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BIOLOGICAL EFFECT OF THE TOTAL AQUEOUS EXTRACT OF THE LEAVES OF *DESMODIUM ADSCENDENS* (SWARTZ) DC ON HEPATOTOXICITY INDUCED WITH PARACETAMOL IN *WISTAR* RATS

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ABSTRACT

Context and Objective: Hepatitis, today has become a deadly disease despite the modern medicine. This reason pushed people to use medicinal plants. In this work, the hepato-protective activity *Desmodium adscendens* leaves was so studied, after paracetamol overdose in *Wistar* rats. **Methodology**: Thirty-six (36) rats are divided in six groups with six rats each. The group 1 received distilled water; we administered paracetamol 200 mg/kg BW in the group 2; the group 3 received paracetamol 200 mg/kg BW followed by vitamin C 100 mg/kg BW; the group 4 received paracetamol 200 mg/kg BW followed by the extract 100 mg/kg BW; we administered paracetamol 200 mg/kg BW followed by the extract 200 mg/kg BW in the group 5 and the group 6 received paracetamol 200 mg/kg BW followed by the extract 400 mg/kg BW. Fifteen days are used to induce hepatitis and fifteen more days for the treatment. We collected the blood samples on the 2nd, 17th and 32nd day. Rats are subsequently sacrificed, the livers removed to study the physical characteristics. **Results**: Our results showed a dose-dependent action of the total aqueous extract. The total extract at 400 mg/kg BW reduced significantly the levels of transaminases (aspartate amino transferase (ASAT) and alanine amino transferase (ALAT)), alkaline phosphatase and blood sugar compared to the group of rats treated only with paracetamol. However, the decreasing action of the aqueous extract on

direct bilirubin and total bilirubin is slight. The total aqueous extract almost restored the physical characteristics (weight, color, consistency and texture) of the liver poisoned following an overdose of paracetamol. **Conclusion**: These studies showed the hepatoprotective effect of the total aqueous extract of the leaves of *Desmodium adscendens*.

KEYWORDS: *Desmodium adscendens*, Hepatitis, Paracetamol.

INTRODUCTION

The liver is the most important of the accessory glands of the digestive tract and constitutes the organ through which all substances reaching the bloodstream pass. It is therefore exposed to different aggressions causing hepatitis capable of reacting negatively on the entire body.[1] In Ivory Coast, in the general population the prevalence of hepatitis C is 3.3%[2] and that of hepatitis B is 12%.[3] The treatments of hepatitis B and C, despite these scary numbers are limited.[4] To treat hepatitis, antiviral drugs are generally used which help control the progression of the disease by suppressing the reproduction of the virus in the liver of most treated patients.[2]

The treatment of hepatitis requires a long time with the expensive hospital stays, and the expected results are very often unsatisfactory.[4] Faced with this situation, the traditional medicine has become an ultimate solution for populations to relieve the hepatitis.[5] Our study was realized on *Desmodium adscendens.* The leaves of this plant is regularly used by ivorian populations from the center-west to treat inflammations such as hepatitis. This work aims to provide a scientific basis for the use of this plant, by evaluating the hepato-protective properties of the aqueous extract of its leaves after inducing hepatitis with the paracetamol in rats. It is also about promoting local flora in the treatment of diseases that modern medicine has difficulty curing.

MATERIEL AND METHODS

Material

Plant material

The leaves of *Desmodium adscendens* constituted the plant material. The harvest was carried out in Daloa (center-west of Ivory Coast).

Animal material

The animals used in our experiments are male and female albino rats of the *Rattus norvegicus* species. These rats weighed between 156 and 211 g and had eight weeks. Pellets from the company FACI® are used to feed the rats. The Laboratory of Physiology, Pharmacology and Pharmacopoeia of Nangui Abrogoua University was the place of the manipulations. Our different experimental protocols are used in accordance with the protocols for the protection of laboratory animals of the European Council of Legislation 87/609/EEC.[6]

Methods

Preparation of the aqueous extract of the leaves of *Desmodium adscendens*

The method of[7] was used to prepare the total aqueous extract of *Desmodium adscendens* leaves. The leaves of *Desmodium adscendens* were washed and dried away from the sun. The dried leaves were reduced to obtain a fine powder. One hundred (100) grams of this powder were extracted in one liter of distilled water by decoction for 15 minutes. The cotton and the Whatman filter paper are used to filter the decoction. The evaporation of the filtrate was realized at 50°C. A blackish green powder was obtained and used to prepare the total aqueous extract of the leaves of *Desmodium adscendens* for the hepatoprotective studies.

Studies of the total aqueous extract of the leaves of *Desmodium adscendens*

Preparation of paracetamol solution

We are realized a preliminary study to obtain the toxic dose of paracetamol. Paracetamol tablets (Doliprane® 1000mg (SANOFI)) are dissolved in distilled water and administered to rats to determine the LD_{50}. After the study, 500 mg/kg BW was considered like the LD_{50}. The dose of 200 mg/kg BW was therefore used to induce hepatotoxicity during 15 days like these authors.[8]

Preparation of vitamin C solution

The dose of this solution was used according to.[9] These authors showed the hepatoprotective effect in rats of vitamin C at 100 mg/kg BW.

Preparation of doses of the total aqueous extract of *Desmodium adscendens* leaves

The recommendations the traditional therapists for an adult man per day are been used to prepare the different doses of the total aqueous extract of the leaves of *Desmodium adscendens*. The different doses of 100, 200 and 400 mg/kg BW were therefore prepared to realize the studies.

Administration of solution

According to ODCE protocol 407[10], the volume of substance to be administered to a rat weighing 100 g is 1 or 2 mL.

Experimentation

Induction of hepatitis with paracetamol

The method of[8] was used. Six groups de rats including each three (3) males and three (3) females received the solutions by gavage:

- Group 1: The rats had not received any solution apart distilled water,
- Group 2: 1 mL of paracetamol (Doliprane®) at 200 mg /kg BW has been administered in rats for two weeks,
- Group 3: The animals received 1 mL of the solution of 200 mg/kg BW of paracetamol (Doliprane®) per day for two weeks followed by 1 mL of the solution of 100 mg/kg BW of vitamin C for two weeks,
- Group 4: The rats received 1 mL of the solution of 200 mg/kg BW of paracetamol (Doliprane®) for two weeks followed by 1 ml of the solution of 100 mg/kg BW of the total aqueous extract of the leaves of *Desmodium adscendens* for two weeks,
- Group 5: The rats receive 1 ml of the solution of 200 mg/kg BW of paracetamol (Doliprane®) for two weeks followed by 1 ml of the solution of 200 mg/kg BW of the total aqueous extract of the leaves of *Desmodium adscendens* for two weeks,
- Group 6: The rats received 1 ml of the solution of 200 mg/kg BW of paracetamol (Doliprane®) for two weeks followed by with 1 mL of the solution of 400 mg/kg of BW of the total aqueous extract of the leaves of *Desmodium adscendens* for two weeks.

The solutions were renewed every day to avoid infections. The blood samples are taken on day 2 (before the induction of hepatitis), day 17 (after induction of hepatitis with paracetamol for two weeks in groups 2, 3, 4, 5 and 6) and day 32 (after treatment with vitamin C and the total aqueous extract of the leaves of *Desmodium adscendens* for two weeks in groups 3, 4, 5 and 6).

Method of collection blood samples

The animals are anesthetized with the ether at the end of the treatment and after fasting for 12 hours. Blood is collected from the retro-orbital sinus using sterile syringes for the measurement of biochemical parameters (transaminases, alkaline phosphatase, bilirubin and blood sugar) according to the methods of.[11]

The dry tubes were used to collect blood for the determination of liver biochemical parameters.

Animal sacrifice and organ removal. After blood sampling, the livers were immediately isolated and washed with 0.9% NaCl physiological fluid. The livers are then observed, photographed and weighed. Livers are preserved in 10% formalin.

Studies of the physical characteristics of the liver

- **Calculation of the liver relative weight**

The relative weight (PR) of the liver is calculated in relation to the body weight according to the formula given by[12]:

PR = Liver weight (LW) / Rat weight (RW) X100

PR = Relative weight, LW = Liver weight, RW = Rat weight

- **Macroscopic examination**

This examination is limited to the macroscopic observation of the external structure of the entire liver removed. It takes into account color, consistency and texture.[13]

Color

Color is an important parameter in the diagnosis of liver diseases. Normally, the liver is bright red in color. A change in color indicates the pathological condition of the liver.

Consistency

The normal liver is firm and soft to the touch. An alteration of these aspects indicates an intoxication of the liver.

Texture

Normal liver has a smooth texture. A change in texture indicates a pathological condition.

Statistical analysis

Results are expressed as means ± SEM (Standard Error of Mean). The analysis of variance test (ANOVA 1) will be used to determine the statistical significance of the results ($p < 0.05$). Graphpad Prism 8 Demo and Excel software are used to carry out these statistical tests and graphs.

RESULTS

Effect of the aqueous extract of the leaves of *Desmodium adscendens* on hepatotoxicity induced by paracetamol in rats

Assay of biochemical parameters

Dosage before administration of paracetamol (Day 2)

Dosage of alkaline phosphatase (PAL), total bilirubin (TB) and direct bilirubin (DB)

Normal alkaline phosphatase levels observed are between 88.7 ± 4.7 and 145.7 ± 6.2 U/L. Those of total bilirubin and direct bilirubin are respectively between 311 ± 2.7 and 512.4 ± 8.5 mg/dL, and between 274.7 ± 2.8 and 354.4 ± 8.5 mg/ dL **(figure 1)**.

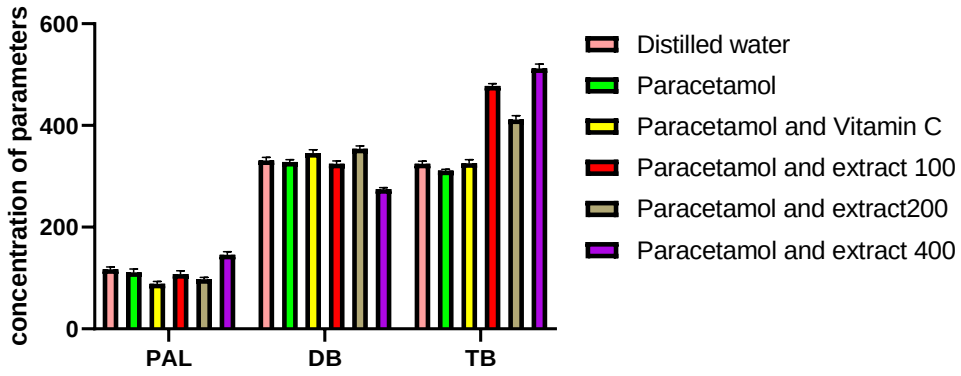


Figure 1: Evolution of PAL, DB and TB on day 2.

Dosage of transaminases (ASAT and ALAT) and blood sugar (BS)

Studies have shown that normal ASAT, ALAT and blood sugar levels are respectively between 16 ± 2.5 and 20.4 ± 5.1 IU/L, between 26.70 ± 6.4 and 32 .4 ± 5.5 IU/L, and between 0.2 ± 0.06 and 0.39 ± 0.1 g/L **(figure 2)**.

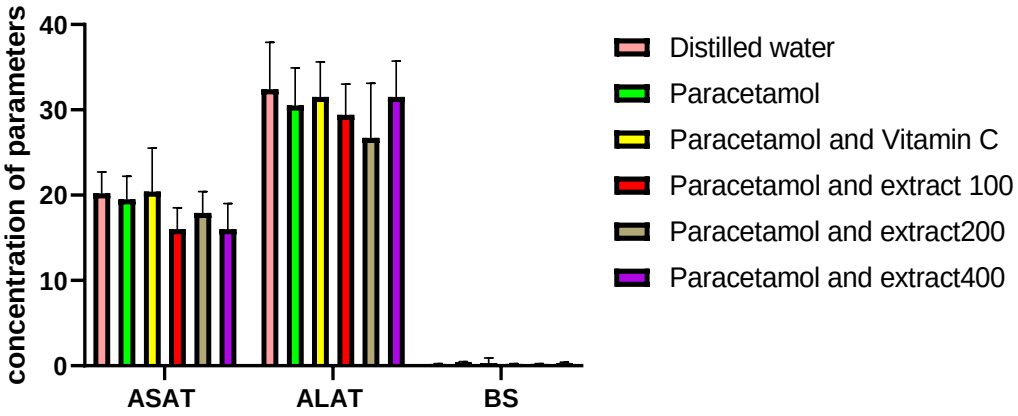


Figure 2: Evolution of ASAT, ALAT and blood sugar on day 2.

Dosage of biochemical parameters after administration of paracetamol (Day 17)

Dosage of alkaline phosphatase (PAL), total bilirubin (TB) and direct bilirubin (DB)

Alkaline phosphatase levels increased significantly after paracetamol administration. A maximum level of 214.4 ± 6.4 U/L is observed in the group of rats which will be treated with the extract at a dose of 400 mg/kg BW. The levels of total bilirubin and direct bilirubin also increased with maximum levels respectively of 747.4 ± 11.2 mg/dL in the group of rats which will be treated with the extract at a dose of 200 mg/kg. PC and 547.5 ± 11.4 mg/dL in the group of rats which will be treated with vitamin C **(Figure 3)**.

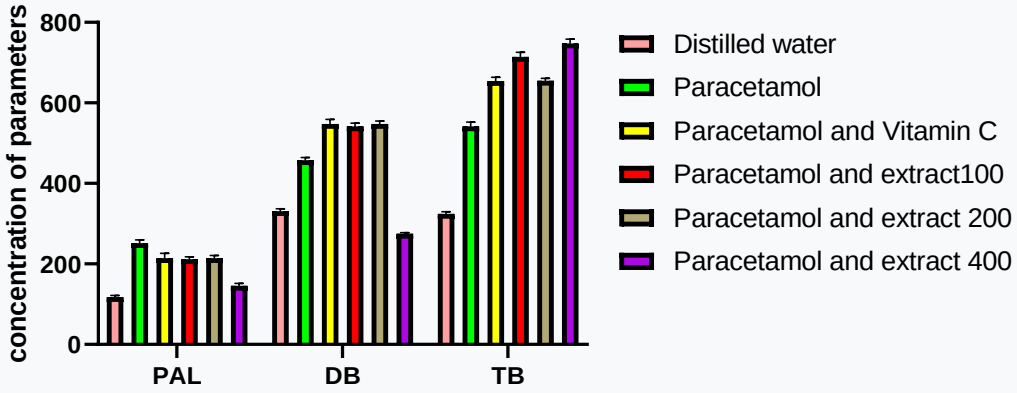


Figure 3: Evolution of PAL, TB and DB on day 17.

Dosage of transaminases and blood sugar (BS)

ASAT, ALAT and blood sugar levels increase after administration of paracetamol with maximum levels respectively of 51.1 ± 2.1 IU/L in the group which receives only paracetamol; of 52.4 ± 4.5 IU/L in the group which received only paracetamol and 0.48 ± 0.5 g/L in the group of rats which will be treated with vitamin C **(figure 4)**.

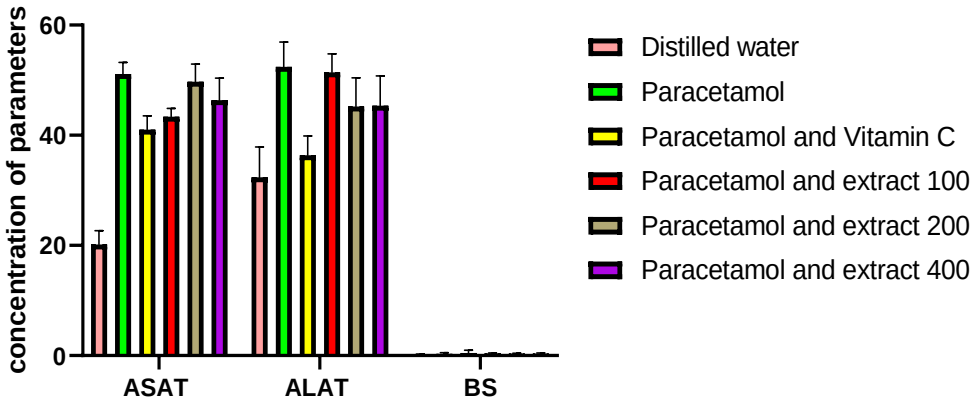


Figure 4: Evolution of ASAT, ALAT and blood sugar on day 17.

Dosage after administration of paracetamol followed by the total aqueous extract of *Desmodium adscendens* leaves (Day 32)

Dosage of alkaline phosphatase (PAL), total bilirubin (TB) and direct bilirubin (DB)

The extract inhibited the action of paracetamol on liver biochemical parameters like the vitamin C. A significant decrease in the level of alkaline phosphatase compared to the group treated only with paracetamol was observed in rats treated with vitamin C and with the extract at the maximum dose of 400 mg/kg BW respectively at percentages of 71, 2% (from 251.4 ± 8.5 to 72.4 ± 6 U/L) and 68.54% (from 251.4 ± 8.5 to 79.1 ± 4.6 U/L). A slight dose-dependent decrease compared to the level of the group treated only with paracetamol of total bilirubin and direct bilirubin was observed with the aqueous extract, respectively at the inhibition rates of 7.42% and 4.39 % at the maximum dose of 400 mg/kg BW **(figure 5)**.

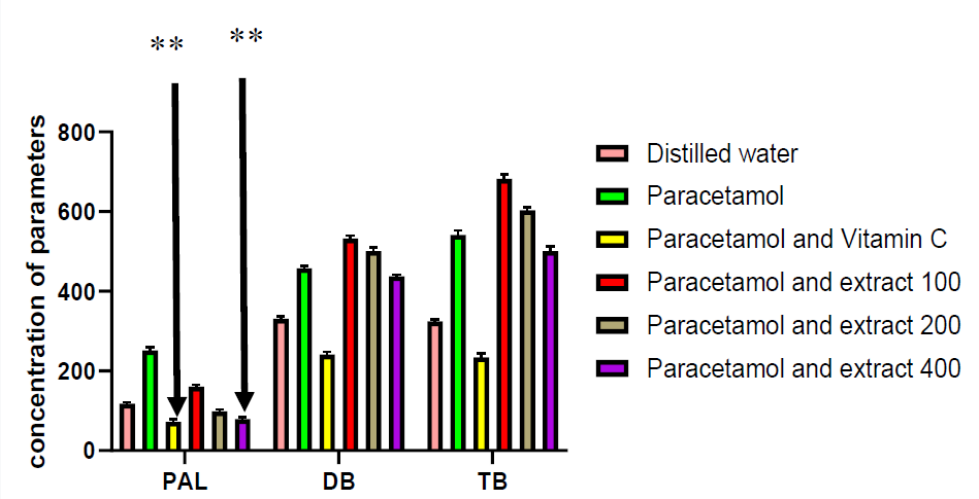


Figure 5: Evolution of PAL, TB and DB on day 32

results are expressed as Means ± SEM. *p < 0.05, **p < 0.01, ***p < 0.001

Dosage of transaminases and blood sugar (BS)

Tshe aqueous extract, in a dose-dependent manner, inhibits the action of paracetamol by reducing transaminases (ASAT and ALAT) and blood sugar levels compared to the control group which received only paracetamol. The ASAT rate of the control group, the value of which is 51.1 ± 2.1, is significantly inhibited by vitamin C at 73.58%, and by the aqueous extract at the maximum dose of 400 mg/kg BW at 63.8%. The level of ALAT is significantly inhibited by vitamin C and aqueous extract at the maximum dose of 400 mg/kg BW at the percentages of 67.18% and 65.46% respectively. Blood glucose was reduced non-significantly from 0.32 ± 0.2 g/L to 0.21 ± 0.5 g/L in rats treated with vitamin C and from 0.32 ± 0.2 g/L to 0.18 ± 0.1 g/L in rats treated with the aqueous extract at 400 mg/kg BW **(Figure 6)**.

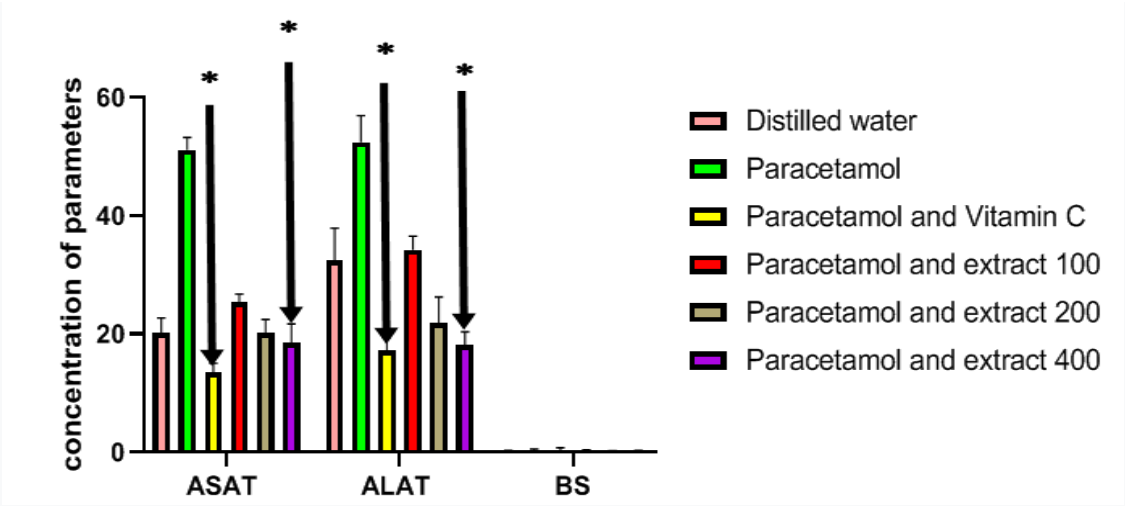


Figure 6: Evolution of ASAT, ALAT and blood sugar on the 32nd day.

results are expressed as Means ± SEM. *p < 0.05, **p < 0.01, ***p < 0.001.

Studies of relative liver weights

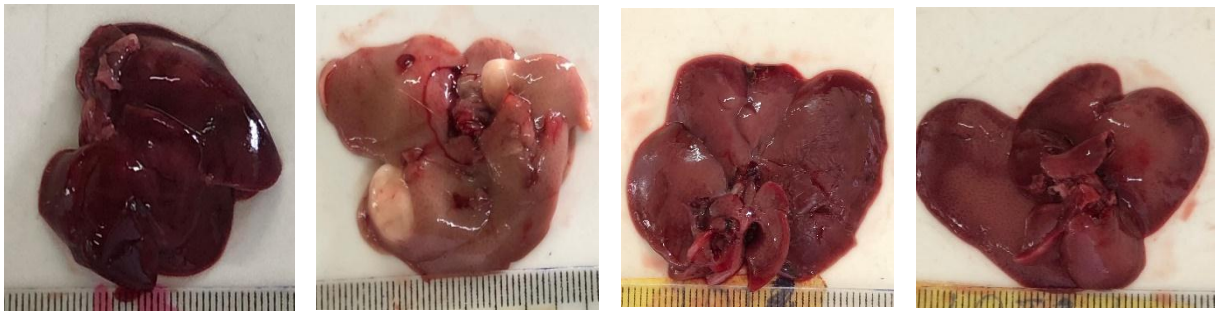
The group of rats which received only paracetamol has a relative weight high and is 4.821 ± 0.210%. This weight decreases significantly in a dose-dependent manner in the animals treated with the aqueous extract and those treated with vitamin C. The relative weight in the rats treated with the aqueous extract 400 mg/kg BW is 2.224 ± 0.4294%, and that in the group treated by vitamin C is 2.125 ± 0.241% **(Table 1)**.

Table 1: Relative weights of livers from different groups of rats.

Group 1 (distilled water)	**Group 2 (paracetamol)**	**Group 3 (paracetamol followed by vitamin C)**	**Group 4 (paracetamol followed by extract 100 mg/kg BW)**	**Group 5 (paracetamol followed by extract 200 mg/kg BW)**	**Group 6 (paracetamol followed by extract 400 mg/kg BW)**
Relative weight **(%)**	Relative weight **(%)**	Relative weight **(%)**	Relative weight **(%)**	Relative weight **(%)**	Relative weight **(%)**
2,427 ± 0,245	4,821 ± 0,210	2,125 ± 0,241*	3,741 ± 0,254	2,474 ± 0,4070	2,224 ± 0,4294*

Macroscopic examination of the liver

This involves comparing the color, texture and consistency of the livers of rats which received only paracetamol and the livers of rats treated with vitamin C and the aqueous extract. The **figure 7A** shows the liver of a healthy rat. The livers of rats receiving only paracetamol lost their consistency, texture and color **(Figure 7B)**. The damaged livers of rats that received paracetamol and treated with vitamin C and the aqueous extract almost regained their color, texture and consistency **(Figure 7C and 7D).**



A B C D

Figure 7: Photos of the livers of the rats observed A-Normal liver, B-Hepatitis-affected liver, C-Liver treated with aqueous extract of *Desmodium adscendens* leaves 400 mg/kg BW, D-Liver treated with Vitamin-C.

DISCUSSION

Liver intoxication with paracetamol is a commonly used method in experimental studies. Biomarkers to assess the physical, physiological and functional state of the liver are mainly transaminases (ALAT and ASAT), alkaline phosphatase and bilirubin (total and direct). An observed increase in its biomarkers indicates liver intoxication.[14] The modifications observed after administration of paracetamol would therefore be due to the latter, which is recognized as a xenobiotic in which the cytochrome P450 enzymatic system intervenes during metabolism.[15]

The studies showed normal values of these parameters in rats. The results carried out by[16] showed concentrations whose values are significantly close to those obtained during our studies.

The administration of paracetamol showed a clear increase in biochemical parameters such as transaminases, alkaline phosphatase, blood sugar, total bilirubin and direct bilirubin. These results are consistent with those of.[1,17] Clinically, the elevation of these parameters are the main indicators for specialists to detect a liver infection according to.[17] The mechanism of liver intoxication by paracetamol has its essential targets the parenchyma cells, leading at the increase of transaminases and blood sugar according to,[18] These early cases were first observed by.[19] Sections made on the parenchyma cells by these same authors made it possible to observe lesions up to necrosis. The metabolization of paracetamol occurs as follows: the cytochrome P 450 metabolizes paracetamol to give an active metabolite the N-Acetyl-P-benzoQuinone-Imine (NAPQI). We observe thus the hepatitis necrosis by peroxidation of membrane lipids (release of peroxyl radicals) leading at the lysis cellular.[8] According to the same authors, liver cells have their main antioxidant which is the

glutathione for their defense. An overdose of the paracetamol actives the NAPQI which causes liver depletion of glutathione.[20] This depletion is caused by the excessive consumption of glutathione which trains immediately the peroxidation of lipids[21] and oxidation of the thiol groups of proteins.[22] All these actions lead to increases transaminases, bilirubin, alkaline phosphatase and blood sugar according to.[8]

Treatment with aqueous extracts of *Desmodium adscendens* leaves at doses of 100, 200 and 400 mg/kg BW, significantly inhibited in a dose-dependent manner the effect of paracetamol overdose compared to the negative control group on certain biochemical parameters such as alkaline phosphatase, ALAT, ASAT and blood sugar. However, a slight inhibition of the action of paracetamol overdose by these extracts was observed with total bilirubin and direct bilirubin. Indeed, total bilirubin is the breakdown product of hemoglobin in red blood cells. It is therefore more concentrated in the blood. Total bilirubin converts to direct bilirubin in the liver. Direct bilirubin therefore remains concentrated in the liver.[12]

The levels of biochemical parameters are therefore restored to normal in the groups of rats treated with aqueous extracts of *Desmodium adscendens* leaves at different doses. These results are consistent with those of[17] with *Sarcocorne* and *Cakilier*,[12] with the aqueous extract of *Rosemarinus officinalis* and[23] with *Alchornea cordifolia* which showed a reduction in these parameters respectively with inhibition percentages varying from 43 to 65%; from 35 to 65% and from 45 to 74%. Also, the studies of[24] showed that the methanolic extract of *Gynandropsis gynandra* had hepatoprotective activity at the maximum dose of 400 mg/kg BW in rats with a significant reduction in biochemical parameters. Studies such as those by[25, 26] have shown a very significant decrease in transaminases.

The relative weights are lower in the groups of rats treated with total aqueous extract and the group treated with vitamin C compared to the control group. These results are consistent with those of.[17] These data indicate the group of rats that received only paracetamol had increased liver.

Paracetamol intoxication showed a change in the characteristics of color, texture and consistency of the liver. These studies are similar to those of[27] who showed liver damage based on these observations. According to these same authors, these changes observed in characteristics are harmless and reversible. After administration of the aqueous extract, the liver practically regained its color, texture and consistency. These results are identical to

those of[28] who showed the action of plant extracts on hepatitis on the macroscopic characteristics of the poisoned liver.

The leaves of *Desmodium adscendens* contains therapeutic phytochemical constituents such as alkaloids, flavonoids, saponins and anthocyanins.[29] The plant is also rich in polyphenols and terpenoids. Also, the anti-hepatotoxic effects of tannins, alkaloids, triterpenes and flavonoids have been demonstrated by.[30] Fatty acids are present in a maximum concentration of 3%, therefore relatively rich in unsaturated acids.[31] One of the significant damages caused by paracetamol is the breakdown of membrane lipids. The aqueous extract, using these fatty acids, could help correct this lipid deficit, thus protecting liver cells against cell lysis.[32] Flavonoids have the ability to capture and deactivate free radicals.[8] According to[33,34], they act by preventing the fixation of free radicals on DNA, by activating the detoxification system and by protecting the capillary walls.[35] showed that flavonoids have a hepatoprotective effect against liver injury caused by carbon tetrachloride. The antioxidant activity of polyphenols from certain plants was studied by.[36] The antioxidant and anti-inflammatory activities of tannins were evaluated by.[37] According to[23], tannins and related compounds can prevent the destructive effects of lipid peroxide in liver cells. Alkaloids have a protective effect on the liver.[23] The authors[38] studied the hepatoprotective activity of saponins.

CONCLUSION

The results of this study showed that the aqueous extract of *Desmodium adscendens* leaves had hepatoprotective. To this end, it significantly reduces the levels of biochemical biomarkers in the liver elevated by paracetamol overload in rats. The aqueous extract reduces the relative weight of livers affected by hepatitis and restores the physical characteristics of the liver which are color, texture and consistency. The phytochemical constituents contained in the aqueous extract of the leaves could be responsible for the effects observed on biochemical parameters and the physical characteristics of the liver.

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Conflicts of interest

There are not conflicts of interest.

REFERENCES

1. Guillouzo A, Clerc C, Malledant Y, Chesne C, Ratanasavanh D, Guillouzo C. Modèles d'étude de la cytoprotection hépatique. Gastroenterology Clinical of Biology, 1989; 725-730.
2. Anzouan-Kacou HK, Dehinsala M, Bangoura AD, Kouamé DH, Doffou AS, Mahassadi AK et al. Aspects socio-économiques de la prise en charge des hépatites virales chroniques en Coted'Ivoire. Annales Africaines de Médicine, 2022; 15(4): e4770-e4778.
3. Enel C, DESGREES DU, LOU A, N'Dri Yoman T, Danel C, LARMARANGE J. Les hépatites virales B et C en Côte d'Ivoire : l'urgence d'une dynamisation de la lutte. Journal Africain d'Hépato-Gastroentérologie, 2015; 9(3): 94-98.
4. Séri BL. Prévalence, incidence et facteurs associés des infections par les virus du VIH, de l'hépatite B et de l'hépatite C chez les donneurs de sang. Analyse de la base de données du Centre National de Transfusion Sanguine (CNTS) d'Abidjan, (1992-2012). Master Recherche épidémiologie et bio-statistique : Université Bordeaux Segalen, 2012; 84.
5. Calzada F, Yepez-Mulia L, Tapia-Contreras A. Effect of Mexican medecinal plant used to treat tricomoniasis on Trichomonasvaginalis trophozoites. Journal of Ethnopharmacology, 2007; 113: 248-251.
6. UE. Protection des animaux utilisés à des fins scientifiques : résolution législative du parlement européen du 5 mai 2009 sur la proposition du conseil relative à la protection des animaux utilisés à des fins scientifiques, (COM (2008)0543-C6-039/20082008/0211(COD)).https://ec.europa.eu/environment/archives/lab_animals/process_en.htm, 2010.
7. Faye PG, Ndiaye EM, Ndiaye B, Cisse OIK, Ayessou NC, Cisse Mady. Effet de la macération, de l'infusion et la décoction sur l'extraction aqueuse des polyphénols des feuilles séchées de *Combretum Micranthum*. Afrique Sciences, 2022; 21(3): 114–126.
8. Dougnon TJ, Kpodekon TM, Ahissou H, Loko F, Laleye, A. Effet protecteur du pédoncule d'ananas au cours de l'intoxication du rat *Wistar* par le paracétamol. International Journal of Biological and Chemical. Sciences, 2009; 3(4): 688-693.
9. Bashandy SH, Alwasel SH & al. Carbon Tétrachloride-Induced Hepatotoxicity and Nephrotoxicity in rats: Protective Role of Vitamin C. Journal of Pharmacology and Toxicology, 2011; 6: 283-292.

10. OCDE. Lignes Directrices de l'OE pour les essais de produits chimiques, 2008; 14.
11. Ndibualonji BB, Mulumba BK, Badipabu M, Mulunda YD, Kabamba NT. Évaluation des fonctions hépatiques chez les peintres en bâtiment de Lubumbashi. Journal of Animal and Plant Sciences, 2022; 52(2): 9395-9403.
12. Sangare MM, Bayala B, Ategbo JM, Loko F, Dramane KL. Effets de l'extrait aqueux de gomphrenacelosioides (amaranthaceae) sur les enzymes hépatiques. Afrique sciences, 2012; 8(3): 107-115.
13. Ouattara Y. Etudes de l'activité des extraits aqueux de plantes hépatotropes sur le foie de souris soumises à une intoxication aigue au tétrachlorure de carbone. Thèse de 3ème cycle en Sciences Biologiques Appliquées; Université Félix Houphouet Boigny, Côte d'Ivoire, Option : Physiologie Animale, 1999; 47: 98.
14. Amacher DE. A toxicologist's guide to biomarkers of hepatic response. Human and Experimental Toxicology, 2000; 21(5): 253-62.
15. Guengerich P. Mammalian cytochrome P450. CRC press. Florida, 1986.
16. Feki A, Kammoun I, Naifar M, Makni Ayadi F, Hakim A, Ben Amara I. Etude du profil biochimique chez les rats traités avec des doses croissantes en thiamethoxane. Journal de l'Information Médicale de SFAX, 2023; 37: 55-63.
17. Gargouri M, Amara IB, Ksouri M, Reghal KM, Feki A, Magne C, Hakim A. Impact de deux plantes halophytes sur l'hépatotoxicité induite par le plomb chez le rat adulte. Journal de l'Information Médicale de SFAX, 2023; 21/22, 15: 72-80.
18. OOreka. Transaminases, www.premiers-secours-ooreka.fr, 2022; 5.
19. Davidson DG, Eastham WN. Acute liver necrosis following overdose of paracetamol. British Medical Journal, 1996; 2(5512): 497-9.
20. Chang L, Xu D, Zhu J, Ge G, Kong X, ZhouY. Herbal therapy for the treatment of acetaminophen-associated liver injury: recent advances and future perspectives. Front of Pharmacology, 2020; 11.
21. Settaf M, Zahidy A, Elimadi R, Sapena I, Abd A. S-15176 reduces the hepatic injury in rats subjected to experimental ischemia and reperfusion. European Journal of Pharmacology, 2000; 406: 281-292.
22. Bridger S, Henderson K, Glucksman E, Ellis A, Henry J. Death from low dose paracetamol poisoning. European Journal of Pharmacology, 2000; 316: 1724-5.
23. Osadebe PO, Okoye FBC, Uzor PF, Nnamani NR, Obiano NC. Phytochemical analysis, hepatoprotective and antioxidant activity of *Alchornea cordifolia* methanol leaf extract on

carbon tetrachloride induced hepatic damage in rats. Asian Pacific Journal of Tropical Medicine, 2012; 5(4): 289-93.

24. Sambasiva R, Jayanthi K, Murthy V. Improved Routing Protocol for Health Care communications, 2013; 2(2): 1-6.
25. Diaby V. Etudes biochimiques, hématologiques et histologiques du sulfate de cadium chez les rats wistars, Thèse, Université Félix Houphouet Boigny, Côte d'Ivoire, 2017; 132.
26. Djigh BN, Bio T, Oungbé MD, Gnahoré GL, Kra AKM, Mak D, Djaman AJ. Effect of repeated administration of *Arachis hypogaea* Hull extract on blood parameters and histological organization of heart, liver and kidner. International Journal of Biochemical and Research Revue, 2020; 29(1): 20-33.
27. Fleurenti J and Joyeux M. Les tests in vivo et in vitro dans l'élevation des propriétés anti-hépatotoxiques de substances d'origine naturelle. Ethnopharmacologie : sources, méthodes, objectifs. Actes du 1er colloque europeen d'Ethnopharmacologie, Metz 22-25 mai. ORSTM, 1990; 248-2: 69493.
28. Fedmann G. Aspects morphologiques de la mort cellulaire. Gastroenterology Clinical and Biology, 1989; 13: 562-567.
29. Lorrain E. Grand Manuel de Phytothérapie, Durand Edition, Collection les nouveaux chemins de la Santé, 2019; 461-470, 1290.
30. Sourabié S, Nacoulma AP, Nikiéma JB and Kiendrebeogo M. Etude du pouvoir hépato-protecteur d'*Argemone mexicana* L (papaveraceae), une plante médicinale du Burkina Faso. Science et Technologie, Sciences de la Santé, 2023; 45(1): 23-37.
31. Makkar HPS. Quantification of tannins in Tree Foliage : A laboratory Manual for the FAO/IAEA Co-ordinate Research Project on Use of Nuclear and Related techniques to Develop simple Tannin Assay for pudicting and Improving the Safety and Efficiency of Feeding ruminants on the Tanninferous Tree Foliage. Vienna, Australia Joint FAO/IAEA division of nuclear Techniques in Food and Agriculture, 1999; 1-29.
32. Bourre JM, Dumont, Durand G. Effet dose de l'acide oléique alimentaire. Cet acide est-il conditionnement essentiel ? Oléagineux, corps gras, lipides, 20007; 5: 1-17.
33. Kawabata TT, Chapman MY, Kim DH, Stevens WD, Holsapple MP. Mechanisms of in vitro immunosuppression by hepatocyte-generated cyclophosphamide metabolites and 4-hydroxycyclophosphamide. Biochemical of Pharmacology, 1990; 40(5): 9-27.
34. Siess MC, Le Bon A, Canivenc-Lavier M, Susch M. Mechanisms involved in the chemoprevention of flavonïds. Biofactors, 2000; 12(4): 193-199.

35. Ma Q, Wang LH, Jiang JG. Hepatoprotective effect of flavonoïds from Cirsium japonicum on hepatotoxicity in comparaison with silymarin. Food Function, 2016; 18: 7(5): 2179-84.
36. Baali N, Belloum Z, Baal S, Chabi B, Pessemesse L, Fouret G, Ameddah S, Benayache F, Benayache S, Feillet-Goudray C, Cabello G, Wrutniak-Cabello C. Protective Activity of Total Polyphenols from *Genista quadriflora* munby and *Teucrium polium geyrii* name in Acetaminophen-Induced Hepatotoxicity in Rats. Nutrients, 2016; 8(4): 193.
37. Perchellet EM, Gali HU, Makkar HPS, Perchellet JP. Ability of tannins extracted from the leaves of various trees and shrubs to inhibit the biomarkers of tumor promotion in mouse skin in vivo. International Journal of Oncology, 1996; 9: 801-809.
38. Germano MP, d'Angelo V, Sanogo R, Morabito A, Pergolizzi S, de Pasquale R. Hepatoprotective activity of *Trichilia roka* on carbone tetrachloride-inducedliver damage in rats. Journal of Pharmacy and Pharmacology, 2001; 53: 1569-1574.