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Pharmacological Effects Of The Improved Traditional Medicine (ITM) Used In The Treatment Of Hepatitis B In Côte d'Ivoire On Paracetamol-Induced Hepatotoxicity In Wistar Rats

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Abstract
The objective of this research was to evaluate the hepatoprotective effect of a phytomedicine derived from the species Combretum micranthum and Terminalia catappa, administered to Wistar rats divided into 6 groups. Hepatitis was induced in groups 2, 3, 4, 5, and 6 by orally administering a paracetamol solution at 200 mg/kg body weight to the rats, with a volume of 2 mL/pc over a period of two weeks. Regarding the study of the hepatoprotective effect, it was carried out on the same rats. In addition, groups 4, 5, and 6 also received the improved traditional medicine (ITM) solution orally for the following 14 days, at doses of 100, 200, and 400 mg/kg pc. Group 3 was control group and it received N-acetylcysteine. During the experimental phase, the rats were observed for and at the end of the experiment, the hematological and biochemical parameters of the blood, as well as the histopathological examination of the liver, were evaluated. Examination of the protective effect of the ITM on paracetamol-intoxicated rats resulted in a reduction of biochemical values towards normal levels without causing liver damage or affecting hematological parameters. Thus, the ITM exerts a protective effect on the liver at the doses examined.

Keywords: *hepatoprotective agents, liver, biochemical, hematological, ITM*

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I. Introduction

Plants have long been used for medicinal properties throughout the world. These natural remedies are often regarded as less toxic and milder alternatives to conventional pharmaceutical drugs. According to the World Health Organization, more than 80% of the world's population relies on traditional medicine for their primary healthcare needs. In Africa, the use of medicinal plants is common practice across the continent. This pratice is deeply rooted in cultural traditions and economic realities (Mahomoodally, 2013). Traditional medicines in Africa: an appraisal of ten potent Africa medicinal plant. Evidence-Based Complementary and alternative Medicine. However, despite its importance, the development of traditional medicine in Africa is still behind that observed in other countries such as India and China.

Medicinal plants are known for their remarkable diversity of applications. A single species can be used to treat a wide range of diseases, from common digestive disorders to chronic diseases such as cancer, hepatitis, and diabetes (Zirihi *et al*., 2003). In recent decades, liver diseases have become a major global public health concern. The WHO estimates that nearly 500 million people worldwide are affected by chronic hepatitis, with about one million deaths each year (Anonymous 1, 2009). In 2020, Africa continent accounted for approximately 26% of global morbidity associated with hepatitis B and C (WHO, 2016; Anzouan-Kacou *et al*., 2022). In Côte d'Ivoire, the situation is alarming: nearly two million people, representing 8 to 10% of the population are living with viral hepatitis, putting them at high risk of developing cirrhosis or liver cancer (Enel *et al*., 2014).

Medicinal plants offer a promising alternative in the management of such diseases, as they contain secondary metabolites with proven therapeutic properties (Yayé *et al*., 2011). Among the medicinal plants, *Terminalia catappa* and *Combretum micranthum have* showed their effectivity to treat numerous diseases such as. The present study aims to evaluate the pharmacological effects of a traditional remedy composed of *Terminalia*

catappa and *Combretum micranthum* plants commonly used in the treatment of hepatitis B on liver toxicity induced by paracetamol in Wistar rats.

II. Materials And Methods

Plant material

The plant product is an infusion of medicinal plants, contained in a vial labeled with the batch number (212). It is officially registered under the number 2084 with the National Program for the Promotion of Traditional Medicine in Côte d'Ivoire (Fig.1).

Fig. 1. Improved Traditional Medicine named "ABRAHAM"

Animal material

Rats of the species *Rattus norvegicus*-(Wistar strain), weighing between 100 and 200 g, were used in this study. The rats were supplied by Biosciences UFR (Training and Research Unit) of the Félix Houphouët Boigny University of Abidjan Cocody. A total of thirty-six (36) specimens were used in experimentation.

Laboratory Equipment

The following equipment was used: EDTA tubes and dry tubes, an Ohaus™ electronic precision balance, a gavage syringe, solvent reservoirs on the chromatographic plate, a Pasteur pipette, a URIT-2900 semi-automatic spectrophotometer, a URIT-2900 analyzer, and a LEMFIELD model 80.2 centrifuge.

Chemical Reagents and Consumables

The chemicals and consumables used included Cooper's ether and paracetamol (Doliprane® (SANOFI)), N-acetylcysteine, a Creatinine / Alkaline picrate kit (BIOLABO), a Cholesterol oxidase / peroxidase kit, the colorimetric enzyme, an AST / GOT IFCC kit (BIOLABO), and an ALT/GPT IFCC kit (BIOLABO). A 2% alcoholic solution of ferric chloride, sodium acetate, iron (III) chloride (FeCl3), ammonia, HCl, and Dragendorff's reagent.

Induction of Hepatitis with Paracetamol

Hepatitis was induced following the protocol described by Dougnon *et al*. (2009). Thirty-six (36) Wistar rats, including both males and females, were randomly divided into six (6) groups and received the treatmants through oral gavage as follows:

- **Group 1 (control):** No treatment was adminstratered.
- **Group 2:** These rats received 2 mL of a solution containing 200 mg / kg body weight of paracetamol daily for 14 days.
- **Group 3:** These rats received 2 mL of a solution containing 200 mg/kg body weight of paracetamol daily for 14 days, followed by 2 mL of solution containing 100 mg/kg body weight of N-acetylcysteine daily for an additional 14 days.
- **Group 4:** received 2 mL of a paracetamol solution (200 mg / kg body weight) for 14 days, followed by 2 mL of ITM solution (100 mg/kg body weight) daily for an additional 14 days.
- **Group 5:** received 2 mL of a solution containing 200 mg/kg body weight of paracetamol daily for 14 days, followed by 2 mL of ITM solution (200 mg/kg body weight) daily for an additional 14 days.
- **Group 6:** These rats received 2 mL of a solution containing 200 mg/kg body weight of paracetamol daily for 14 days, followed by 2 mL of ITM solution (400 mg / kg body weight) daily for an additional 14 days.

Fresh solutions were prepared daily based on the individual body weight of each animal. Blood samples were collected at three time points: day 0 (D0, before hepatitis induction), day 14 (D14, after hepatitis induction in Groups 2–6), and day 28 (D28, after administration of N-acetylcysteine or ITM in Groups 3–6).

Statistical Analysis

Data analysis and visualization were performed using GraphPad Prism® version 7.00 and Microsoft Excel 2007.

III. Results

Effect of ITM on the Liver Structure of Rats Intoxicated with Paracetamol

Status of Relative Liver Weights

In rats that received only paracetamol, the proportion of the liver is higher, at 4.91 ± 0.15%. With N-acetylcysteine treatment, a progressive decrease in weight is observed in the rats. The weight proportion in rats subjected to a 400 mg/kg BW treatment is 3.15 ± 0.42%, while in rats treated with N-acetylcysteine it is 2.40 ± 0.39% (Table I).

Group 1 (distilled water)	Group 2 (intoxicated and untreated)	Group 3 (100 mg/kg BW N-acetyl)	Group 4 (100 mg/kg BW Extract)	Group 5 (200 mg/kg BW Extract)	Group 6 (400 mg/kg BW Extract)
Relative Weight (%)	Relative Weight (%)	Relative Weight (%)	Relative Weight (%)	Relative Weight (%)	Relative Weight (%)
3,58 ± 0,46	4,91 ± 0,15	2,40 ± 0,39	3, 27 ± 0,22	3,16 ± 0,40	3,15 ± 0,42

Table I : Relative Liver Weights

Macroscopic Examination of the Liver

Figure 2 illustrates the macroscopic examination of the livers of the rats. The color, texture, and consistency of the livers of rats that were solely under paracetamol should be compared with those treated with N-acetylcysteine and the various doses of aqueous extracts. The liver of the intoxicated and untreated rats (group 2) was damaged by the paracetamol, which altered its consistency, texture, and color. The livers of the rats in the other four groups intoxicated with paracetamol and treated with N-acetylcysteine as well as various quantities of ITM extracts show a resemblance to the non-intoxicated liver (group 1).

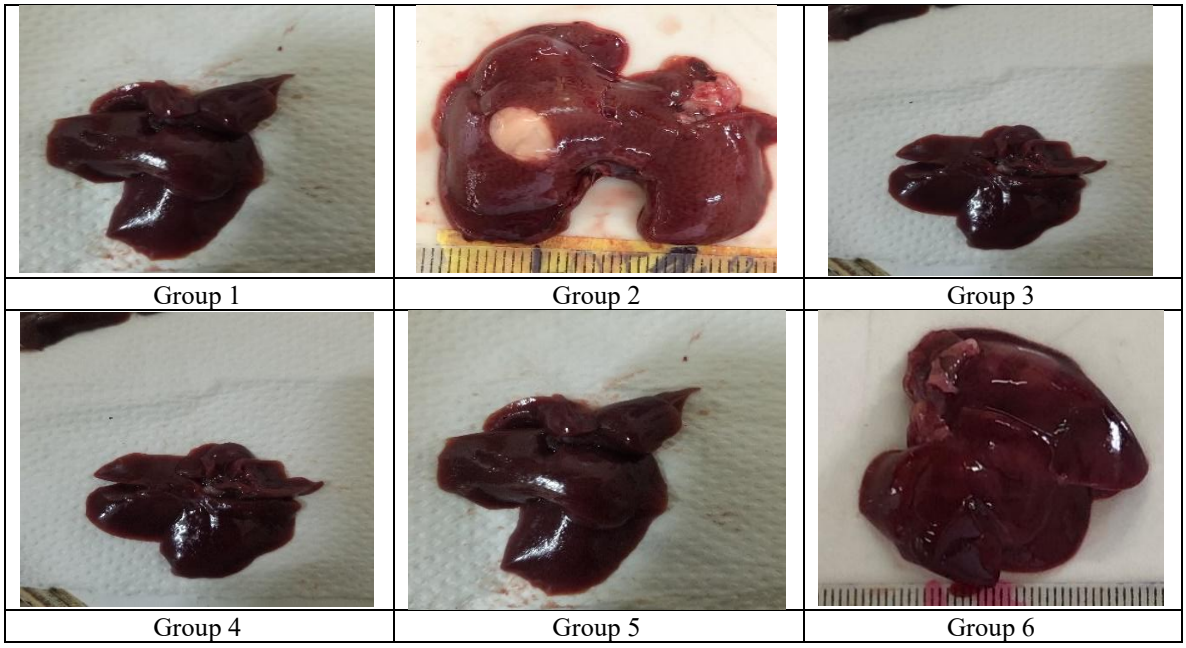

Fig.2. Photographs of the Livers

A - Normal Liver B - Liver treated only with paracetamol C - Liver treated with the 400 mg/Kg BW extract D - Liver treated with N-acetylcysteine

Hematological Parameters of Paracetamol-Induced Hepatotoxicity in Rats

Before the intoxication, the normal values for white blood cells, red blood cells, hemoglobin, hematocrit, MCV, MCH, MCHC, and blood platelets were 11.43 ± 1.234 (10^3/µL), 8.657 ± 1.4992 (10^6/µL), 17.58 ± 1.5896 (g/dL), 40.99 ± 1.25 (%), 70.71 ± 6.62 (fL), 27.23 ± 1.504 (pg.), 33.48 ± 1.123 (g/dL), and 335.8 ± 63.82 (10^3/µL), respectively (Table II).

Following the treatment, the values of MCV (40.25 ± 0.8947 fL) and MCH (17.18 ± 0.1641 pg) decreased compared to the levels of red blood cells (20.89 ± 1.1073 x 10^6/µL), white blood cells (16.48 ± 1.15 x 10^3/µL), hematocrit (47.3 ± 0.4787%), hemoglobin (20.58 ± 1.1216 g/dL), MCHC (40.47 ± 0.4485 g/dL), and platelets (650.4 ± 50.75 x 10^3/µL) according to Table II.

Table II: Hematological Parameters of Rats Before Intoxication and After Treatment

Hematological Parameters	Sample before induction	Sample after induction
White blood cells (10^3/µL)	11,43 ± 1,234	16,48 ± 1,15
Red blood cells (10^6/µL)	8,657 ± 1,4992	20,89 ± 1,1073
Hemoglobin (g/dL)	17,58 ± 1,5896	20,58 ± 1,1216
Hematocrit(%)	40,99 ± 1,25	47,3 ± 0,4787
MCV (fl)	70,71 ± 6,62	40,25 ± 0,8947
MCH (pg)	27,23 ± 1,504	17,18 ± 0,1641
MCHC (g /dL)	33,48 ± 1,123	40,47 ± 0,4485
Platelets (10^3/µL)	335,8 ± 63,82	650,4 ± 50,75

Biochemical Parameters of Paracetamol-Induced Hepatotoxicity in Rats

Before the introduction (Day 0), all six groups of rats were administered only distilled water. The administration of paracetamol at a dose of 200 mg/kg BW, from the first to the fourteenth day, altered the values of several biochemical parameters in the intoxicated rats compared to those of the control group (group 1). Therefore, during the treatment period (from day 1 to day 28) of group 3 at a dose of 100 mg/kg BW of N-Acetylcysteine and groups 4, 5, and 6 at respective doses of (100, 200, and 400 mg/kg BW) of the ITM extract, good activity was observed in the treated rats compared to the untreated intoxicated rats.

Effect of ITM on Total Protein Concentration

At the initial date, the protein level in the non-intoxicated rats of all groups did not show any notable variation. On the 14th day, the administration of paracetamol caused a significant increase ($p < 0.0001$) in the total protein level in the different intoxicated groups (groups 2, 3, 4, 5, and 6), compared to group 1 (distilled water) (Figure 3).

On the 28th day, the preventive administration of N-acetylcysteine (100 mg/kg BW) and the ITM extract at doses (100, 200, 400 mg/kg BW) in the rats led to a reduction in total proteins (8.000 ± 2.828; 8.500 ± 3.536; 10.50 ± 0.7071; and 12.50 ± 3.536 mg/L), compared to the intoxicated and untreated control group (14.50 ± 0.7071 mg/L), with a significant level of significance ($P < 0.001$). Furthermore, the statistical analysis of groups 4, 5, and 6, which received various doses of the ITM extract on the 28th day, showed comparable results to those of group 3 (N-acetylcysteine). However, the variations between these concentrations are not significant, unlike what was observed for group 2 (untreated control group).

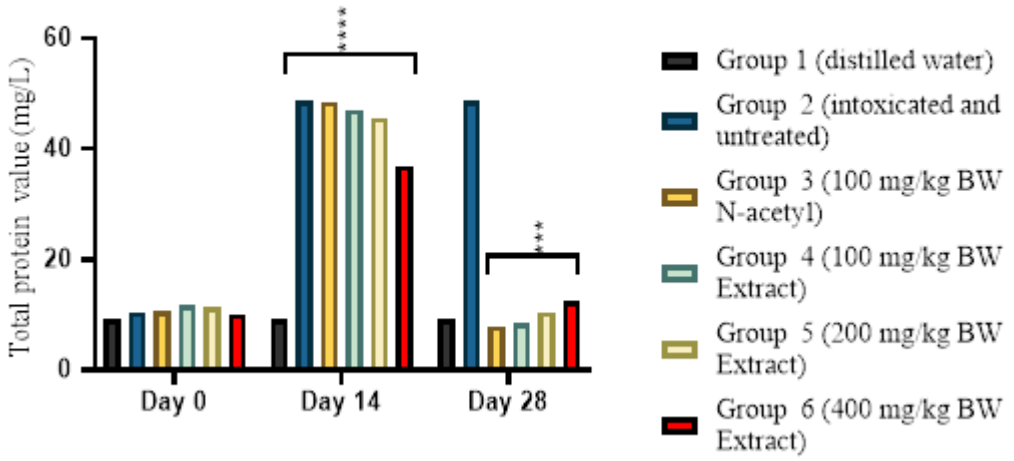

Fig. 3. Variation in Total Proteins After Treatment of Intoxicated Rats with ITM and N-acetylcysteine

Effect of ITM on the Enzymatic Activity of Transaminases

Initially (D0), the AST (Aspartate Aminotransferase) value of the non-intoxicated rats in the experimental groups is equal to the control group (group 1).

On the 14th day, the administration of paracetamol caused a significant increase ($p < 0.0001$) in the AST level (101.20 ± 3.606; 98.50 ± 1.364; 112.2 ± 4.950; 96.40 ± 1.155; 120.50 ± 1.70 UI/L) respectively in the various intoxicated groups (groups 2, 3, 4, 5, and 6), compared to group 1 (83.50 ± 20.57 UI/L) (Figure 4).

On the 28th day, the administration of N-acetylcysteine at a dose of 100 mg/kg body weight (BW) and ITM extracts at doses of 100, 200, and 400 mg/kg BW led to a reduction in the AST level (45.4 ± 1.7071; 50.80 ± 1.657; 46.7 ± 1.02; 37.7 ± 1.61 UI/L), compared to the intoxicated and untreated control group (101.20 ± 3.707

UI/L), with a highly significant level (P < 0.0001). Moreover, the analysis of groups (4, 5, and 6) containing different doses of the ITM extract on the 28th day revealed virtually identical results to those of group 3 (N-acetylcysteine). It is noted that the variations between these concentrations are negligible. This is not observed in group 2 (untreated control group). Furthermore, on the 28th day, a marked difference (P < 0.0001) is noted between the groups that received the N-acetylcysteine dose and the ITM doses compared to those in group 1.

Regarding ALT (Alanine Aminotransferase) at the initial date (D0), the parameters of the non-intoxicated rats in groups (2, 3, 4, 5, and 6) did not show any significant change, unlike group 1 on day 0.

However, on the 14th day, the administration of paracetamol resulted in a significant increase (p < 0.0001) in the ALT level (67.2 ± 22.51; 82.50 ± 34.13; 89.4 ± 30.70; 81.50 ± 30.58; 71.40 ± 26.28 UI/L) in various intoxicated groups (groups 2, 3, 4, 5, 6) compared to that of group 1 (50.25 ± 18.11 UI/L) (Figure 5).

On the 28th day, the treatment of rats with N-acetylcysteine (100 mg/kg body weight) and the ITM extract at doses of 100, 200, 400 mg/kg body weight shows a reduction in the ALT level (49.10 ± 18.53; 60.7 ± 30.24; 54.7 ± 19.65; 49.10 ± 17.071 UI/L), compared to that of the intoxicated and untreated control group (67.2 ± 22.51 UI/L), with a very strong significance level (P < 0.0001). Moreover, the analysis of groups (4, 5, and 6) containing different quantities of the ITM extract on the 28th day showed almost identical results to those of group 3 (N-acetylcysteine) and group 2 (untreated control group). The variations observed between these doses are not significant. Furthermore, on the 28th day, a notable difference (P < 0.0001) is noted between the groups that received the N-acetylcysteine dose and the various ITM doses compared to what is observed in the animals of group 1 on day 0.

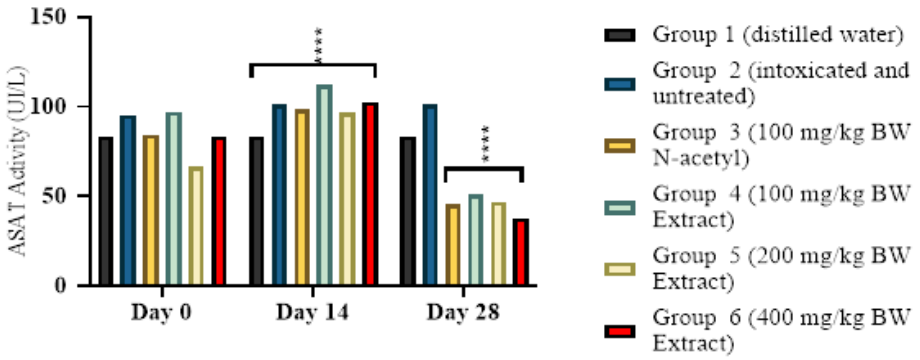

Fig. 4. Variation in AST Activity After Treatment of Intoxicated Rats with ITM and N-acetylcysteine
The values expressed represent the mean ± SEM, with n = 4; *** P < 0.001; **** p < 0.0001.

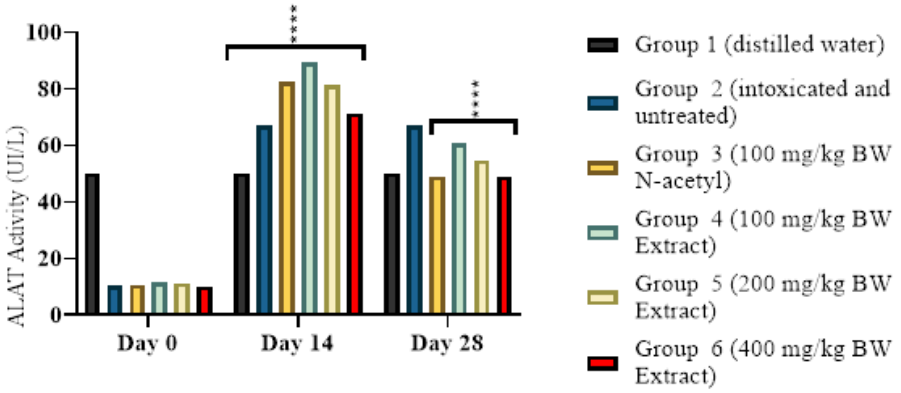

Fig. 5. Variation de l'activité de l'ALAT après traitement des rats intoxiqués avec le MTA et N-acétylcystéine
*The values expressed represent the mean ± SEM, with n = 4; *** P < 0.001; **** p < 0.0001*

Effect of ITM on the Enzymatic Activity of Alkaline Phosphatase (ALP)

At the initial date (D0), the ALP activity of the non-intoxicated rats in groups (1, 2, 3, 4, and 6) did not show any notable variation.

On the 14th day, the administration of paracetamol caused a significant increase (p < 0.0001) in ALP activity (41.5 ± 17.23; 42 ± 17.60; 39.50 ± 15.78; 37.7 ± 15.6; 38.50 ± 15.76 UI/L) among the different intoxicated

groups (groups 2, 3, 4, 5, and 6), compared to the initial group (group 1) whose measurement was 21.50 ± 8.737 UI/L (Figure 6).

On the 28th day, the administration of N-acetylcysteine to rats at a dose of 100 mg/kg BW, as well as the ITM extract at doses of 100, 200, and 400 mg/kg BW, resulted in a marked reduction in the ALP level (respectively 13.38 ± 2.11; 12.77 ± 1.81; 12.92 ± 2.00; 13.46 ± 2.1 UI/L), compared to the intoxicated and untreated control group (41.50 ± 17.23 UI/L). Furthermore, the examination of groups (4, 5, and 6) containing various quantities of ITM extract on the 28th day showed almost identical values to those of group 3 (N-acetylcysteine). It is noted that the variations between these concentrations are not very significant, which contrasts with group 2 (untreated control), where the difference is evident. Also, on the 28th day, a significant difference ($p < 0.05$) is observed in the groups that received the N-acetylcysteine dose and the ITM doses compared to those in group 1 on day 0.

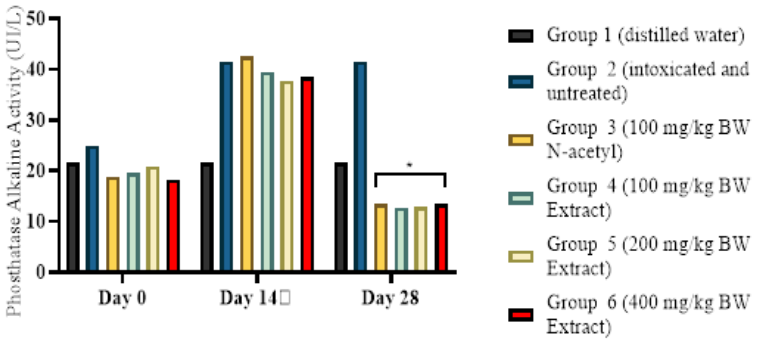

Fig. 6. Variation in Alkaline Phosphatase Activity After Treatment of Intoxicated Rats with ITM and N-acetylcysteine

The values expressed represent the mean ± SEM, with n = 6; * $p < 0.05$.

IV. Discussion

Severe liver diseases arise from a multitude of interactions between environmental and metabolic factors. They are distinguished by an alteration in the structure and functions of the liver, leading to effects on the organism. This research evaluated the hepatoprotective effect of an ITM derived from Ivorian traditional medicine on paracetamol-intoxicated rats.

Paracetamol-induced hepatotoxicity showed a highly significant increase ($p < 0.0001$) in the activity of glutamic-oxaloacetic transaminase (AST) and glutamic-pyruvic transaminase (ALT). Furthermore, the elevation of alkaline phosphatase (ALP) and total bilirubin levels was also very significant ($p < 0.0001$) in the intoxicated and untreated rats compared to the non-intoxicated control rats. The increase in these biochemical parameters in the blood indicates that paracetamol caused liver damage, one of the repercussions of which is the release of intracellular enzymes following the degradation of liver cells.

Observations made on rats pretreated with ITM extract and subsequently intoxicated with paracetamol demonstrate that this extract attenuated the hepatic toxicity of paracetamol. Indeed, the drug treatment reduced the activity of transaminases (AST, ALT) in the intoxicated rats. It is likely that the protective effect of ITM on the liver is attributed to the flavonoids present in the leaves of *Terminalia catappa*. According to Lin *et al*. (1999) and Chen *et al*. (2006), compounds like flavonoids would exert a protective effect on the liver thanks to their antioxidant power.

This liver-protective action could also be attributed to a bioflavonoid derived from the leaves of *Combretum micranthum*, particularly vitexin extracted by Tine *et al*. (2021) and Lei *et al*. (2022). Moreover, these researchers have shown that vitexin, an ellagitanin, lowers ALT and AST levels and also reduces the infiltration of inflammatory T lymphocytes and CD4 cells. In addition, a decrease in the levels of alkaline phosphatase (ALP), total proteins, and total bilirubin was observed in the animals treated with ITM compared to the intoxicated rats that did not receive treatment.

Our research is in agreement with that of Bruneton (1993), who conducted a study on the leaves of *Terminalia catappa*. This study highlighted the astringent properties of tannins, which combat infections due to their ability to bind to macromolecules, including proteins: digestive enzymes and others, fungal or viral proteins. This is what would occur if we opt for this ITM solution.

It should also be noted that the ITM extract is significantly more effective at a dose of 400 mg/kg. Thus, the marked decrease ($p < 0.0001$) in the activity of transaminases (AST and ALT) due to the medicinal extract at this concentration (400 mg/kg) of ITM indicates not only a stabilization of hepatocyte membranes but also a

regeneration of liver tissue induced by paracetamol. These conclusions corroborate the studies of these scientists (Lin *et al*., 2001) who demonstrated the antioxidant power of *Terminalia catappa*, which may explain its use in liver diseases, particularly viral hepatitis.

Just like N-acetylcysteine, treatment with the ITM extract leads to a decrease in total protein levels in these animals, thus signaling a return to normal hepatocyte function. Furthermore, the effectiveness of our ITM could also be confirmed by the attribution of the antiviral activity of *Combretum micranthum* against herpes simplex viruses (type 1 and 2) to tannins (Ferrea & coll., 1993). Regarding liver weights, it is important to mention that the lowest values were observed in rats that received ITM and N-acetylcysteine, respectively at the maximum dose of 400 mg/kg BW and 100 mg/kg BW for N-acetylcysteine. These results are in agreement with those of Gargouri *et al*. (2023). The information collected also shows that rats exposed only to paracetamol, without any treatment, showed significant growth of their livers.

Paracetamol intoxication caused a change in properties such as the color, texture, and consistency of the liver. Our research is similar to that of Fleurenti & Joyeux (1990), who demonstrated liver damage following intoxication. However, the administration of the medicinal extract helped to restore the color, texture, and consistency of the liver. These conclusions coincide with those of Felmann (1989), who demonstrated the effect of plant extracts on the macroscopic properties of the liver in a state of intoxication.

Furthermore, the post-treatment analyses showed a notable increase in the levels of red blood cells, white blood cells, hematocrit, hemoglobin, and blood platelets compared to the values observed before induction. The increased number of white blood cells and the hemoglobin level noted in our research could be attributed to an activation of the immune system due to the ITM extract, which would stimulate the production of immune cells (Fahim *et al*., 2012). The notable increase in the number of blood platelets induced by the ITM extract could be explained by the role of these sentinel cells in the immune defense against infections (Chabert *et al*., 2017). The hemoglobin level remained practically constant, while those of red blood cells and hematocrit increased. According to Etame *et al*. (2017), the use of *Terminalia catappa* demonstrated a reduction in the levels of MCH (mean corpuscular hemoglobin) and MCV (mean corpuscular volume) after treatment with ITM.

After treatment with ITM, an increase in the levels of red blood cells, hemoglobin, hematocrit, MCHC (mean corpuscular hemoglobin concentration), and platelets was observed, while a decrease in MCV and MCH levels was noted. This indicates that ITM could exert a positive influence on the immune system (Muttaka *et al*., 2016).

V. Conclusion

ABRAHAM is an optimized traditional preparation, formulated from the species *Combretum micranthum* and *Terminalia catappa*, used in the traditional therapy of hepatitis. The oral administration of the improved traditional medicine solution at doses of 100, 200, and 400 mg/kg BW to paracetamol-intoxicated rats resulted in a reduction of AST, ALT, ALP, and total protein levels and did not cause any harm to hematological indices or the liver. The use of the improved traditional medicine named ABRAHAM in the management of hepatitis is therefore justified.

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