International Journal of Pharmaceutics & Pharmacology

Available Online: https://ijpp.edwiserinternational.com

Effect of Alcornea cordifolia Aqueous and Methanolic Leaf Extracts against Antituberculosis Drugs Induced Liver Damage in Rats

Effo KE[1], N'Da KJ[2], Abouna AD[2], Adehouni YA[1], Djadji ATL[1], Kouakou SL[1], Irié-N'Guessan G[1]and Kouakou-Siransy NG[1]*

[1]Pharmacology Department, Clinical and Therapeutic Pharmacy, University of Félix Houphouët-Boigny, Abidjan - Côte d'Ivoire
[2]Laboratory of Pathological Anatomy, University of Félix Houphouët-Boigny, Abidjan - Côte d'Ivoire

Article info

Received 01 January 2021
Revised 27 January 2021
Available Online 03 February 2021

*Corresponding author: Effo Kouakou Etienne, Pharmacology Department, Clinical and Therapeutic Pharmacy, University of Félix Houphouët-Boigny, Abidjan - Côte d'Ivoire

Abstract

The hepatoprotective properties of Alchornea cordifolia, a medicinal plant was studied in hepatotoxicity induced animal model with a high dose of paracetamol or carbon tetrachloride. Knowing that antituberculosis drugs also represent a risk factor for hepatotoxicity, could A. cordifolia play a key role to limit their hepatotoxicity? The objective of this study was to assess the histological changes of antituberculosis drugs in rat livers and their evolution after administration of an aqueous and a methanolic leaf extracts of A. cordifolia and therefore estimate their polyphenol and flavonoid contents.

Rats were divided into three (3) groups: group 1 was treated with isoniazid; group 2 received the combination of isoniazid and rifampicin and group 3 was given the combination of isoniazid, rifampicin and pyraziamide. For each group of rats, the hepatotoxicant was either administered alone or two hours before administration of an aqueous (200, 400, or 800 mg/kg) or a methanolic (200, 400, or 800 mg/kg) leaf extracts of A. cordifolia each day for 10 days. Animals were sacrificed on day 11 and their livers removed for histolopathological analysis. In addition, total polyphenol and flavonoid contents were estimated in both extracts.

Antituberculosis drug combinations caused peliosis lesions, steatosis and hepatocyte necrosis. The liver histology of rats that received extracts after administration of antituberculosis drug combinations showed the ability of extracts to annihilate or alleviate hepatocellular damage caused by such drugs. The methanolic extract, richer in total polyphenols (0.55 ± 0.02 mg EGA) than the aqueous extract (0.35 ± 0.01 mg EGA) demonstrated a greater hepatoprotective effect.

Thus, according to liver histological analysis, the aqueous and methanolic leaf extracts of A. cordifolia could attenuate the hepatotoxicity induced by antituberculosis drugs in rats.

Keywords: Liver damage; Hepatoprotective; Alchornea cordifolia; antituberculosis drugs

Introduction

The liver is the main organ involved in the metabolism, detoxification and in the excretion of various endogenous and exogenous substances [1,2] and also exposed to numerous drug attacks. Among hepatotoxic drugs, TB drugs represent a major risk because the liver remains the main site of their biotransformation [1]. As

free radicals are commonly involved in the mechanisms of aggression, causing hepatic necrosis [1,3,4], administration of antioxidant compounds could contribute in limiting the oxidative damage related to these hepatitis induced drugs.

For the time being, conventional medicine provides very few drugs that could effectively protect liver against hepatitis induced drug, scientific studies were conducted for novel natural hepatoprotective substances. For this purpose, several medicinal plants like *Alchornea cordifolia* were investigated [5-7] which methanolic and ethanol extracts showed hepatoprotective properties in an hepatotoxicity induced animal model using high dose of paracetamol or carbon tetrachloride [7-9].

Our previous studies demonstrated that the aqueous and methanolic leaf extracts of *A. cordifolia* normalized the biochemical parameters (AST and ALT) of hepatotoxicity disturbed by antituberculosis drugs administration, moreover the aqueous extract exhibited an in vitro antioxidant activity [10-12].

However, this hepatoprotective effect of *A. cordifolia* leaf extracts was not investigated on liver tissue. The aim of this study was to analyse histological changes of antituberculosis drugs in rat livers and their evolution after administration of the aqueous and methanolic leaf extracts of *A. cordifolia* and to estimate their polyphenol and flavonoid contents.

Materials

Plant materials

This study was carried out on *Alchornea cordifolia* (Schum. and Thonn.) leaves (Euphorbiaceae), collected from Yakassemé in the department of Adzopé, 75 km far from Abidjan, (Côte d'Ivoire). A plant voucher specimen (herbarium N° AC 2016) was deposited at the laboratory of Pharmacology. Plant was identified and authenticated by the National Floristic center of Abidjan (Côte d'Ivoire). Fresh leaves weighing 4204 g were washed and dried for one week in a shaded room at 18°C at the laboratory of Pharmacology, faculty of pharmaceutical and biological sciences (University of Félix Houphouët-Boigny). Then, dried leaves weighing 1703 g were grounded to powder.

Animal materials

Naïve albino wistar rats of the strain *Rattus norvegicus* of both sex, weighing between 150 and 250 g were used for the experiment. They were provided by the animal husbandry of the Laboratory of pharmacology, faculty of pharmaceutical and biological sciences (University of Félix Houphouët-Boigny, Côte d'Ivoire). Animals were maintained in controlled environmental conditions (24 ± 1°C) and a 12-hour dark / light cycle and were allowed free access to food and water *ad libitum*. They were fed with animal food pellets from a Food Manufacturing Company in Côte d'Ivoire (FACI®). Prior to experiment, animals were kept fasted for 12 hours with free access to water.

Chemicals, reagents and solvents

A wide range of chemicals, reagents and solvents were used for this study namely isotonic saline 0.9%, diethyl ether (Gifrer), distilled water, antituberculosis drugs (Isoniazid (Lupin LTD), Rifampicin (Remedica LTD), Pyrazinamide (Cadila Pharmaceuticals Limited)); formaldehyde, ethanol, toluene, liquid kerosene, Harris hematoxylin, eosin, xylene, lithium carbonate, eukitt, acetified water, phosphomolybdic acid, Folin-Ciocalteu reagent, calcium carbonate, gallic acid, sodium nitrite, aluminum chloride and soda.

Methods

Extract preparation

Dried leaf powder of plant (100 g) was macerated for 24 hours in 1 L of distilled water for the aqueous extract or in 1 L mixture of methanol-water (70:30) for the methanolic extract. The mixture was filtered on cotton and then on filter paper (WHATMAN). Filtrate was dried in an oven at 60 °C for 72 hours for the aqueous extract and evaporated using a rotary evaporator for the methanolic extract. Dry residue obtained was scraped off with a spatula and collected in clean flasks and kept at 4 °C for experiments. This residue was used to prepare stock solutions of the aqueous or methanolic extracts of *A. cordifolia*. Concentrations used for this study were 80 mg/ml, 40 mg/ml and 20 mg/ml respectively for doses of 800 mg/kg, 400 mg/kg and 200 mg/kg for each type of extract. Experiment doses were determined according to our previous study [12].

Effect of extracts on hepatic lesions induced by antituberculosis drugs

This study consisted in inducing hepatotoxicity in laboratory rats using high dose of antituberculosis drugs in different combinations [1,13] for 10 days.

Effect of aqueous and methanolic leaf extracts of *A. cordifolia* alone on liver

Forty two (42) rats of both sexes were randomly divided into 7 groups of 6 animals each and daily treated with different substances for 10 consecutive days as follows: Group I (negative control) received normal saline; Groups 2, 3 and 4 treated with aqueous extract of A cordifolia (AEAc) at doses of 200 mg/kg/day, 400 mg/kg/day or 800 mg/kg/day; Group 5, 6 and 7 were administered the methanolic extract of A cordifolia (MEAc) at doses of 200 mg/kg/day, 400 mg/kg/day or 800 mg/kg/day. Substances were given to animals by oral route.

Effect of aqueous and methanolic leaf extracts of *A. cordifolia* on isoniazid-induced liver injury

Fifty four (54) rats of both sexes were divided into 9 groups of 6 animals each and were daily treated for 10 consecutive days by different substances as follows: Group 1, received normal saline; Group 2 was administered INH (100 mg/kg/day) ; Groups 3, 4 and 5 were treated with (MEAC) at doses of 200, 400 and 800 mg/kg/day, 2 hours after administration of INH (100 mg/kg/day); Groups 6, 7 and 8 received (AEAC) at doses of 200, 400 and 800 mg/kg/day, 2 hours after administration of INH (100 mg/kg/day); Group 9 was treated with silymarin (100 mg/kg/day) 2 hours after administration of INH (100 mg/kg/day). All animals were given substances through oral route.

Effect of aqueous and methanolic leaf extracts of *A. cordifolia* on hepatic injury induced by the combination of isoniazid and rifampicin

A total of 54 rats of both sexes were divided into 9 groups of 6 animals each and daily treated for 10 consecutive days by different substances as follows: Group 1, was given normal saline; Group 2, received the combination of INH (100 mg /kg / day) + RIF (100 mg/kg/day); Groups 3, 4 and 5 were respectively treated with MEAc at doses of 200, 400 and 800 mg/kg/day, 2 hours after administration of the combination INH (100 mg/kg/day) + RIF (100 mg /kg /day); Groups 6, 7 and 8 respectively received AEAc at doses of 200, 400 and 800 mg/kg/day, 2 hours after being given the combination INH (100 mg/kg/day) + RIF (100 mg/kg/day); Group 9 was given silymarin (100 mg/kg/day), 2 hours after receiving the combination INH (100 mg/kg/day) + RIF (100 mg/kg/day). All animals received substances by oral route.

Effect of aqueous and methanolic leaf extracts of *A. cordifolia* on hepatic injury induced by the combination of isoniazid, rifampicin and pyrazinamide

Forty four (54) rats of both sexes were divided into 9 groups of 6 animal each and daily received for 10 consecutive days different substances as follows: Group1, received normal saline; Group 2 was administered the combination INH (100 mg/kg/day) + RIF (100 mg/kg/day) + PZA (100 m/kg/day) ; Group 3, 4 and 5 were respectively given MEAc at doses of 200, 400 and 800 mg /kg / day, 2 hours after administration of the combination INH (100 mg/kg/day) + RIF (100mg/kg/day) + PZA (100 mg /kg/day) ; Groups 6, 7 and 8 were respectively treated with AEAc at doses of 200, 400 and 800 mg/kg/day, 2 hours after administration of the combination INH (100 mg/kg/day) + RIF (100 mg/kg/day) + PZA (100 mg/kg/day); Group 9 was given silymarin 100 mg/kg/day, 2 hours after administration of the combination INH (100 mg/kg/day) + RIF (100 mg/kg/day) + PZA (100 mg/kg/day). All animals were given substances by oral route.

On completion of 10 days experimentation, animals were sacrificed under diethyl ether anesthesia, livers of all animals were collected, washed with cold saline solution and blotted with filter paper. They were then fixed in a 10% formalin solution for histological analysis.

Liver histopathological examination

The histopathological examination was designed for a gross examination of liver whole organ and then performed microscopic examination of liver tissues after staining each cell structure [14]. The histopathological study was carried out as follow: fixation of liver tissue structures by 10% formalin; macroscopic examination; inclusion in paraffin using an automatic tissue machine; slicing of liver into thin sections of 3 to 5 µm using a microtome, then spread on slides; staining of slides with haematoxylin-eosin. Cell changes were considered minimal when they occurred on 1/3 of the observation field, moderate if they occupy half of the observation field, and severe if they occupy more than half of the observation field.

Determination of total polyphenols and flavonoids

Total polyphenol content in extracts was determined by the method of Singleton et al. (1965) [15] using the Folin-Ciocalteu reagent. Whereas flavonoid quantification was done using an adapted method by Zhishen et al. (1999) [16] with aluminium trichloride and soda.

Ethical considerations

Animals were used according to international ethical principles on animal experiments [17].

Statistical analysis

The results were expressed as mean ± SD. Statistical analysis used the Wilcoxon test. The difference between the mean values was considered significant if $p < 0.05$.

Results

Drying and extraction yield

Fresh weight of leaves was 4204 g and dry weight of leaves was 1703 g with a drying yield of 40.51%. Extraction with 70% methanol (MEAc) provided 15.96 g of dried residue for 100 g leaf powder, giving a drying yield of 15.96%. The dry residue from aqueous extraction (AEAc) was 8.14 g for 100 g of leaf powder, with a yield of 8.14%.

Results of histopathological analysis

Animal liver structures were observed and represented in Figures 1 to 4. Abnormalities observed were elementary lesions of clarification, ballooning, acidophilic necrosis, peliosis and micro and macrovacuolar steatosis. Table 1 below showed different elementary lesions, we should notice that a same rat liver can associate several lesions at the same time.

Results of histopathological analysis of unintoxicated liver

Observation of the section of unintoxicated rat liver showed in figure 1a a normal hepatic parenchyma with regular rows of hepatocytes, a portal space and a centrolobular vein.

Table 1: Elementary lesions observed with tuberculosis drugs and total number of livers.

	Clarification	Ballooning	Acidophilic necrosis	Peliosis	Steatosis
INH	1/6 (16,67%)	1/6 (16,67%)	4/6 (66,67%)	2/6 (33,33%)	2/6 (33,33%)
INH+RIF	3/6 (50%)	1/6 (16,67%)	3/6 (50%)	1/6 (16,67%)	2/6 (33,33%)
INH+RIF+PZA	0/6 (0%)	0/6 (0%)	2/6 (33,33%)	3/6 (50%)	2/6 (33,33%)

Results of extract effects alone on liver histology

Microphotography of liver sections receiving *A. cordifolia* extracts alone were confined in Figures 1b and 1c. They showed a normal liver structure with no particularities.

Histopathology results of isoniazid-intoxicated liver receiving *A. cordifolia* extracts

Figure 2a showed the microphotography of INH intoxicated liver rats with acidophilic necrosis and inflammatory infiltrate. Sections of INH intoxicated liver rats treated with MEAc at doses of 800 mg/kg and 400 mg/kg or AEAc at a dose of 800 mg/kg were represented in Figures 2b, 2c and 2d and showed normal liver parenchyma. Howerver, the other doses of extracts had no effect on INH-induced hepatocyte lesions in the same way as MEAc at 200 mg/kg, AEAc at 400 mg/kg and AEAc at 200 mg/kg with liver microphotography of rats showing micro and macrovacuolar steatosis (Figures 2e and 2f), clarification, sinusoidal dilatation and steatosis (Figures 2g).

Results of histopathology of liver intoxicated by the association isoniazid + rifampicin receiving extracts of *A. cordifolia*

Observation of the section of INH+RIF intoxicated liver rat showed in Figure 3a a clarification, a moderate

acidophilic necrosis with trabecular disorganization and hepatocytes associating micro and macrovacuolar steatoses. Microphotographies of sections of INH+RIF intoxicated liver rat treated with MEAc at doses of 800 mg/kg and 400 mg/kg or AEAc at a dose of 800 mg/kg represented in Figures 3b, 3c and 3d, showed a liver structure with regular rows for MEAc (800 mg/kg), minimal steatosis with MEAc (400 mg/kg) and minimal clarification and ballooning with AEAc (800 mg/kg). Livers of rats intoxicated with INH+RIF and treated with AEAc (400 mg/kg) or MEAc (200 mg/kg) showed clarification and ballooning also acidophilic necrosis with trabecular disorganization (Figures 3e and 3f).

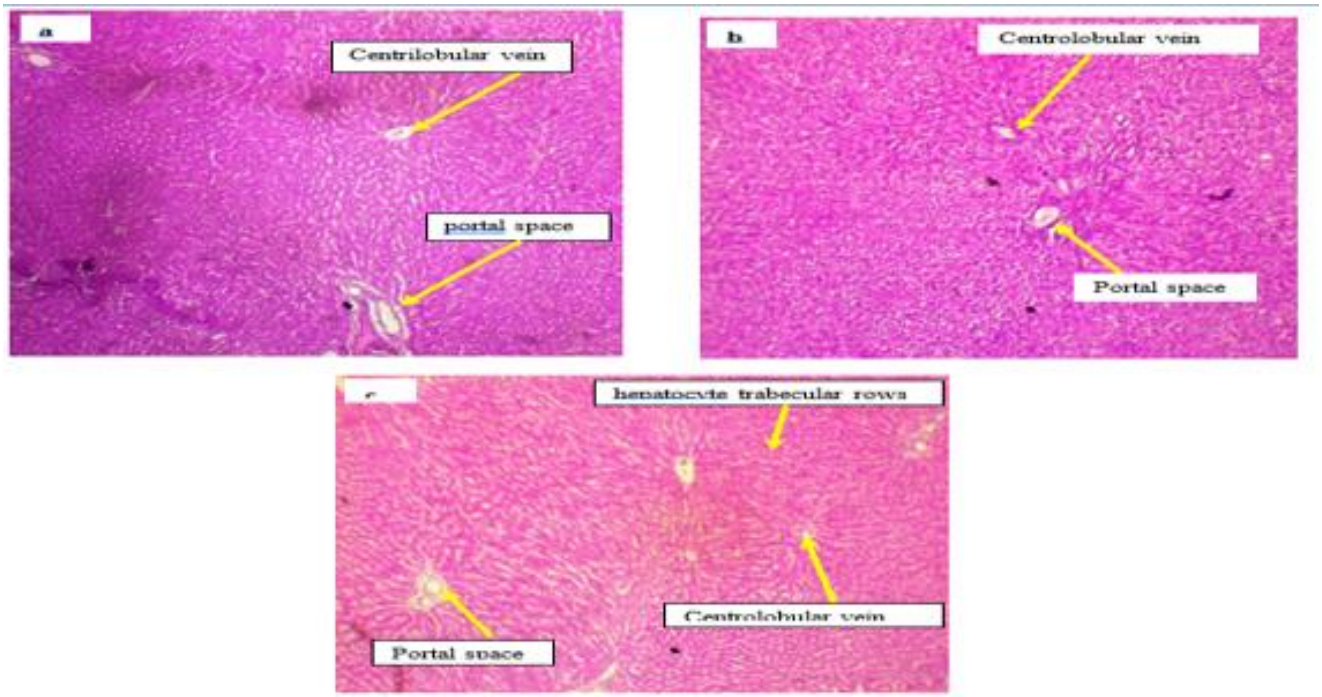

Figure 1: Microphotography of non-intoxicated rat liver by antituberculosis drugs. **1a** (HE x 250): Liver of non-intoxicated control rat showing normal hepatic parenchyma with portal space and centrilobular vein; **1b** (HE x 250): Liver of rat treated with MEAc (800 mg/kg) showing normal hepatic parenchyma with portal space and centrilobular vein; **1c** (HE x 250): Liver of rat treated with AEAc (800 mg/kg) showing normal hepatic parenchyma with portal space, centrilobular vein and hepatocyte trabecular rows. MEAc: Methanolic extract of *A. cordifolia*; AEAc: aqueous extract of *A. cordifolia.*

Results of liver histology intoxicated by the combination isoniazid + rifampicin + pyrazinamide and treated by A cordifolia extracts.

Figure 4a showed a section of a rat liver intoxicated by INH+RIF+PZA, exhibiting peliosis, foci of dilated sinus capillaries and acidophilic necrosis. Sections of liver intoxicated with INH+RIF+PZA and treated with MEAc at doses of 800 mg/kg and 400 mg/kg, AEAc (800 mg/kg) or AEAc (400 mg/kg) were respectively represented in Figures 4b, 4c, 4d and 4e, showed a dilatation of the centrilobular vein with MEAc at 800 mg/kg, steatosis with MEAc at 400 mg/kg, peliosis and clarification with AEAc at 800 mg/kg ; steatosis and peliosis with AEAc at 400 mg/kg.

Total polyphenol and flavonoid contents

Total polyphenol content of each extract was expressed in mg equivalent gallic acid per gram of extract (mg EGA / g). MEAc contained 0.055 ± 0.002 mg EGA / g and AEAc contained 0.035 ± 0.001 mg EGA / g. This difference in value is statistically significant (p = 0.02). The flavonoid content of the aqueous and methanolic extracts of *A. cordifolia* was expressed in mg quercetin equivalent per gram of extract (mg QE/g). MEAc contained 0.054 ± 0.002 mg QE/g, and AEAc contained

0.048 ± 0.001 mg QE/g with a non-significant difference (p = 0.06).

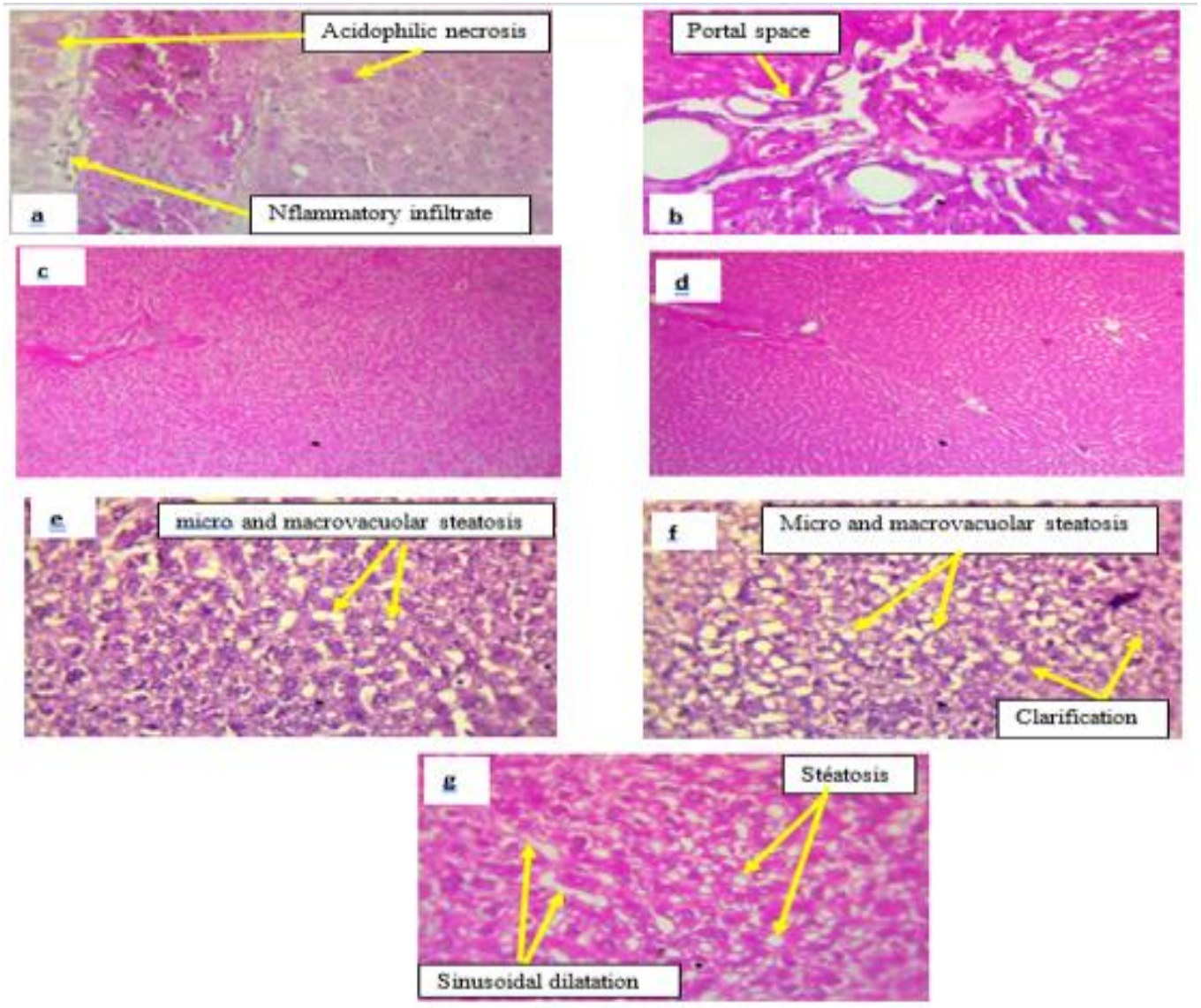

Figure 2: Microphotography of rat liver intoxicated by isoniazid and treated or untreated with extracts**. 2a** (HE x 400): Liver of rat intoxicated by isoniazid, showing acidophilic necrosis and inflammatory infiltrate; **2b** (HE x 400): Liver of rat intoxicated by Isoniazid and treated with MEAc 800 mg/kg, showing portal space and disappearance of isoniazid-induced necrosis; **2c** (HE x 250): Liver of rat intoxicated by isoniazid and treated with AEAc (800 mg/kg), showing normal structure; **2d** (HE x 250): Liver of rat intoxicated by isoniazid and treated with MEAc (400 mg/kg) , showing normal structure; **2e** (HE x 400): Liver of rat intoxicated by isoniazid and treated with AEAc 400 mg/kg, showing micro and macrovacuolar steatosis; **2f** (HE x 400): Liver of rat intoxicated by isoniazid and treated with MEAc (200 mg/kg), showing micro and macrovacuolar steatosis; **2g** (HE x 400): Liver of rat intoxicated by isoniazid and treated with AEAC (200 mg/kg), showing sinusoidal dilatation and steatosis; **2g** (HE x 400): Liver of rat intoxicated by isoniazid and treated with AEAc (200 mg/kg), showing sinusoidal dilatation and steatosis.

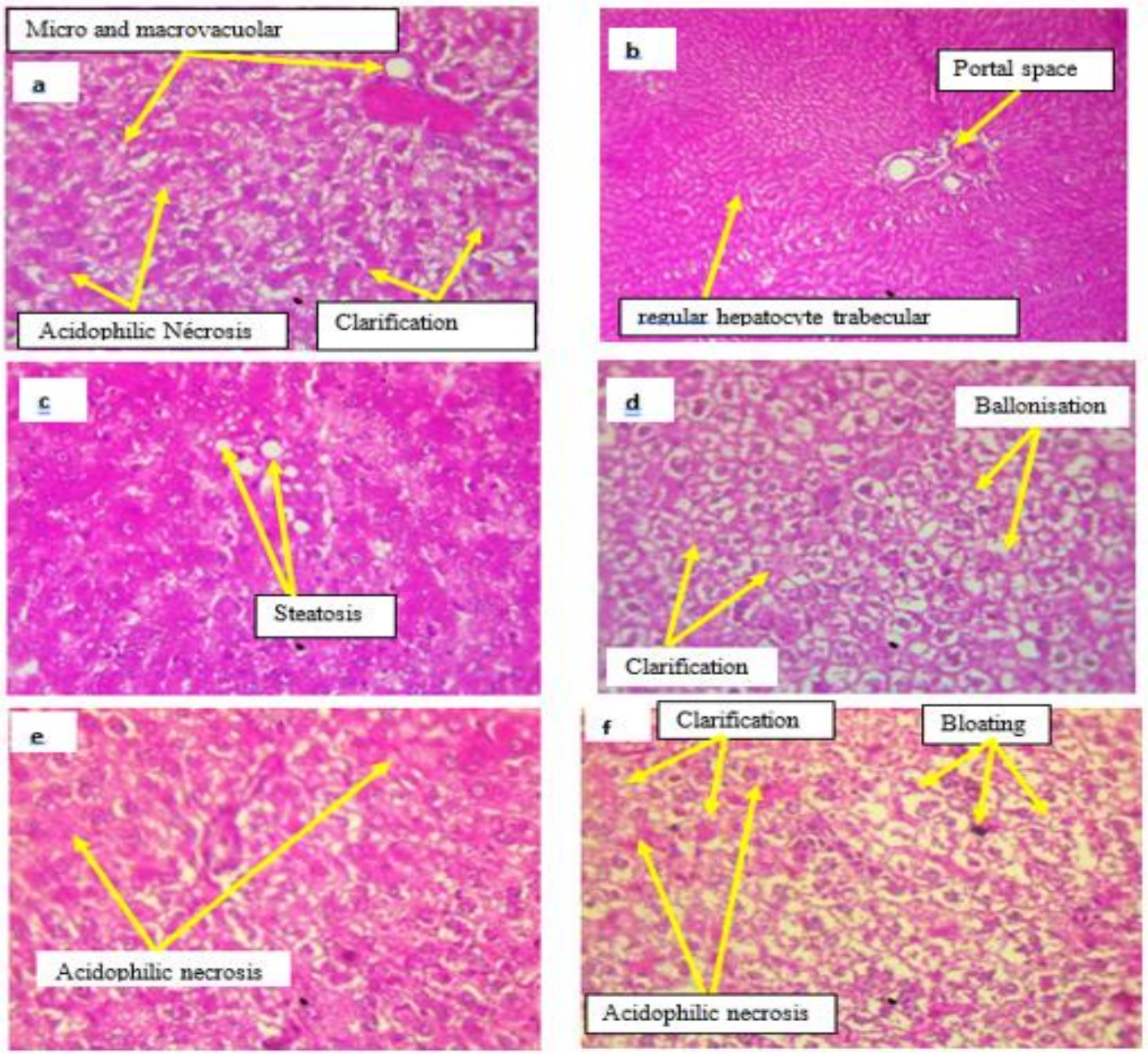

Figure 3: Microphotography of rat liver intoxicated by isoniazid+rifampicin and treated or untreated with extracts. 3a (HE x 400): Liver of rat intoxicated by isoniazid and rifampicin, showing acidophilic necrosis, micro and macrovacuolar steatosis and clarification lesions; 3b (HE x 250): liver of rat intoxicated by isoniazid and rifampicin and treated with MEAc (800 mg/kg), showing regular hepatocyte trabecular and portal space; 3c (HE x 400): liver of rat intoxicated by isoniazid and rifampicin and treated with MEAc (400 mg/kg), showing minimal steatosis; 3d (HE x 400): Liver of rat intoxicated by isoniazid and rifampicin and treated with AEAc (800 mg/kg), showing lesions of clarification and ballooning; 3e (HE x 400): Liver of rat intoxicated by isoniazid and rifampicin and treated with AEAc (400 mg/kg), showing foci of acidophilic necrosis, clarification and ballooning with trabecular disorganization; 3f (HE x 400): Liver of rat intoxicated by isoniazid and rifampicin and treated with MEAc (200 mg/kg), showing foci of acidophilic necrosis, clarification and bloating with trabecular disorganization.

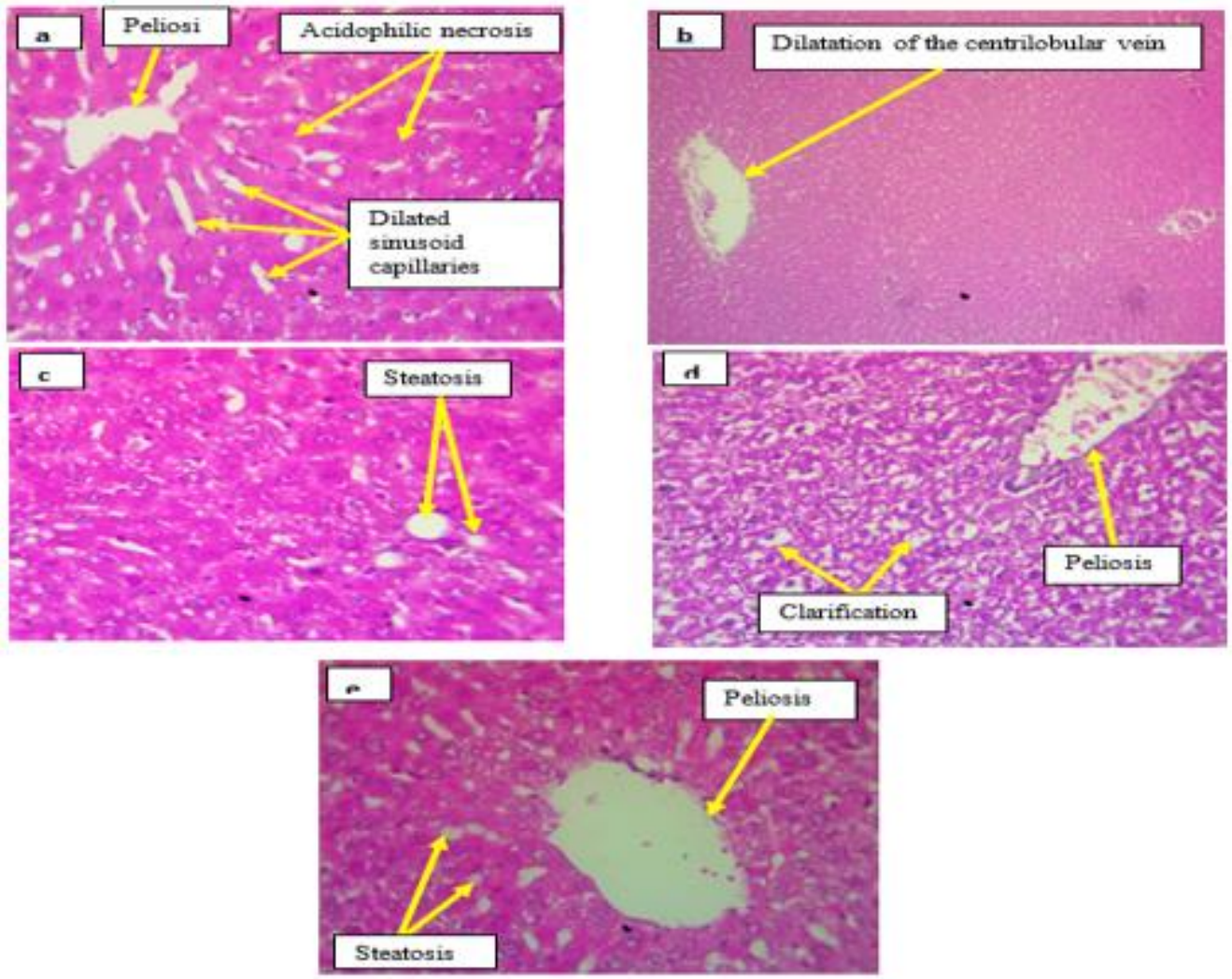

Figure 4: Microphotography of rat liver intoxicated by isoniazid + rifampicin+ pyrazinamide and treated or untreated with extracts. 4a (HE x 400): liver of rat intoxicated by isoniazid + rifampicin + pyrazinamide, showing peliosis, foci of dilated sinusoid capillaries and acidophilic necrosis; 4b (HE x 250): Liver of rat intoxicated by isoniazid, rifampicin and pyrazinamide and treated with MEAc (800 mg/kg), with dilatation of the centrilobular vein; 4c (HE x 400): Liver of rat intoxicated by isoniazid, rifampicin and pyrazinamide and treated with MEAc 400 mg/kg, showing steatosis; 4d (HE x 400): Liver of rat intoxicated by isoniazid, rifampicin and pyrazinamide and treated with AEAc 800 mg/kg, showing clarification and peliosis; 4e (HE x 400): Liver of rat intoxication by isoniazid, rifampicin and pyrazinamide and treated with AEAc (400 mg/kg), showing steatosis and peliosis.

Discussion

Tuberculosis drugs administered in this study were toxic to the liver. Isoniazid caused acidophilic necrosis lesions and inflammatory infiltrate; isoniazid and rifampin caused clarification, acidophilic necrosis, steatosis and trabecular disorganization; and isoniazid, rifampin and pyrazinamide caused peliosis lesions, foci of sinus capillary dilation and acidophilic necrosis. Various animals and human case studies showed that hepatotoxicity induced by the combination of antituberculosis drugs was mainly manifested by hepatocellular steatosis and centrilobular necrosis associated with cholestasis, by covalent binding of drug molecules to cellular macromolecules [18]. Administration of *A. cordifolia* extracts, such as the methanolic extract at doses of 400 mg/kg and 800 mg/kg and the aqueous extract at a dose of 800 mg / kg, reduced damage caused by these antituberculosis drugs as shown in the histopathological study. The methanolic extract, at all doses, prevented isoniazid-induced necrosis lesions and inflammatory infiltrate. As for the

aqueous leaf extract of *A. cordifolia* at a dose of 200 mg/kg, it did not protect the liver. However, at high doses the aqueous leaf extracts of *A. cordifolia* (400 mg/kg and 800 mg/kg) combined with isoniazid clearly protected the liver since histological sections did not reveal any lesions. Histopathology images of rat livers treated with isoniazid + rifampicin and methanolic extract (800 mg/kg) were examined, the hepatocellular lesions disappeared and the hepatocyte trabecular came to normalcy. With the methanolic extract at 400 mg/kg, a minimal steatosis still persists. The methanolic extract at a dose of 200 mg/kg had no effect on the histological damage caused by the combination of isoniazid and rifampicin. The aqueous extract at a dose of 800 mg/kg, showed a regression of acidophilic necrosis and the microphotography showing only a clarification and ballooning. The other doses of the aqueous extract failed to protect the liver. As for the association isoniazid + rifampicin + pyrazinamide, there was peliosis, acidophilic necrosis and dilatation of sinusoid capillaries which were attenuated by *A. cordifolia* extracts. Indeed, microphotographies of rat livers treated with the methanolic extract at a dose of 800 mg/kg showed only dilatation of the centrolobular vein with resorption of peliosis and acidophilic necrosis. Like the methanolic extract at a dose of 400 mg/kg, showing a disappearance of peliosis and acidophilic necrosis with a persistence of steatosis. The aqueous extract at doses of 800 mg/kg and 400 mg/kg did not seem to have protected the liver because liver photomicrographies still show foci of peliosis, clarification and steatosis. However, these extracts administered alone, did not cause necrosis, clarification, ballooning or hepatic steatosis. The microphotography of rat livers that received the extracts alone did not show any biochemical parameter disturbances. The results of this study were in agreement with the study of Jacob et al (2014), [9] in which *A. cordifolia* attenuated hepatocellular lesions induced by paracetamol at high doses. However, Ajibade and Olayemi (2015) [19] showed that methanolic extract of *A. cordifolia*, administered alone at doses of 800 mg/kg and 1600 mg/kg for 8 consecutive days, caused hepatocellular damage. However, *A. cordifolia* is considered to be a plant with a high margin of safety in single administration [20].

Furthermore, during extraction, 70% methanol was used as for Ajibade and Olayemi (2015) [19] who used pure methanol. The low methanol concentration could explain the non-toxic effect of our extract. The harvest location could back up the non- toxic effect of our extract at 800 mg/kg. Indeed, A cordifolia was harvested for this study in its natural environment in Côte d'Ivoire while Ajibade and Olayemi (2015) [19] harvested it in a botanical garden in Nigeria. It was the same case with the plant studied by Jacob et al (2014) [9] which was harvested in its natural environment on uncultivated agricultural land. Protective effects against hepatocellular damage were observed with the methanolic extract of *A. cordifolia* at doses of 400 mg/kg and 800 mg/kg, as well as with the aqueous extract at a dose of 800 mg/kg. This superiority of activity of the methanolic extract could be partly justified by the higher total polyphenol content in the methanolic extract compared to the aqueous extract. Indeed, the methanolic extract was found to be richer in total polyphenols (0.055 ± 0.002 mg EGA) than the aqueous extract (0.035 ± 0.001 mg EGA). Studies showed that the presence of polyphenols conferred its antioxidant activity [21]. Manga et al (2004) [22-24] also found that flavonoids had antioxidant activities.

Conclusion

Histopathological analysis of rat livers that received the aqueous and methanolic leaf extracts of *A. cordifolia* after intoxication with antituberculosis drug combination, showed extracts ability to annihilate or attenuate hepatocellular damage of antituberculosis drugs. This observed protection against hepatocellular damage was most pronounced with the methanolic extract of *A. cordifolia* at doses of 400 mg/kg and 800 mg/kg, as well as the aqueous extract (800 mg/kg). This high activity of the methanolic extract could be partly justified by the higher total polyphenol content in the methanolic extract compared to the aqueous extract. Thus, the aqueous and methanolic leaf extracts of *A. cordifolia* significantly reduced hepatotoxicity induced by antituberculosis drugs in rats.

Acknowledgement

We express our gratitude to the head of department of the pathological anatomy laboratory of the UFR Medical Sciences of Abidjan, Pr Diomandé Mohenou I. Jean-Marie and to all his team, for helping us in carrying out this work.

Conflicts of Interests

The authors declare no conflict of interest.

Funding

None declared.

References

1. Santhosh S, Sini TK, Anandan R, et al. Hepatoprotective activity of chitosan against isoniazid and rifampicin-induced toxicity in experimental rats. Eur J Pharmacol 2007; 572: 69-73.
2. Akindele AJ, Ezenwanebe KO, Anunobi CC, et al. Hepatoprotective and in vivo antioxidant effects of Byrsocarpus coccineus Schum. And Thonn (Connaraceae). J Ethnopharmacol 2010; 129: 46-52.
3. Georgieva N, Gadjeva V, Tolekova A. New isonicotinoylhydrazones with SSA protect against oxidative-hepatic injury of isoniazid. Trakia J Sci 2004; 2: 37-43.
4. Pramod K, Deva RG, Lakshmayya, Ramachandra SS. Antioxidant and hepatoprotective activity of tubers of Momordica tuberose Cogn. against CCl4 induced liver injury in rats. Ind J Exp Biol 2008; 46: 510-513.
5. Olaleye MT, Adegboye OO and Akindahunsi AA. *Alchornea cordifolia* extract protects wistar albino rats against acetaminophen-induced liver damage. Afr J Biotechnol 2006; 5: 2439-2445.
6. Kouakou-Siransy G, Sahpaz S, N'guessan GI, et al. Effects of *Alchornea cordifolia* on elastase and superoxide anion produced by human neutrophils. Pharm Biol; 2010; 48: 128-133.
7. Osadebe PO, Okoye FBC, Uzor PF, et al. Phytochemical analysis, hepatoprotective and antioxidant activity of *Alchornea cordifolia* methanol leaf extract on carbon tetrachloride-induced hepatic damage in rats. As Pac J Trop Med; 2012: 289-293.
8. Olaleye MT, Kolawole AO and Ajele JO. Antioxidant Properties and Glutathione S Transferases Inhibitory Activity of *Alchornea cordifolia* Leaf Extract in Acetaminophen-Induced Liver Injury IJPT; 2007; 6: 63-66.
9. Jacob JM, Olaleye MT, Olugbuyiro JAO. Hepatoprotective effect of *Alchornea cordifolia* leaf on liver damage in albino rats. Int J Appl Sci Biotechnol 2014; 2: 217-221.
10. Etienne EK, Landry KS, Geneviève IGA, et al. Hepatoprotective effects of methanol extract of *Alchornea cordifolia* leaves against anti-tubercular drugs induced hepatotoxicity in rats. Afr J Pharm Pharmacol 2017; 11: 501-508.
11. Effo KE, Kouakou SL, Irie-N'Guessan G, et al. Antioxidant Activity and Hepatoprotective Effect of an Aqueous Extract of *Alchornea cordifolia* Leaves. Pharmacol & Pharmacy 2017; 8: 369-380.
12. Effo KE, Kouakou-Siransy G, Irie-Nguessan G, et al. Acute toxicity and antipyretic activities of a methanolic extract of *Alchornea cordifolia* leaves. Pharmacol Pharm 2013; 4: 1-6.
13. Saraswathy SD, Suja V, Prema G, et al. Effect of Liv. 100 against antitubercular drugs (isoniazid, rifampicin and pyrazinamide) induced hepatotoxicity in rats. Ind J Pharmacol 1998; 30: 233-238.
14. Redman RS, Ball WD, Mezey E, et al. Dispersed donor salivary gland cells are widely distributed in the recipient gland when infused up the ductal tree. Biotech Histochem 2010; 84: 253-260.
15. Singleton VL, Rossi JA. Colorimetry of total phenolics with phosphomolybdic-phosphotungstic acid reagents. Am J Technol and Viticult 1965; 16: 144-153.
16. Zhishen J, Mengcheng T et Jianming W. The determination of flavonoid contents in Mulberry and their scavenging effects on superoxide radicals. Food Chem 1999; 64: 555-559.
17. Veissier I. Expérimentation animale: biologie, éthique, réglementation. INRA Prod. Anim 1999; 12: 365-375.
18. Tostmann A, Boeree MJ, Aarnoutse RE, et al. Antituberculosis drug-induced hepatotoxicity: Consise up-to-date review. Gastroenterol Hepatol 2008; 23: 192-202.
19. Ajibade TO et Olayemi FO. Reproductive and toxic effects of methanol extract of *Alchornea cordifolia* leaf in male rats. Andrologia 2015; 47 :1034-1040.
20. OCDE. Système intégré harmonisé de classification des dangers pour la santé humaine et les effets environnementaux des substances chimiques. Organisation de coopération et de développement économiques 1998; Paris, France.
21. Shiney RB, Ganesh P. Phytochemical analysis and comparative effect of Cinnamomum zeylanicus, Piper nigrum and Pimpinella anisum with selected antibiotics and its antibacterial activity against Enterobacteriaceae family. Int J Pharmac and Biol Arch 2012; 3: 914-917.
22. Manga HM, Brkic D, Marie DEP, et al. In vivo anti-inflammatory activity of *Alchornea cordifolia*. J Ethnopharmacol 2004; 92: 209-214.
23. Jahangir MA, Anand C, Muheem A, et al. Nano Phytomedicine Based Delivery System for CNS Disease. Curr Drug Metabol 2020.
24. Muheem A, Jahangir MA, Jaiswal CP et al. Recent Patents, Regulatory Issues and Toxicity of Nanoparticles in Neuronal Disorders. Curr Drug Metabol 2020.

Citation: *Effo KE, N'Da KJ, Abouna AD et al. Effect of Alcornea cordifolia aqueous and methanolic leaf extracts against antituberculosis drugs induced liver damage in rats. Int J Pharm Pharmacol 2021; 5: 151. doi: 10.31531/2581-3080.1000151*

This manuscript was peer-reviewed
Mode of Review: Single-blinded
Academic Editor: Dr. Bijaya Kumar Mohanty