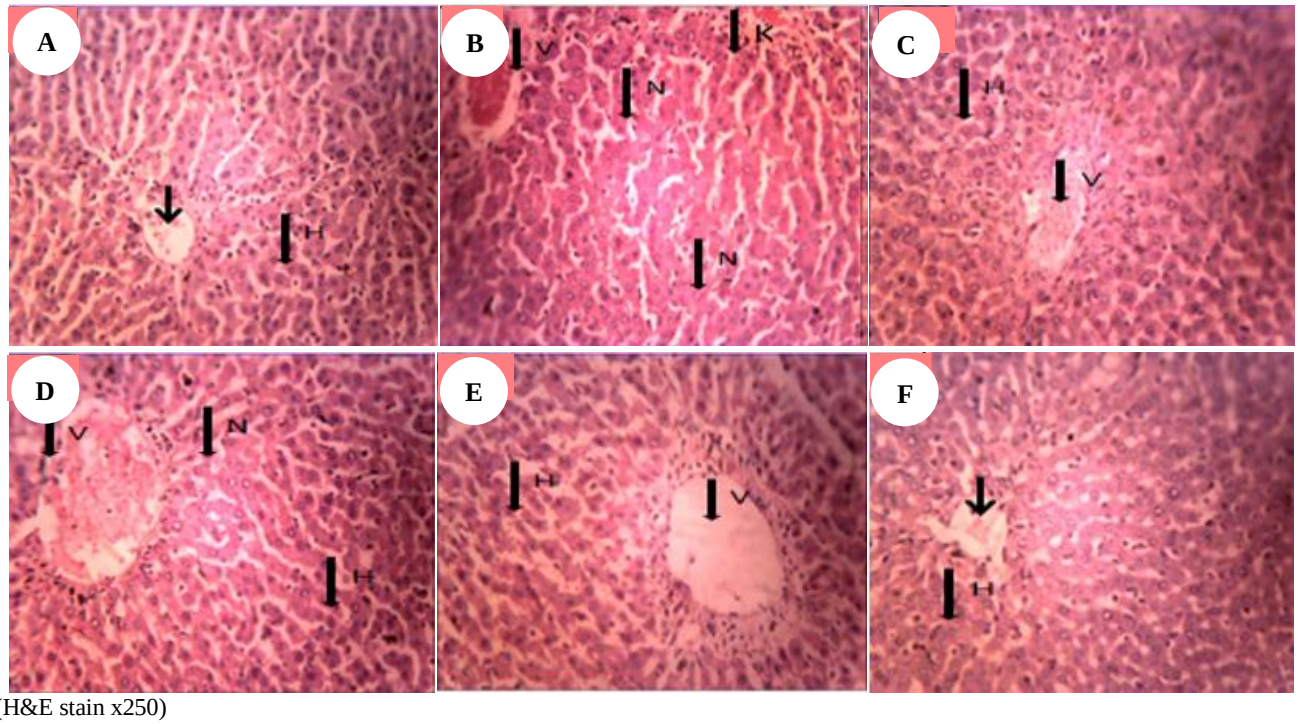
Group	TCH (mmol/L)	TAG (mmol/L)	HDL (mg/dL)
Normal control	1.84±0.27^{b}	0.54±0.11^{b}	1.44±0.43^{b}
Olive oil only	2.26±0.18^{b}	0.62±0.08^{b}	1.04±0.43^{b}
CCl_4 only	9.04±0.83^{ac}	1.26±0.11^{ac}	0.42±0.08^{a}
CCl_4 + 100mg extract	2.52±0.28^{b}	0.88±0.19^{ab}	0.64±0.17^{a}
CCl_4 + 300mg extract	2.30±0.16^{b}	0.80±0.07^{b}	0.92±0.13*
CCl_4 + 500mg extract	2.18±0.20^{b}	0.78±0.19^{b}	1.14±0.11^{b}
CCl_4 + 100mg sylimarin	2.28±0.23^{b}	0.78±0.15^{b}	0.94±0.18*

Note: n=5; values are in mean±standard deviation; values with different superscripts down the columns are significantly different at P<0.05; a= significantly different from the normal control group (P<0.05); b= significantly different from the group treated with CCl_4 without extract or standard drug treatment (P<0.05); c= significantly different from the group treated with CCl_4 and standard drug treatment (P<0.05); *= not significantly different from any of the three groups

Table 3. Hematological indices of CCl_4-induced liver-damaged albino rats treated orally with an n-butanol fraction of methanolic leaf extract of *F. Glumosa*

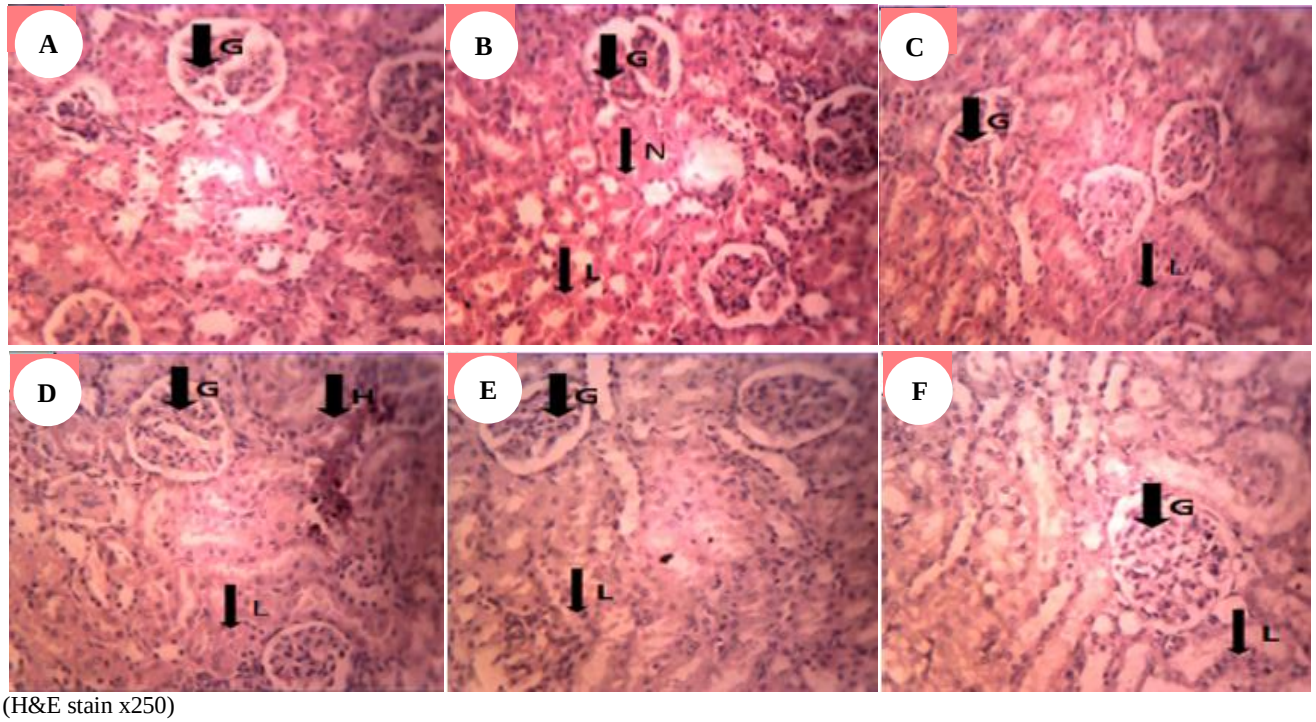
Group	PCV (%)	Hb (g/dL)	WBC (10^3)
Normal control	40.40±2.41^{b}	11.42±0.24^{b}	08.22±1.00^{b}
Olive oil only	41.00±4.30^{b}	11.16±1.72^{b}	07.00±0.43^{b}
CCL4 only	20.20±1.92^{ac}	05.42±0.41^{ac}	13.68±1.87^{ac}
CCL4 + 100mg extract	26.20±6.01^{ac}	08.98±1.06^{b}	08.90±0.54^{b}
CCL4 + 300mg extract	34.20±1.30^{ab}	09.00±2.09^{b}	08.98±1.77^{b}
CCL4 + 500mg extract	37.40±1.14^{b}	09.36±0.93^{b}	08.64±1.39^{b}
CCL4 + 100mg sylimarin	39.20±2.45^{b}	09.38±1.32^{b}	07.86±1.07^{b}

Note: n=5; values are in mean±standard deviation; values with different superscripts down the columns are significantly different at P<0.05; a. significantly different from the normal control group (P<0.05); b. significantly different from the group treated with CC_{l4} without extract or standard drug treatment (P<0.05); c. significantly different from the group treated with CCl_4 and standard drug treatment (P<0.05)



(H&E stain x250)

Figure 2. Representative photomicrograph of liver of CCl_4-induced liver-damaged albino rats treated with an n-butanol fraction of methanol extract of *F. glumosa* leaves. A. Normal control group, B. 1 mL/kg CCl_4-induced but not treated, C. 100 mg/kg of Sylimarin group, D. 100 mg/kg of *F. glumosa* extract, E. 300 mg/kg of *F. glumosa* extract, F. 500 mg/kg of *F. glumosa.* V: vascular congestion, N: necrosis, K: kupffer cells, H: hepatocytes



(H&E stain x250)

Figure 3. Representative photomicrograph of kidney of CCl_4-induced liver damaged albino rats treated with an n-butanol fraction of methanol extract of *F. glumosa* leaves. A. Normal control group, B. CCl_4-induced (1 mL/kg), C. 100 mg/kg of Sylimarin group, D. 100mg/kg of *F. glumosa* extract., E. 300 mg/kg of *F. glumosa* extract, F. 500 mg/kg of *F. glumosa* extract. G: glomerulus, N: Necrosis, L: lymphocyte

The release of CCl_4 reactive species [trichloromethyl ($CCl_3^{\cdot}$) and trichloromethyl peroxy ($CCl_3OO^{\cdot}$)] might have possibly caused the significant ($P<0.05$) transient decrease in the Hb concentration and PCV level due to hemolytic anemia caused by oxidation of sulphydryl groups of the erythrocyte membrane in addition to disturbing hematopoiesis, destruction of erythrocytes, reduction in the rate of their formation and/or their enhanced removal from circulation (Khalid et al. 2013; Maduka et al. 2014; Mariam et al. 2015). On the other hand, the CCl_4 treatment significantly ($P<0.05$) increased WBCs count, which may be attributed to lymphocyte infiltration of poisoned cells, a clear case of immune response to a chemical antigen by the body's defensive mechanism of the immune system (Saba et al. 2010). Meanwhile, treatment with an n-butanol fraction of methanol extract of *F. glumosa* leaves showed significant ($P<0.05$) reversal effects of these indices comparable with silymarin and normal control rats. The consequent reduction in red blood cells hemolysis and enhanced hematopoiesis with the decrease in the WBCs count may be ascribed to the stabilization of the free radicals by some antioxidants present in the *n*-butanol fraction of methanol extract of *F. glumosa* leaves, an effect that was in agreement with the findings of Yakubu et al. (2020) where an aqueous extract of *C. aconitifolius* leaves produced similar action against CCl_4-induced hepatotoxicity and haemotoxicity in rats.

The histopathological findings of the liver and kidney in the CCl_4-induced control group showed that CCl_4 caused intense vascular congestion, vacuolation, necrosis, and lymphocyte infiltrations in both organs (liver and kidney). These results agree with Akram et al. (2010) and Venkatanarayana et al. (2012), that reported similar effects on rats intoxicated with carbon tetrachloride. However, following the administration of the *n*-butanol fraction of methanol extract of *F. glumosa* leaves, the organs showed excellent recovery from both hepatotoxicity and nephrotoxicity to normal cellular architecture. That may be attributed to the ability of the extract to stabilize cellular structural components such as lipids, protein, and carbohydrates or a wound healing effect of the extract.

In conclusion, it was obvious from the result obtained that the induced but treated groups showed almost normalization of the hepatic cells (moderate hepatic necrosis). The extract could reverse the deleterious effects on lipid profile, hematological parameters, and liver and kidney architectural integrities. Those findings suggest that the extract can be used to manage anemia, hyperlipidemia, and liver and kidney disorders owing to its ameliorative effect on these cells, thereby returning biochemical parameters and the architectural integrity to near normal.

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