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Hepato-protective effects of aqueous extract of *Ficus dicranostyla* Mildbr. (Moraceae) leaves on paracetamol-induced hepatotoxicity in Wistar rats

Odile Baponwa [1, *], Haman Adamou [2], Christophe Mezui [3, 4], Tchokomeni Gaël Siwe [5], Vandza Luc Vandi [2], Hacheked Mbida [2], Joseph Fleurie Emakoua [5] and André Perfusion Amang [2]

[1] *Department of Biological Sciences of Living Organisms, Faculty of Science, University of Garoua, P.O. Box 346, Garoua, Cameroon.*
[2] *Department of Biological Sciences, Faculty of Science, University of Maroua, P.O. Box 814, Maroua, Cameroon.*
[3] *Department of Biological Sciences, Higher Teachers' Training College, University of Yaoundé I, P.O. Box 047, Yaoundé, Cameroon.*
[4] *Department of Biotechnology and Pharmacognosy, Faculty of Science, University of Ebolowa, P.O. Box 118, Ebolowa, Cameroon.*
[5] *Department of Animal Biology and Physiology, Faculty of Science, University of Yaoundé I, P.O. Box 812,Yaoundé, Cameroon.*

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Abstract

Ficus dicranostyla Mildbr. is a plant of the Moraceae family widely used in Cameroonian ethnomedicine for the treatment of several pathologies, including hepatitis. The aim of this study was to evaluate the hepatoprotective activity of the aqueous extract of *F. dicranostyla* leaves (AEFD) on paracetamol-induced hepatitis in rats. Thirty male rats were divided into 6 groups of 5 animals each, including 3 control groups (normal, negative and positive) and 3 test groups. These animals received distilled water (normal and negative controls), silymarin (positive control) and the extract at doses of 75, 150 and 300 mg/kg (test groups) daily for 5 days. Hepatotoxicity was induced on day 5 by single-dose *per os* administration of paracetamol (2000 mg/kg) to all groups except the normal control group. Hematological and biochemical parameters such as transaminases, alkaline phosphatase, bilirubins, total proteins, lipid profile and oxidative stress were evaluated. AEFD, particularly at doses of 150 and 300 mg/kg, significantly reduced total white blood cell counts, serum transaminases, alkaline phosphatase, bilirubins, total cholesterol, low density lipoproteins-cholesterol and triglycerides compared with the negative control. The extract also significantly increased levels of red blood cells, hemoglobin, hematocrit, total protein and high density lipoproteins-cholesterol compared with the negative control. In the extract-treated groups, hepatic malondialdehyde levels were significantly reduced, while reduced glutathione, catalase and superoxide dismutase levels were significantly increased compared with the negative control. AEFD has hepatoprotective effects resulting from its ability to strengthen antioxidant status and prevent alterations in lipoprotein and cholesterol metabolism.

Keywords: *Ficus dicranostyla*; Paracetamol; Hepatotoxicity; Hepatoprotection; Antioxidants

1. Introduction

Hepatitis refers to any acute or chronic inflammatory attack on hepatocytes [1]. Depending on the type of attack, a distinction is made between viral hepatitis caused by viruses and non-viral hepatitis due to the ingestion of hepatotoxic substances in the example of high-dose paracetamol [2].

*Corresponding author: Odile Baponwa

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Paracetamol is the most widely used analgesic/antipyretic in the world, due to its high frequency in self-medication and prescriptions. In Cameroon, a study carried out in the city of Douala revealed that paracetamol accounts for 67.39 % of the analgesics most in demand for self-medication in pharmacies [3]. In the event of overdose, paracetamol is hepatotoxic. Worldwide, paracetamol is responsible for around 7 % of annual deaths due to drug-induced hepatotoxicity [4].

Hepatitis is generally asymptomatic, but sometimes the patient may present nausea, vomiting, asthenia, rash, abdominal and joint pain, fever, headache, insomnia, abdominal bloating, diarrhea and, above all, jaundice, the expression of which is the determining factor [5,6]. These symptoms manifest themselves at different stages of the disease and can therefore evolve into complex forms such as fibrosis, cirrhosis, hepatocellular carcinoma or liver cancer [6,7].

Hepatotoxicity is treated by suppressing the cause and then taking hepatoprotective agents such as silybon or silymarin [8]. In view of the absence of vaccines against non-viral hepatitis, and the high cost and side effects of treatment molecules, people in developing countries are opting to treat themselves with medicinal plants. Many plants have shown hepatoprotective effects, such as *Opilia celtidifolia* [9], *Haematostaphis barteri* [10], *Terminalia chebula* [11], *Moringa oleifera* [12], *Jatropha curcas* [13], *Vernonia amygdalina* [14].

Ficus dicranostyla is an edible plant, and is also widely used in ethnomedicine for the treatment of numerous diseases, including hepatitis [15, 16]. Previous studies have demonstrated its nutritional composition and protective activity against carbon tetrachloride-induced hepatotoxicity in rats [16, 17]. The overall aim of this study was to evaluate the hepatoprotective activity of the aqueous extract of *F. dicranostyla* leaves on paracetamol-induced hepatitis in rats.

2. Materials and methods

2.1. Plant material

The plant material was *F. dicranostyla* leaves, collected on the Mandara Mountains in the Walamaï-Dimeo locality (10°32'32".4 N; 013°56'23.7 E), arrondissement of Mokolo, Department of Mayo-Tsanaga (Far North Region, Cameroon). The species was identified by Pr. Tchobsala, Botanist at the University of Maroua. The sample was then authenticated at the Herbarium of Garoua Wildlife School (North Cameroon) by Mme Ngwa Adeline Neh through comparison with the specimen registered under number HEFG/1811. Post-harvest *F. dicranostyla* leaves were washed, shade-dried at room temperature for two weeks, and then reduced into powder. Four hundred grams (400 g) of this fine *F. dicranostyla* leaves powder was boiled in 4 L of distilled water for 15 minutes. After cooling, the mixture was filtered through Wattman paper No. 3. The filtrate was evaporated in an oven at 50 °C for 24 hours. The mass of dry extract obtained was 35.10 g, giving a yield of 8.77 %.

2.2. Animal material

The animal material consisted of male albino rats of Wistar strain, aged between 7 and 8 weeks and with a body mass of between 120 and 150 g. The rats were bred at the animal house of the Laboratory of Biological Sciences, Faculty of Science, University of Maroua, Cameroon. They were housed in cages covered with wire mesh and maintained at room temperature with a natural light/dark cycle. All animals were fed a standard diet and were provided with *ad libitum* access to food and tap water. Experimentation was carried out in accordance with the European Convention for the Protection of Vertebrate Animals used for Experimental and other Purposes [18]. Prior authorization for the use of laboratory animals in this study was obtained from the National Ethics Committee of Cameroon (Reg. N. FWA-IRB 00001954).

2.3. Phytochemical screening of *aqueous extract of F. dicranostyla* leaves

In order to determine the classes of bioactive compounds contained in the aqueous extract of *F. dicranostyla* leaves (AEFD), phytochemical screening was carried out according to the protocols described by Harborne [19].

2.4. Experimental protocol

The method of Ajith *et al.* [20] was used with a few modifications. Thirty (30) male rats were randomized into six (06) groups of five (05) rats each. The animals received distilled water at 5 mL/kg (normal and negative control groups), silymarin at 100 mg/kg (positive control group) and AEFD at 75, 150 and 300 mg/kg (test groups), respectively, orally for five days. Hepatotoxicity was induced on day 5th and 1 h after the different treatments by administration of paracetamol *per os* at a single dose of 2000 mg/kg, to all animals except those in the normal control group.

2.5. Animal sacrifice and sample collection

After administration of paracetamol, all animals were fasted for 24 hr. On day 6th, all animals were sacrificed under ketamine (2.5 mg/kg, i.p)/diazepam (5 mg/kg, i.p) anaesthesia. After rupture of the jugular vein, blood from each animal was collected in EDTA and dry tubes for analysis of hematological and serum biochemical parameters respectively. Liver and kidney samples were taken for oxidative stress parameters.

2.6. Analysis of hematological and serum biochemical parameters

Hematological parameters were determined by blood count using an automatic analyzer of the manufacturer « Évolution 3000 ».

Blood samples collected in dry tubes were centrifuged at 2000 rpm for 5 min, and the sera obtained were collected for serum biochemical parameter determination. Aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), bilirubin, alkaline phosphatase, total protein, total cholesterol, high/low density lipoproteins-cholesterol (HDL/LDL cholesterol) and triglycerides were determined using kits manufactured by SGMitalia S.r.L (Italy).

2.7. Determination of oxidative stress parameters

Liver homogenates were prepared by grinding 0.5 g of fresh tissue from each animal in 2.83 mL phosphate buffer (0.1 M pH 7.5). These homogenates were centrifuged at 3000 rpm for 5 minutes. The supernatants collected were used to assay malondialdehyde [21], superoxide dismutase [22], catalase [23] and reduced glutathione [24].

2.8. Data analysis

Data were analyzed by one-way ANOVA followed by Tukey's test using Graph Pad Prism software version 8.0.2. Results were presented in tables, histograms and expressed as mean ± standard error on the mean. Differences with p-values below 0.05 were considered significant.

3. Results

3.1. Results of qualitative phytochemical analysis of the aqueous extract of *F. dicranostyla* leaves

Qualitative phytochemical analysis revealed the presence of flavonoids, alkaloids, saponins and quinones in AEFD.

3.2. Effects of aqueous extract of *F. dicranostyla* leaves on hematological parameters

Table 1 Effects of aqueous extract of *F. dicranostyla* leaves on some hematological parameters

Groups	HGB (g/L)	RBC ($x10^{12}$/L)	WBC ($x10^9$/L)	PLT ($x10^9$/L)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/L)
Normal control	130.00 ± 08.24	7.52 ± 0.44	11.08 ± 1.10	1220.00 ± 38.86	36.66 ± 3.56	54.52 ± 3.52	21.00 ± 1.90	381.40 ± 31.16
Negative control	87.24 ± 04.01***	1.88 ± 0.36***	17.00 ± 1.40***	1315.00 ± 107.60	14.64 ± 0.59***	51.26 ± 1.56	16.82 ± 0.38	311.40 ± 23.47**
positive control	145.20 ± 5.52$^{###}$	5.70 ± 0.34$^{###}$	13.92 ± 0.49$^{##}$	1429.00 ± 199.20	38.40 ± 1.80$^{###}$	51.78 ± 1.12	17.94 ± 0.32	346.60 ± 18.94
AEFD 75	141.60 ± 6.13$^{###}$	1.12 ± 0.21	13.40 ± 1.37$^{##}$	1269.00 ± 60.07	38.18 ± 1.71$^{###}$	52.36 ± 3.16	17.46 ± 0.92	394.20 ± 24.70$^{#}$
AEFD 150	143.60 ± 7.56$^{###}$	3.51 ± 1.63$^{#}$	12.68 ± 1.00$^{##}$	1458.00 ± 93.68	36.26 ± 0.79$^{###}$	53.68 ± 2.35	16.40 ± 1.22	340.00 ± 22.45
AEFD 300	162.61 ± 3.14$^{###}$	6.00 ± 0.92$^{###}$	12.20 ± 1.15$^{###}$	1373.00 ± 97.60	34.18 ± 0.48$^{###}$	52.08 ± 2.74	18.62 ± 11.89	417.00 ± 36.00$^{##}$

Values were expressed as Mean ± MSE; n = 5; HGB: Hemoglobin, RBC: Red blood cells, WBC: White blood cells, PLT: Platelets, HCT: Hematocrit, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration. AEFD 75, AEFD 150 and AEFD 300: groups treated with aqueous extract of *F. dicranostyla* leaves at doses of 75, 150 and 300 mg/kg respectively. $^{***}p < 0.001$ significant difference from normal control, $^{#}p < 0.05$, $^{##}p < 0.01$, $^{###}p < 0.001$ significant difference from negative control.

A significant decrease in hemoglobin, red blood cell, hematocrit and mean corpuscular hemoglobin concentration ($p < 0.001$) and a significant increase in total white blood cell count ($p < 0.001$) in rats in the negative control group compared with those in the normal control group were noted (Table 1). However, AEFD at 300 mg/kg resulted in a significant increase in hemoglobin, red blood cells, hematocrit ($p < 0.001$) and mean corpuscular hemoglobin concentration ($p < 0.01$), as well as a significant decrease in white blood cell count ($p < 0.001$) compared to the negative control group.

3.3. Effects of aqueous extract of *F. dicranostyla* leaves on serum biochemical parameters related to liver function

Table 2 shows variations in the levels of transaminases (ASAT/ALAT), alkaline phosphatase (ALP), bilirubins and total proteins in different groups of animals. In the negative control, administration of paracetamol resulted in a significant increase ($p < 0.001$) in ASAT, ALAT, ALP, bilirubin (conjugated, unconjugated and total) and a significant decrease ($p < 0.001$) in total protein levels, compared with the normal control. In the test groups, AEFD, particularly at doses of 150 and 300 mg/kg, significantly decreased ($p < 0.001$) serum transaminase, ALP and bilirubin levels, and significantly increased ($p < 0.001$) total protein levels, compared with the negative control group.

Table 2 Effects of aqueous extract of *F. dicranostyla* leaves on some liver functions parameters

Groups	ASAT (UI/L)	ALAT (UI/L)	ALP (UI/L)	BT (µmol/L)	BC (µmol/L)	BUC (µmol/L)	PT (mg/dL)
Normal control	71.20 ± 2.20	35.80 ± 2.81	114.80 ± 4.55	9.48 ± 0.76	9.24 ± 0.85	0.78 ± 0.01	72.60 ± 3.09
Negative control	119.60 ± 3.30***	106.80 ± 8.66***	357.80 ± 19.37***	26.02 ± 2.14***	18.60 ± 2.22***	5.14 ± 0.085***	43.60 ± 2.73***
positive control	78.80 ± 1.39###	21.20 ± 1.74###	191.80 ± 5.43###	6.72 ± 0.63###	5.70 ± 0.68###	0.54 ± 0.05###	70.40 ± 1.63###
AEFD 75	66.00 ± 2.60###	39.80 ± 3.54###	264.00 ± 11.40##	8.52 ± 0.73###	7.16 ± 0.78###	1.36 ± 0.34###	60.00 ± 1.64#
AEFD 150	38.40 ± 1.56###	25.20 ± 1.71###	222.20 ± 7.20 ###	3.20 ± 0.22###	2.84 ± 0.18###	0.42 ± 0.03###	70.60 ± 2.78###
AEFD 300	29.00 ± 1.67###	15.20 ± 1.77###	177.60 ± 8.26###	2.62 ± 0.28###	2.20 ± 0.45###	0.32 ± 0.05###	61.80 ± 1.82##

Values were expressed as Mean ± MSE; n = 5; ASAT: Aspartate aminotransferase, ALAT: Alanine aminotransferase, ALP: Alkaline phosphatase, BT: Total bilirubin, BC: Conjugated bilirubin, BUC: Unconjugated bilirubin and PT: Total protein. AEFD 75, AEFD 150 and AEFD 300: groups treated with aqueous extract of *F. dicranostyla* leaves at doses of 75, 150 and 300 mg/kg respectively. ***$p < 0.001$ significant difference from normal control, #$p < 0.05$, ##$p < 0.01$, ###$p < 0.001$ significant difference from negative control.

3.4. Effects of aqueous extract of *F. dicranostyla* leaves on lipid profile parameters

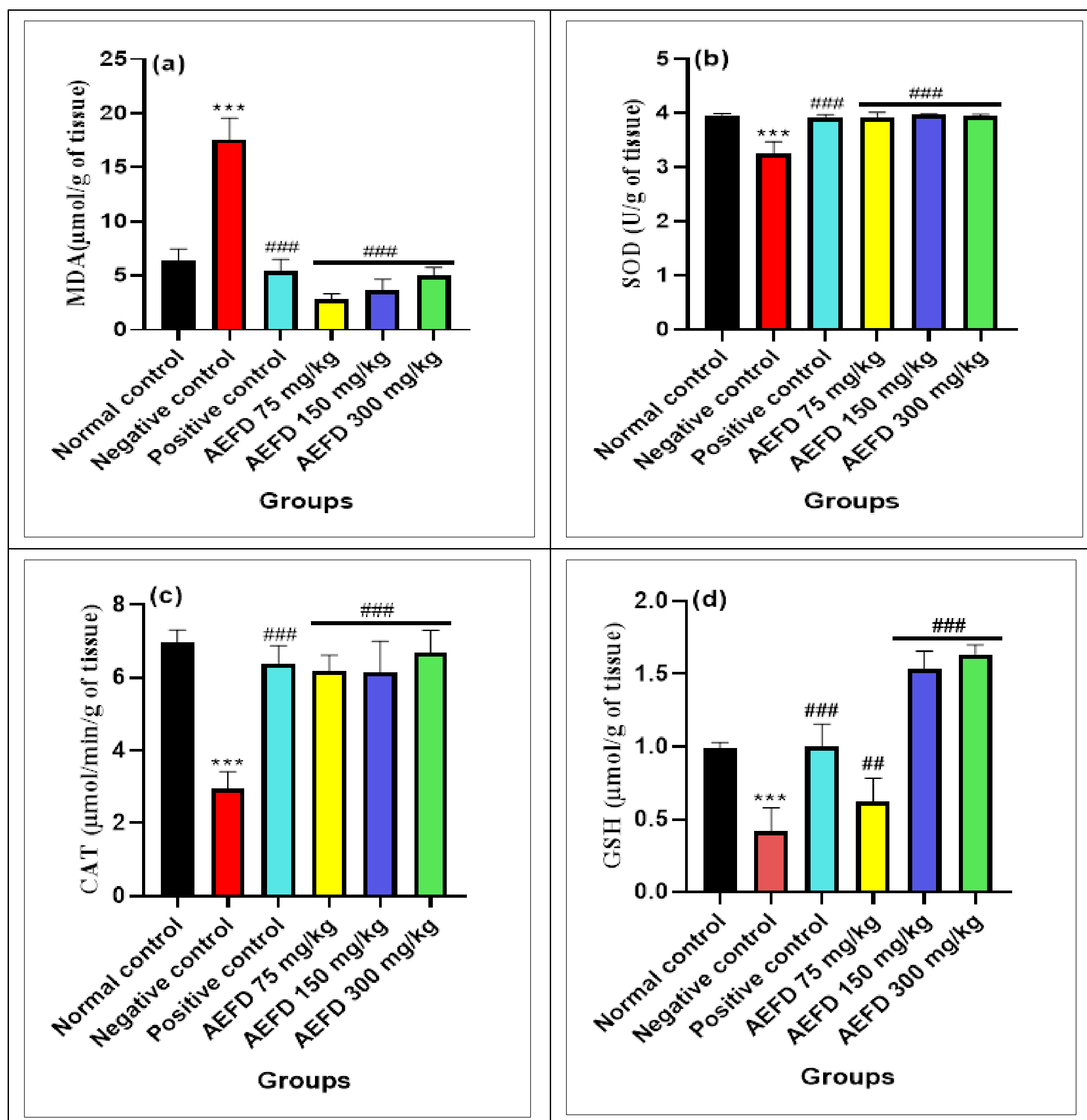
Table 3 Effects of aqueous extract of *F. dicranostyla* leaves on lipid profile parameters

Groups	Total Cholesterol (mg/dL)	HDL-Cholesterol (mg/dL)	LDL-Cholesterol (mg/dL)	Triglycérides (mg/dL)
Normal control	62.32 ± 2.36	40.92 ± 1.22	12.49 ± 1.16	44.56 ± 1.20
Negative control	102.70 ± 1.90***	26.90 ± 1.28***	60.64 ± 1.28***	75.80 ± 4.16***
positive control	75.36 ± 2.37###	42.12 ± 0.98###	24.47 ± 1.72##	43.84 ± 1.54###
AEFD 75	77.76 ± 1.85#	37.84 ± 1.22##	31.08 ± 1.18##	44.20 ± 1.06###
AEFD 150	71.36 ± 1.80###	42.66 ± 0.79###	20.52 ± 1.68###	40.88 ± 0.49###
AEFD 300	68.26 ± 2.36###	44.16 ± 1.68###	16.62 ± 1.42###	37.40 ±1.12###

Values were expressed as Mean ± MSE; n = 5; AEFD 75, AEFD 150 and AEFD 300: groups treated with aqueous extract of *F. dicranostyla* leaves at doses of 75, 150 and 300 mg/kg respectively. ***$p < 0.001$ significant difference from normal control, #$p < 0.05$, ##$p < 0.01$, ###$p < 0.001$ significant difference from negative control.

Lipid profile results (total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides) showed a significant increase in total cholesterol, triglycerides and LDL-cholesterol levels ($p < 0.001$), combined with a significant drop in HDL-cholesterol levels ($p < 0.001$) in animals in the negative control group compared with the normal control (Table 3). In AEFD-treated animals, particularly at doses of 150 and 300 mg/kg, there was a significant decrease in total cholesterol, triglycerides and LDL-cholesterol ($p < 0.001$) and a significant increase in HDL-cholesterol ($p < 0.001$) compared with the negative control.

3.5. Effects of aqueous extract of *F. dicranostyla* leaves on oxidative stress parameters



Values were expressed as Mean ± MSE; n = 5; MDA: malondialdehyde, SOD: superoxide dismutase, CAT: catalase and GSH: reduced glutathione. AEFD 75, AEFD 150 and AEFD 300: groups treated with aqueous extract of *F. dicranostyla* leaves at doses of 75, 150 and 300 mg/kg respectively. ***p < 0.001 significant difference from normal control, ##p < 0.01, ###p <0.001 significant difference from negative control.

Figure 1 Effects of aqueous extract of *F. dicranostyla* leaves on hepatic malondialdehyde (a), superoxide dismutase (b), catalase (c) and reduced glutathione (d) levels

Figures 1 show the hepatic concentrations of malondialdehyde (MDA), superoxide dismutase (SOD), catalase (CAT) and reduced glutathione (GSH), respectively, in the different animal groups. In the negative control group, MDA levels in liver tissue were significantly ($p < 0.001$) higher than in the normal control group (Figure 1a). This increase in MDA levels was accompanied by a decrease ($p < 0.001$) in hepatic SOD (Figure 1b), CAT (Figure 1c) and GSH (Figure 1d)

levels. In animals treated with the aqueous extract of *F. dicranostyla* leaves, there was a significant decrease in liver MDA levels ($p < 0.001$) compared with the negative control. AEFD, particularly at doses of 150 and 300 mg/kg, also significantly increased ($p < 0.001$) SOD, CAT and GSH levels in liver tissue, compared with the negative control.

4. Discussion

Hepatotoxicity due to drugs such as paracetamol is common [5, 25]. When paracetamol is used in overdose, it causes liver damage. Indeed, paracetamol metabolism in normal use is predominantly sulfoconjugation and glucuroconjugation in the liver. A small fraction is oxidized *via* cytochrome P450 and transformed into a toxic metabolite (mainly N-acetyl-p-quinone imine or NAPQI). NAPQI is rapidly conjugated to glutathione, and then excreted in the urine as mercapturate. In the event of massive intoxication, the glutathione pool is rapidly depleted, hence the significant drop in GSH levels observed in the negative control group. In addition to glutathione depletion, a large quantity of unbound reactive species is released, leading to oxidative stress. NAPQI being highly reactive binds to hepatocyte and mitochondrial surface proteins and leads to necrosis by lipid peroxidation [26]. According to Mas-Bargues et al. [27], MDA is one of the main biomarkers for assessing lipid peroxidation. On the other hand, enzymes of the first line of antioxidant defense such as SOD and CAT, decrease in case of paracetamol overdose [28, 29]. SOD is a family of enzymes involved in the neutralization of superoxide by dismutation into oxygen and hydrogen peroxide [30]. Enzymes such as CAT convert hydrogen peroxide to water [31]. In the present study, hepatic MDA concentration increased significantly following overdose administration of paracetamol in animals in the negative control group compared with the normal control group. This increase in MDA levels was accompanied by a significant decrease in SOD and CAT activity in these animals. In groups pre-treated with aqueous extract of *F. dicranostyla* leaves, there was a significant increase in GSH levels and SOD and CAT activity in liver tissue, and a significant decrease in MDA levels compared to the negative control group. Similar results were obtained with *Spirulina platensis* extract by Sangeetha et al. [32]; they attributed the extract of this plant is rich in antioxidant compounds capable of activating and/or strengthening the antioxidant defense system. According to Dolara et al. [33], classes of bioactive compounds such as flavonoids and alkaloids possess antioxidant and hepatoprotective properties. These antioxidants provide protection against paracetamol-induced toxicity by scavenging free radicals and reactive oxygen species, thus preventing oxidative cell destruction [34, 35]. They also activate hepatocyte regeneration and the antioxidant defense system, and prevent or limit membrane lipid peroxidation [36].

In addition to reducing the antioxidant defense system, paracetamol overdose leads to hepatocellular damage. The covalent binding of NAPQI to the sulfudryls of the liver intramolecular proteins Liver X receptor and Carbohydrate responsive element-binding protein leads to hepatocyte lysis [37]. The formation of these adducts leads to a decrease in serum protein levels. Increased serum levels of ALAT and ASAT are a sign of the destruction of the structural integrity of liver cells, as these enzymes are normally localized in the cytoplasm, mitochondria or microsomes [38]. They are released into the bloodstream in the event of destruction or alteration of hepatocyte cell membrane permeability [39]. ALP is a marker enzyme of the biliary tract and cholestasis, whose increase also characterizes liver failure. Bilirubin is also a product of erythrocyte destruction. After its production in peripheral tissues, bilirubin is transported to the liver, where it is conjugated with glucuronic acid for elimination via the digestive tract. An increase in bilirubinemia characterizes hepatocyte metabolic dysfunction and the presence of hepatobiliary disorders [40]. In the negative control group, the significant decrease in serum protein levels and the significant increase in serum ALAT, ASAT, ALP and Bilirubin levels compared to the normal control batch testified to the loss of hepatocyte structural integrity. On the contrary, in animals fed *F. dicranostyla* extract, an increase in serum total protein and a significant decrease in serum ALAT, ASAT, ALP and Bilirubin levels were noted compared with the negative control. Ogunka-Nnoka et al. [41] showed that the aqueous extract of *Measobotrya barteri* leaves prevented hepatocyte destruction linked to the formation of adducts with proteins. Many authors have shown that plant extracts that reduce these parameters following paracetamol intoxication have an anti-hepatotoxic effect [10, 13, 42]. According to Ezekiel et al. [43], these extracts contain compounds that stabilize hepatocyte membranes by maintaining the integrity of mitochondrial permeability transition pores and intramolecular hepatic proteins.

With regard to lipid profile parameters, the results of this work showed that overdose administration resulted in a significant decrease in serum HDL-Cholesterol levels and a significant increase in serum total cholesterol, LDL-Cholesterol and triglyceride levels in the negative control group compared to the normal control group. According to Kobashigania and Kasiska [44], paracetamol alters lipoprotein and cholesterol metabolism. In animals in the AEFD groups, serum HDL-cholesterol levels were significantly increased, while total cholesterol, LDL-cholesterol and triglycerides were significantly reduced compared with the negative control group. Similar results were obtained from the work of Adegboye et al. [14], who showed that daily administration of the methanolic extract of *Vernonia amygdalina* leaves for 7 days resulted in a normalization of these lipid profile parameters. They concluded that this extract had the capacity to prevent paracetamol-induced alterations in lipoprotein and cholesterol metabolism. Almajwal & Elsadek

[45] had attributed the hypolipidemic effect of *Vitis vinifera* seed extract in paracetamol-induced hepathotoxicity to the flavonoids and polyphenols it contained. According to Balasundram et al. [46], secondary metabolites such as saponins exert hypocholesterolemic activities.

The hepatotoxicity of paracetamol in overdose is associated with an inflammatory aspect leading to an increase in the total white blood cell count. Indeed, damaged hepatocytes release various (pro-inflammatory) molecules, leading to the recruitment and consequent increase in the number of white blood cells such as neutrophils, oesinophils and macrophages [47]. Hence the increase in total white blood cell count observed in the negative control group compared with the normal control. Oyedeji et al. [48] showed that administration of paracetamol in excess led to lower levels of hematological parameters such as hemoglobin, red blood cells, mean corpuscular hemoglobin concentration and mean corpuscular volume. In animals fed the aqueous extract of *F. dicranostyla* leaves, the total white blood cell count fell significantly, and the levels of hemoglobin, hematocrit, red blood cells and mean corpuscular hemoglobin concentration (MCHC) increased significantly compared with the negative control. These results are similar to those of Abubakar et al. [49], who showed that oral administration of *Haematostaphis barteri* fruit extract in rats resulted in a significant increase in hemoglobin, red blood cell, hematocrit and MCHC levels. These authors suggested that the aqueous extract of this plant had an effect in the treatment of anemia due to paracetamol-induced hepatocyte cytolysis, by intervening in the processes of blood cell production and hemoglobin synthesis.

5. Conclusion

In conclusion, this study has demonstrated that the bioactive compounds contained in the aqueous extract of *F. dicranostyla* leaves possess hepatoprotective activity against paracetamol toxicity. This effectiveness in maintaining the integrity of hepatocyte cells stems from its ability to strengthen antioxidant status and prevent alterations in lipoprotein and cholesterol metabolism.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that they have no competing interests.

Statement of ethical approval

Prior authorization for the use of laboratory animals in this study was obtained from the National Ethics Committee of Cameroon (Reg. N. FWA-IRB 00001954).

The experiments on rats in this study were carried out in accordance with the European Convention for the Protection of Vertebrate Animals used for Experimental and other Purposes.

References

[1] Theise ND, Bodenheimer HC, Ferrell LD. Acute and chronic viral hepatitis. In: Burt AD, Portmann BC, Ferrell LD, eds MacSween's Pathology of the Liver. Sixth Edition. Churchill Livingstone; 2012, 361-401.

[2] OMS, Global health sector strategy against viral hepatitis 2016-2021; towards the elimination of viral hepatitis, 2016.

[3] Etame GL, Ngoule CC, Ngene JP & Kidik MCP. Evaluation of self-medication with analgesics in adults: the case of customers of dispensing pharmacies in Douala, Cameroon. *International Journal of Biological and Chemical Sciences*. 2017 ; 11(4) : 1461-70.

[4] Mégarbane B. Paracetamol intoxication: what's new? *Intensive Care Medecine*. 2017; 26: 383-95.

[5] Rotundo L & Pyrsopoulos N. Liver injury induced by paracetamol and challenges associated with intentional and unintentional use. *World Journal of hepatology*. 2020; 12(4): 125-36.

[6] Kozyk M, Strubchevska K, Yuzkiv V, Bezkorovayna U & Nedilko R. Symptoms of Acute and Chronic Viral Hepatitis: Effects on Human Body. *Journal of Medicinal and Chemical Sciences*. 2023; 6: 2580-87.

[7] Abdelhamed W & El-Kassas M. Hepatitis B virus as a risk factor for hepatocellular carcinoma: There is still much work to do. *Liver Research*. 2024; 8: 83-90.

[8] Oyman A, Unsal G, Aydogdu N & Usta U. Protective effects of Silymarin on Acetaminophen-induced toxic hepatitis. *Eurasian Journal of Medicinal Advances.* 2022; 2(1):1-6.

[9] Amang AP, Kodji E, Mezui C, Baane MP, Siwe GT, Kuissu TM, Emakoua J & Tan PV. Hepatoprotective effects of aqueous extract of *Opilia celtidifolia* (Opiliaceae) Leaves against Ethanol-induced liver damage in rats. *Evidence Based Complementary and Alternative Medicine*, 2020; 24: 1-8.

[10] Mohammed N, Yaro AH & Nazifi AB. Evaluation of hepatoprotective activity of methanol stem bark extract of *Haematostaphis barteri* Hook. F. against paracetamol and carbon tetrachloride-induced liver injury in rats. *African Journal of Pharmacology and Therapeutics.* 2017;6 (2): 88-95.

[11] Balakrishna V & Lakshmi T. Hepatoprotective activity of ethanolic fruit extract of *Terminalia chebula* on ethanol induced hepatotoxicity in rats. *European Journal of Pharmaceutical and Medical Research*. 2017; 4(4): 533-6.

[12] Islam R, Alam MJ, SB Shanta, MH Rahman, S Mahmud &AS Khan. Evaluation of liver protective activity of *Moringa oleifera* bark extract in paracetamol induced hepatotoxicity in rats. *Journal of Pharmaceutical Research International*. 2018; 25(4): 1-9.

[13] Andaluri S, Pitchaiah G & Dhachinamoorthi D. Hepatoprotective effect of *Jatropha curcas* Fruit extracts against carbon tetrachloride induced Liver Fibrosis in rats. *European Journal of Pharmaceutical and Medical Research*. 2018; 5(8): 448-53.

[14] Adegboye AA, Aadunmo GO, Bolaji M, Jimoh AA & Dan MI. Hepatoprotective effect of methanolic leaf extract of *Vernonia amygdalina* against acetaminophen-induced hepatotoxicity in Wistar albino rats. *Texila International Journal of Public Health*. 2017; 5 (4): 2520-3134**.**

[15] Arbonnier M. Trees, shrubs and lianas of the dry zones of West Africa. Versailles. ed. Quae, MNHN. 2009: p574.

[16] Tabi OY, Tsague MV, Deli M, Tembe AE, Ngono MR, Fokunang NC, Ngadjui TB, Dimo T, Ndongo EJ & Ze Minkande J. Nutritional composition, constituents, and antioxidant activity of powder fractions of *Ficus dicranostyla* mildbread leaves. *Universal Journal of Pharmaceutical Research*. 2022; 7(4): 50-58.

[17] Tabi OY, Tsague MV, Temdie GRJ, Tembe AE, Ngono MR, Fokunang NC, Ngadjui TB, Dimo T, Ndongo EJ & Ze Minkande J. Hepatoprotective and in vivo antioxidant effects of granulometric classes and decoction of *Ficus dicranostyla* Mildbread leaves powders against carbon tetrachloride-induced hepatotoxicity in Wistar rats. *Food Science and Nutrition*. 2023; 11(10): 6403-12.

[18] Anderson D. Revision of Council of Europe Convention ETS 123 Guidelines for the Accommodation and Care of Animals Used for Experimental and Other Scientific Purposes. *Alternatives to Laboratory Animals*. 2004; 32(1):183-185.

[19] Harborne JB. Textbook of Phytochemical Methods, A Guide to Modern Techniques of Plant Analysis. 5th Edition. London: Chapman and Hall Ltd; 1998.

[20] Ajith TA, Hema U & Aswathy MS. *Zingiber officinale* Roscoe prevents acetaminophen-induced acute hepatotoxicity by enhancing hepatic antioxidant status. *Food Chemestry and Toxicology*. 2007; 45(11): 2267-72.

[21] Wilbur KM, Bernheim F, Shapiro OW. Determination of lipid peroxidation. *Archives of biochemistry and biophysics*. 1949; 24: 305-10.

[22] Misra H & Fridovich I. The role of superoxyde anion in the autoxidation of epinephrine and simple assay for superoxyde dismutase. *The Journal of Biological Chemistry*. 1972; 247(10): 3170-75.

[23] Sinha AK. Colorimetric assay of catalase, *Analytical Biochemestry*. 1972; 47: 389-94.

[24] Ellman GL. Tissue sulfhydryl groups. *Archives of Biochemistry and Biophysics*. 1959; 82: 70-7.

[25] Sultana N, Sadia CS & Tanveer MHP. Effects of ashwagandha (*withania somnifera*) root extract on architecture of liver tissue against gentamicin induced hepatotoxic rats. *International Journal of Pharma and Biosciences*. 2016; 7(3): 78-82.

[26] Gulati K, Reshi MR, Rai N. & Ray A. Hepatotoxicity: its mechanisms, experimental evaluation and protective strategies. *American Journal of Pharmacology*. 2018; 1(1): 1-9.

[27] Mas-Bargues C, Escrivá C, Dromant M, Borrás C & Viña J. Lipid peroxidation as measured by chromatographic determination of malondialdehyde. Human plasma reference values in health and disease. *Archives of Biochemistry and Biophysics*. 2021; 709: 1-7.

[28] Ighodaro OM & Akinloye OA. First line defence antioxidants-superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX): Their fundamental role in the entire antioxidant defence grid. *Alexandria Journal of Medicine*. 2018; 54: 287-93.

[29] Okoko, paracetamol and hydrogen peroxide-induced tissue alterations are reduced by Costus afer extract, *American Journal of Research in Medical Sciences*. 2018; 2(2): 1-7.

[30] Guarini G, Hugi A, Morrone D, Capozza P, Todiere G & Marzilli M. Pharmacological approaches to coronary microvascular dysfunction. *Pharmacology & Therapeutics*. 2014; 144 (3): 283-302.

[31] Wang Y, Branicky R, Noë A & Hekimi S. Superoxide dismutase: dual roles in controlling ROS damage and regulating ROS signaling. *Journal of Cell Biology*. 2018; 217(6): 1915-28.

[32] Sangeetha L, Samixaben DP & Pandana CSB. Hepato-Protective Effects of Blue-Green Alga *Spirulina platensis* on Diclofenac-Induced Liver Injury in Rats. *Malaysian Journal of Nutrition*. 2016; 22 (2): 289-299.

[33] Dolara P, Luceri C & De Filippo C. Red wine polyphenols influence carcinogenesis, intestinal microflora, oxidative damage and gene expression profiles of colonic mucosa in F344 rats. *Mutation Research*. 2005; 591: 237-246.

[34] Valko, Rhodes MCJ, Moncol J, Izakovic M & Mazur M. Free radicals, metals and antioxidant. *Interaction*, 2006; 160: 1-40.

[35] Raza M, Alghasham A, Alorainy MS & El-Hadiyah TM. Beneficial interaction of thymoquinone and sodium valproate in experimental models of epilepsy: reduction in hepatotoxicity of valproate. *Journal of Pharmaceutic Sciences*. 2006; 74: 159-173.

[36] Jin X, Qian J & Lu Y. The role of hepatoprotective effect of a flavonoid-rich extract of *Salvia plebeia* R.Br. on carbon tetrachloride induced acute hepatic injury in mice. *Journal Medicinal Plants Research*. 2011; 5(9): 1558-63.

[37] Seirafi M, Iten A & Hadengue A. Acetaminophen: hepatotoxicity at therapeutic doses and risk factors. *Revue Médicinale Suisse*. 2007; 3: 2345-9.

[38] Salli SSC, Tuschl G, Hrach J, Hewitt PG & Mueller SO. Application of hepatocyte cultures to predict toxicities, In: Hepatotoxicity: From genomics to invitro and in vivo models. England. (ed.) John Wiley and Sons; 2008.

[39] Nuduka NK, Tang W & Makuuchi M. Artificial and bioartificial liver support: A review of perfusion treatment for hepatic failure patients. *World Journal of Gastroenterology.* 2007; 13: 1516-21.

[40] Berthélémy S. Le bilan hépatique. *Actualités Pharmaceutiques*. 2015 ; 54(544) : 59-61.

[41] Ogunka-Nnoka CU, Onwumere BT & Igwe FU. Protective effect of *Maeasobotrya barteri* aqueous leaf extract on Acetamionophen-induced hepatic injury in Wistar albino rats. 2017; 4: 2321-9122.

[42] Mohamed A & Abdelazem MA. Hepatoprotective effect of aqueous extract of cardamom against gentamicin induced hepatic damage in rats. *International Journal of Basic and Applied Sciences.* 2016; 5 (1): 1-4.

[43] Ezekiel JS, Adamu HM, Chindo IY & Garba IH. Phytochemical profile and antioxidant activities of solvent fractions of *Haematostaphis barteri* Hook F. (Anacardiaceae) stem bark extracts. *International Journal of Pharmacognosy and Phytochemestry Research*. 2016; 8: 51-56.

[44] KobashiganiaJA & KasiskaBL. Hyperlipidemia in solid organ transplantation. *Transplantation*. 1997; 63:333-8.

[45] Almajwal AM & Elsadek MF. Lipid-lowering and hepatoprotective effects of *Vitis vinifera* dried seeds on paracetamol-induced hepatotoxicity in rats, *Nutrition Research and Practice.* 2015; 9(1): 37-42.

[46] Balasundram N, Sundram K & Samman S. Phenolic compounds in plants and agri-industrial by-products: antioxidant activity, occurrence, and potential uses. *Food Chemestry*. 2006; 99: 191-203.

[47] Xu L, Yang Y, Wen Y,Jeong JM., Emontzpohl C, Atkins CL, Sun Z, Poulsen KL, Hall DR, Bynon JS, Gao B, Lee WM., Rule J, Elizabeth A, Jacobsen EA, Wang H & Ju C. Hepatic recruitment of eosinophils and their protective function during acute liver injury. *Journal of Hepatology*. 2022; 77(2): 344-52.

[48] Oyedeji KO, Okeke OE, Adeleke KO & Oyawale G. Effect of Amlodipine (Calcium Channel Blocker) on haematological and biochemical parameters in male Wistar rats. *International Journal of Pharmaceutical Sciences Review and Research*. 2019; 54(1): 146-50.

[49] Abubakar EI, Hussaini B & Friday I. Changes in heamatological parameters following oral administration of blood plum (*Haematostaphis barteri*) fruit extract in albinos rats. *Extensive Journal of Applied Sciences*. 2014; 2 (1): 14-17.