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Biological Effect of Vegetable Oil from *Carapa Procera* D.C Seed After Induction of Hepatotoxicity with Paracetamol Overdose in Rats

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Abstract

This work consisted of studying the biological effect of *Carapa procera* seed oil on the one hand on the macroscopic properties of the liver (relative weight, color, texture, and consistency), and on the other hand on blood parameters in rats poisoned with paracetamol overdose.

Doses of 50, 100 and 200 mg/kg bw were used in 36 rats divided into 6 groups of 6 rats. Group 1, group 2, group 3, group 4, group 5 and group 6 respectively received distilled water, paracetamol only, paracetamol followed by vitamin C, paracetamol followed by oil at 50 mg/kg bw, paracetamol followed by oil at 100 mg/kg bw and paracetamol followed by oil at 200 mg/kg bw. The solutions are administered by gavage for 30 days. The first fortnight for the induction of hepatitis with paracetamol overdose and the second fortnight for its treatment. Samples are taken on the 1st, 15th and 30th day to evaluate blood parameters. Then the rats are sacrificed, and the livers are removed to carry out macroscopic studies.

The relative weight in rats that received only paracetamol was higher. This weight decreased in a dose-dependent manner in animals treated with oil and those treated with vitamin C. The liver of rats receiving only paracetamol lost its consistency, texture and color. The damaged livers of rats given paracetamol and treated with vitamin C or oil almost regained their color, texture and consistency. In general, an overdose of paracetamol causes an increase in the body's defense cells and modifies blood parameters. These observed changes are partly restored by the action of the oil and vitamin C.

The observed effects could be explained by the hepatoprotective and hematostabilizing activities of *Carapa procera* vegetable oil.

Keywords

Blood parameters, *Carapa procera*, Hepatitis, macroscopic properties.

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INTRODUCTION

The liver plays an important role in metabolizing and degrading the majority of substances after oxidation, conjugation or methylation **[1]**. It is therefore subject to several attacks causing hepatitis **[2]**. Hepatitis causes many deaths worldwide. In Ivory Coast, according to **[3]**, the prevalence of hepatitis C is 3.3% in the general population; and 12% for hepatitis B according to **[4].** There are therefore several types of hepatitis: viral, alcoholic, drug-induced and bacterial hepatitis, etc. **[5]**. Viral hepatitis is treated with antiretroviral drugs which are very often expensive and produce unsatisfactory results. Today, another form of hepatitis kills populations very often through ignorance. This is the case with drug-induced hepatitis. Thus, over-the-counter paracetamol, delivered without a prescription or dosage, is most often cited as the drug whose overdose can lead to hepatitis **[1]**. The lack of resources and the unsatisfactory results in the use of modern medicines have led populations towards another alternative which is the use of medicinal plants **[6]**. Thus, over the last ten years, populations have paid very particular attention to medicinal plants **[7]**. Medicinal plants are widely used in the prevention and treatment of various pathologies in Africa and in developing countries, and today constitute a real source of natural substances used in the treatment of several diseases **[6]**. *Carapa procera,* which is the subject of our study, is a plant commonly used in the traditional treatment of inflammations such as hepatitis by the Ivorian populations through its oil contained in the seed of the fruit. This work aims to evaluate the effect of *Carapa procera* oil on the liver poisoned by an overdose of paracetamol. To achieve our objective, we will study the macroscopic parameters of the poisoned liver after treatment with the oil, after evaluating the effect of the oil on the blood parameters in rats subjected to an overdose of paracetamol.

MATERIAL AND METHODS

Material

Plant material.

The plant material is an oil obtained from the seed contained in the fruit of the *Carapa procera* plant. The seeds are harvested at the start of the rainy season between late May and July in northern Ivory Coast. The species was identified at Nangui Abrogoua University in Abidjan, at the Laboratory of Physiology, Pharmacology and Pharmacopoeia (LPPP).

Animal material

The rats used in these experiments are male and female albino rats of the *Rattus norvegicus* species from the animal facility of the Laboratory of Physiology, Pharmacology and Pharmacopoeia of Nangui Abrogoua University. These adult rats are eight (8) weeks old and older, with a body mass between 155 and 208 g (figure 1). These rats are acclimated to the ambient temperature of 25±3C° for 05 days before the start of the manipulation. These animals are fed with pellets from the company FACI®. The tap water used to water them in bottles was constantly renewed. The different experimental protocols are followed in accordance with the protocols for the protection of laboratory animals of the European Council of Legislation 87/609/EEC **[8]**.

Figure 1 : Rat, *Rattus norvegicus*

Methods

- **Steps in traditional oil extraction from *Carapa procera* seeds [6]**

The oil extraction is done as follows: firstly, the nuts are collected from the month of May to July. Then comes the boiling of the collected nuts to facilitate their resistance during their conservation in the hole which runs from June to November. After digging up, the seeds are hulled, rolled or pounded, roasted and the dried paste is kneaded in a pot. Water is added to the paste and the mixture is cooked to obtain the vegetable oil from the *Carapa procera* seed (figure 2) which is taken from the pot using a ladle.

- **Study of the induction of hepatitis by paracetamol overdose and its treatment**

Preparation of paracetamol solution

Preliminary studies were carried out to obtain the toxic dose of paracetamol. Paracetamol tablets (Doliprane® 1000mg (SANOFI)) are made into powder and dissolved in distilled water then administered to rats by gavage to determine the LD_{50}. At a dose of 500 mg/kg body weight (bw), half of the animals died during the experiment. The dose of 200 mg/kg bw was therefore used for 15 days to induce hepatotoxicity in rats in accordance with the studies of **[1]**.

Preparation of vitamin C solution

This solution is obtained according to the method used during the work of **[9]**. These authors showed that vitamin C at a dose of 100 mg/kg bw had a hepatoprotective effect in rats.

Preparation of doses of *Carapa procera* seed oil

The different doses of *Carapa procera* fruit seed oil to be tested are 50, 100 and 200 mg/kg bw. These doses were determined taking into account the volumes prescribed by traditional therapists for an adult man per day.

Solution administration

The volume of substance to be administered to a 100 g rat is 1 mL or 2 mL according to OCDE protocol 407 **[10]**.

Experimentation

The studies are carried out according to the methods of **[1]**. Thirty-six (36) rats are divided into six (6) groups, each comprising three (3) males and three (3) females, and the solutions will be administered orally with the feeding tube:

• **Group 1**: They have access to water and food; the animals will not receive any treatment,

• **Group 2**: The rats receive 2 mL of the solution of 200 mg / kg of paracetamol bw (Doliprane®) for two weeks,

• **Group 3**: The animals receive 2 mL of the solution of 200 mg/kg bw of paracetamol (Doliprane®) per day for two weeks, then 2 mL of the solution of 100 mg/kg bw of vitamin C for two weeks.

• **Group 4**: The rats received 2mL of the solution of 200 mg/kg bw of paracetamol (Doliprane®) for two weeks, then 1 ml of the solution of 50 mg/kg bw of *Carapa procera* seed oil for two weeks,

• **Group 5**: The rats receive 2ml of the solution of 200 mg/kg bw of paracetamol (Doliprane®) for two weeks, then 1 ml of the solution of 100 mg/kg bw of *Carapa procera* seed oil for two weeks,

• **Group 6**: The rats received 2 ml of the solution of 200 mg / kg bw of paracetamol (Doliprane®) for two weeks then with 1 mL of the solution of 200 mg / kg bw of *Carapa procera* seed oil for two weeks.

Every two days, new solutions were prepared taking into account the new weight acquired per animal per group, until the end of the experiment. The first samples are taken on the 1st day (day 1) before administration of the solutions. The second blood samples are taken on the 15th day (day 15) after induction of hepatitis in groups 2, 3, 4, 5 and 6. The last samples are taken on the 30th day (day 30) after treatment with vitamin C and *Carapa procera* oil will be produced in groups 3, 4, 5 and 6.

Blood sample

At the end of the treatment and after fasting for 12 hours, the animals are anesthetized with ether. Blood is collected from the retro-orbital sinus using sterile syringes to measure hematological parameters. Blood from each rat was collected immediately in EDTA tubes to determine the complete blood count and to count blood cells with the hematological analyzer (INSEM-UPS-ENVT, France) after centrifugation with a centrifuge (HERAEUS SEPATECH, Allemagne).

Dosage of blood parameters [11]

In practice, a quantity of 50 µl of the sample is sucked up by the needle of the machine. The blood is then diluted in a physiological solution, then distributed into the different chambers of the machine. In the leukocyte measurement chamber, the sample remains for 10 seconds and then the size and number of leukocytes are determined. In the erythrocyte measurement chamber, the size and number of erythrocytes and thrombocytes are also determined from the measured values. The other parameters are calculated in the automaton microprocessor. These are: the blood count (FNS), where we find the following parameters: red blood cells (RBC), hematocrits (HCT), platelets (PTL), white blood cells (WBC), hemoglobin (HGB), measurement

of hemoglobin content of red blood cells (MHC) and mean corpuscular hemoglobin concentration (MCHC). During the incubation time, the erythrocytes are dissolved under the influence of lysis and the hemoglobin is released and then transformed into methemoglobin. A portion of the sample from this chamber is introduced into the hemoglobin flow bowl. This study was carried out at the laboratory of the Clinique "Grand Espace Médical'' (Lanema) in Adjamé (Abidjan – Ivory Coast) near the police headquarters.

Animal sacrifice and organ removal

After blood collection, the livers were immediately isolated and washed with 0.9% NaCl, the physiological solution. The livers are then observed, photographed and weighed with an electronic scale (Denver Instrument S-234, Allemagne).

- **Macroscopic parameters**

Calculation of the relative weight of the liver

The liver is removed, weighed and photographed at the end of all treatments. Livers are preserved in 10% formalin. The relative weight (PR) of the liver is calculated in relation to the body weight according to the formula given by **[6]**:

RW = [Liver Weight (LW) / Animal Weight (AW)] X100

RW = relative weight, LW = liver weight, AW = animal weight

Physical characteristics

This examination is limited to the observation of the external structure of the entire liver removed. It takes into account color, consistency and texture **[6]**:

Color

Color is an important parameter in the diagnosis of liver diseases. Normally, the liver is bright brown 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 intoxication.

Texture

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

Photographs highlighting the physical characteristics of the livers of the animals from each experimental group are taken using a Kodak camera.

Statistical analysis

The results are expressed as means ± SEM (Standard Error of Mean). The analysis of variance test (ANOVA 1) associated with Student test-t was used to determine the statistical significance of the results ($p < 0.05$). Graph pad Prism 8 software was used to carry out these statistical tests and graphs.

RESULTS

Effect of *Carapa procera* D.C seed oil on macroscopic parameters of the liver after paracetamol induction

- **Studies of relative liver weights**

The relative weight in rats which received only paracetamol is higher, i.e. 4.911 ± 0.1535%. This weight decreases in a dose-dependent manner in animals treated with oil and those treated with vitamin C. The relative weight in rats treated with oil at 200 mg/kg bw is 3.153 ± 0.4294%, and that in rats treated with vitamin C is 2.403 ± 0.3976% (table 1).

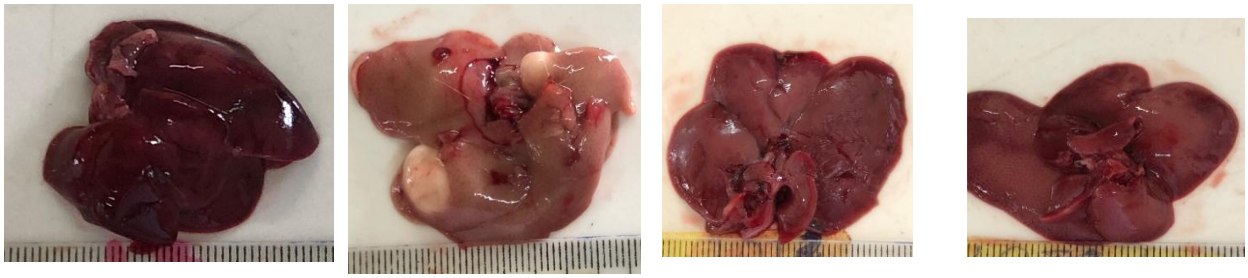
Table 1 : Relative weight of livers in the different groups

Group 1 (distilled water)	**Group 2 (Paracetamol)**	**Group 3 (paracétamol and vitamin C)**	**Group 4 (paracétamol and oil 50 mg/kg bw)**	**Group 5 Lot (paracétamol and oil 100 mg/kg bw)**	**Group 6 (paracétamol and oil 200 mg/kg bw)**
relative weight **(%)**	relative weight **(%)**	relative weight **(%)**	relative weight **(%)**	relative weight **(%)**	relative weight **(%)**
3,588 ± 0,4651	4,911 ± 0,1535	2,403 ± 0,3976	4,271 ± 0,2271	3,160 ± 0,4070	3,153 ± 0,4294

- **Examination of the physical characteristics 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 or oil. The livers of rats receiving only paracetamol lost their consistency, texture and color (see figure 3B). The damaged livers of rats given paracetamol and treated with vitamin C or oil almost regained their color, texture, and consistency (see Figures 3C And 3D).

Figure 2 : *Carapa procera* seed oil sold on the market



A **B** **C** **D**

Figure 3 : Photos of rats livers observed. A- Normal liver, B- Liver treated only with the paracetamol, C- Diseased liver treated with *Carapa procera* oil, D- Diseased liver treated with the vitamin C

Dosage of blood parameters

- Dosage on the 1st day

Dosage of red blood cells (RBC), white blood cells (WBC), lymphocytes (LP), hemoglobin (HB) and hematocrit (HC) before administration of paracetamol

Normal levels of red blood cells, white blood cells, hemoglobin, hematocrit and lymphocytes are respectively between 4.6 ± 0.67 and 5.93 ± 0.67 106/uL; between 1.78 ± 0.2 and 3.83 ± 1.78 103/uL; between 12.67 ± 0.7 and 13.48 ± 0.5 g/dL; between 23.82 ± 3.3 and 31.33 ± 3.1% and between 1.23 ± 0.9 and 2.23 ± 0.7 103/uL (figure 4).

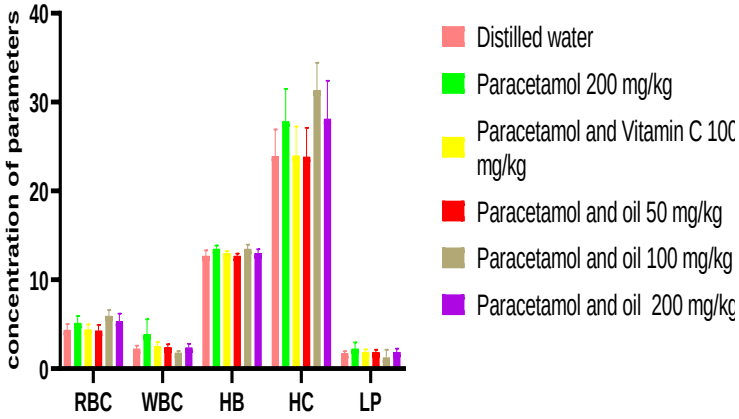


Figure 4 : Evolution of RBC, WBC, HB, HC and LP on the 1st day

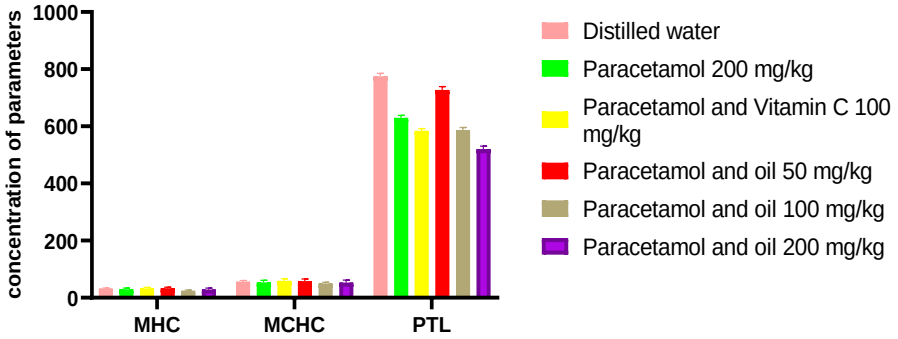


Figure 5 : Evolution of MHC, MCHC and PTL on the 1st day

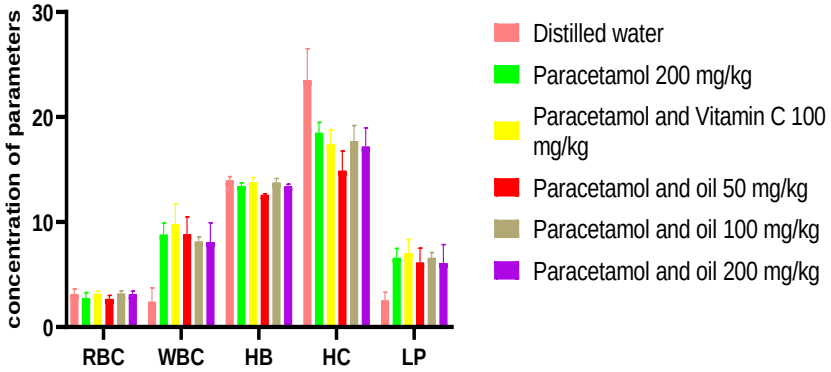


Figure 6 : Evolution of RBC, WBC, HB, HC and LP on the 15th day

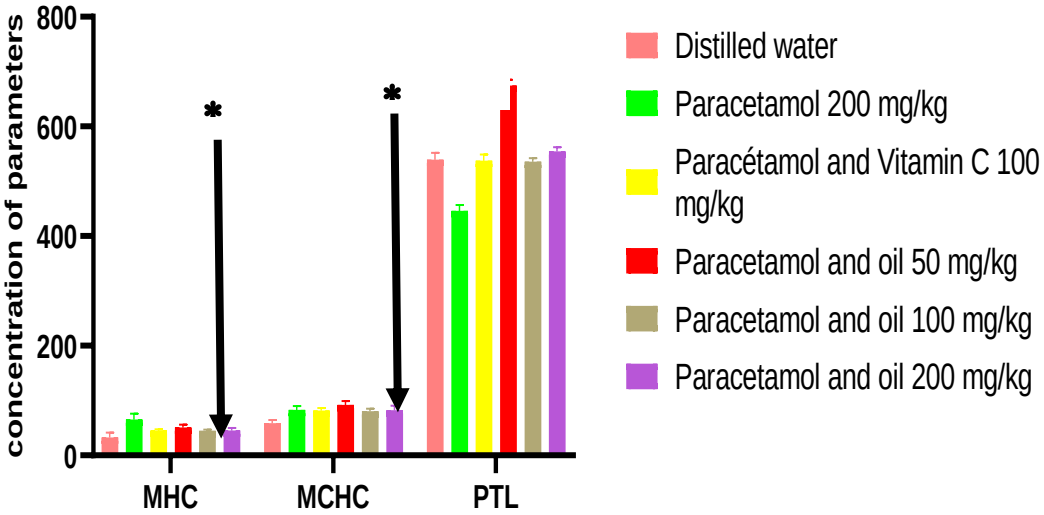


Figure 7 : Evolution of MHC, MCHC and PLT on the 15th day

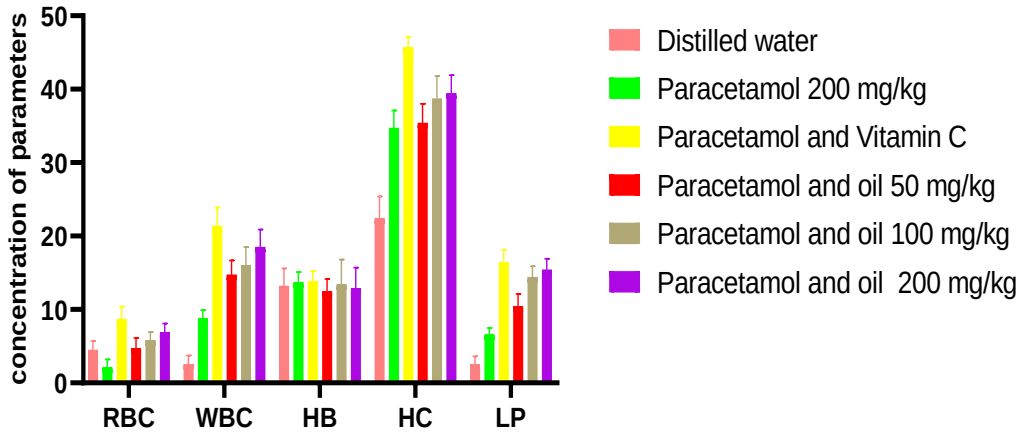


Figure 8 : Evolution of RBC, WBC, HB, HC and LP on the 30th Day ($p < 0.05$)

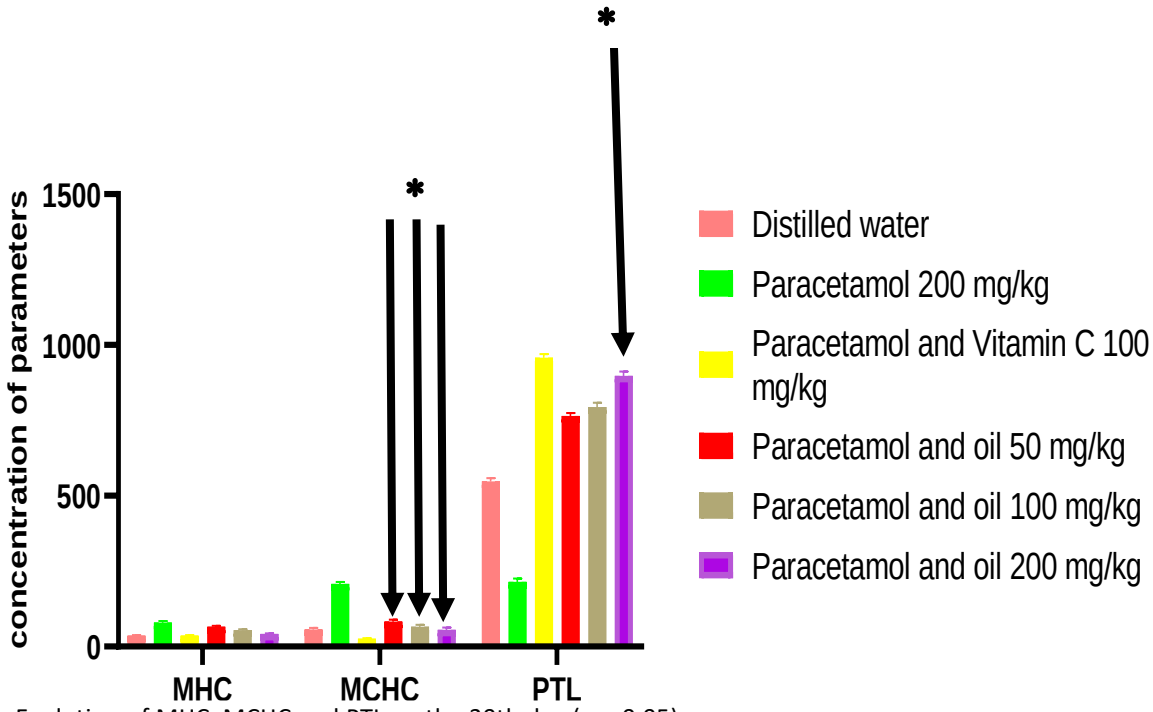


Figure 9 : Evolution of MHC, MCHC and PTL on the 30th day ($p < 0.05$)

Dosage of MCH, MCHC and Platelets (PTL)

Normal levels of MHC (measurement of hemoglobin content of red blood cells), MCHC (mean corpuscular hemoglobin concentration) and PLT (platelets) are respectively between 24.08 ± 2.5 and 32.87 ± 4 pg; between 49.8 ± 4.15 and 58.27 ± 7.6 g/dL and between 519.7 ± 11 and 774.5 ±11 103/uL (Figure 5).

- Dosage on the 15th day

Dosage of red blood cells (RBC), white blood cells (WBC), lymphocytes (LP), hemoglobin (HB) and hematocrit (HC)

The number of red blood cells drops to 2.67 ± 0.3 106/uL in rats which are treated with the oil at 50 mg/kg bw. The white blood cell level, on the other hand, rises and reaches a maximum of 9.77 ± 1.9 103/uL in the group of rats which will receive vitamin C. The hemoglobin level remains stable. That of the hematocrit drops and reaches a minimum of 14.87 ± 1.9% in the group which will receive the oil at 50 mg/kg BW. The level of lymphocytes increases and reaches 7.02 ± 1.2 103/uL in the group which will be treated with vitamin C (figure 6).

Dosage of MHC, MCHC and Platelets (PTL) after administration of paracetamol

After administration of paracetamol, the levels of MCH and MCHC increase respectively reaching 65 ±

11 pg in the group of rats which will receive only paracetamol and 91.53 ± 7.6 g/dL in the rats which will be treated with the oil. the dose of 50 mg/kg BW. The level of blood platelets decreases and reaches 445.6 ± 11,103/uL in rats which will receive only paracetamol (figure 7).

- Dosage on the 30th day

Dosage of red blood cells (RBC), white blood cells (WBC), lymphocytes (LP), hemoglobin (HB) and hematocrit (HC)

The oil significantly increases the level of red blood cells in a dose-dependent manner with an inhibition percentage of 69.56% at the maximum dose of 200 mg/kg bw. This action is similar to that of vitamin C which increases the level of red blood cells to 75.86%. The oil at a dose of 200 mg/kg bw and vitamin C significantly increase white blood cells to 18.5 ± 2.4 103/uL and 21.4 ± 2.5 103/uL respectively compared to the control lot which is 8.79 ± 1.1 103/uL. The oil and vitamin C had no effect on hemoglobin concentration. The hematocrit percentage increases slightly with inhibition rates of 1.97; 10.33 and 11.92% respectively of the oil at doses of 50, 100 and 200 mg/kg bw. The lymphocyte count continues to increase with 15.4 ± 1.5 103/uL and 16.4 ± 1.7 103/uL respectively for the oil at a dose of 200 mg/kg bw and vitamin C compared to the control batch which is 6.58 ± 0.9 103/uL (figure 8).

Dosage of MHC, MCHC and Platelets (PTL)

The MCH level decreases in a dose-dependent manner after administration of the oil or vitamin C. The 400 mg/kg bw dose of the oil has a percentage reduction of 47.08%. The MCHC level also significantly decreased at doses of 50, 100 and 200 mg/kg bw respectively at percentages of reduction of 60.11: 68.17 and 73.49%. The blood platelet level increased significantly to 77.62% for the batch treated with vitamin C and 76.13% for the batch which received the oil at the maximum dose of 200 mg/kg bw (figure 9).

DISCUSSION

Liver intoxication with paracetamol is a commonly used method in experimental studies. Biomarkers to assess the physiological and functional state of the liver are mainly transaminases, alkaline phosphatase, and bilirubin. An observed increase in its biomarkers indicates liver intoxication **[12]**. Physically, these effects result in an increase in liver weight and profound changes in its color, consistency, and texture. The disturbances observed after administration of an overdose 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 **[13]**.

The administration of paracetamol showed changes in the macroscopic characteristics of the liver. These changes indicate liver intoxication. The mechanism of liver intoxication by paracetamol essentially targets parenchyma cells: which explains the increase in transaminases and blood sugar according to **[14]**. These first cases were observed for the first time by **[15]** in 1966. Sections made on the parenchyma cells by these same authors made it possible to observe lesions up to necrosis. Paracetamol is metabolized by cytochrome P 450 to give an active metabolite N-Acetyl-P-benzoquinone-Imine (NAPQI) leading to hepatic necrosis by peroxidation of membrane lipids (release of peroxyl radicals) which subsequently causes a cell lysis **[1]**. Also, according to these latter authors, liver cells have glutathione for their defense, which constitutes their main antioxidant. Paracetamol overdose. Paracetamol intoxication causes liver depletion of glutathione **[16]**. The active metabolite NAPQI produced by paracetamol overdose consumes glutathione, thus explaining the depletion of the liver in glutathione, the immediate consequence of which is lipid peroxidation **[17]** and oxidation of protein thiol groups **[18]**. All these actions lead not only to the increase in transaminases, bilirubin, alkaline phosphatase, and blood sugar, but also to changes in the physical characteristics of the liver and blood parameters according to **[1].**

Carapa procera oil treatment at the maximum dose of 200 mg/kg bw significantly inhibited the effect of paracetamol compared to the control group on the physical characteristics of the liver.

The relative weights are lower in the groups of rats treated with *Carapa procera* oil and the group treated with vitamin C compared to the control group, with a relative weight of 3.153 ± 0.294% at the maximum oil dose. of 200 mg/kg BW. These results are consistent with those of **[7]**. This data indicates that rats that received only paracetamol without vitamin C or oil treatment had increased liver weight due to induced hepatitis.

Paracetamol intoxication showed a change in the characteristics of color, texture, and consistency of the liver. These studies are like those of **[19]** who showed liver damage based on these observations. According to these same authors, these observed changes in characteristics are harmless and reversible. After administration of the oil, the liver practically regained its color, texture, and consistency. These results are identical to those of **[20]** who showed the action of plant extracts on

hepatitis on the macroscopic characteristics of the poisoned liver.

Indeed, *Carapa procera* oil essentially contains fats (oleic, myristic, palmitic, volatile and linoleic acids) and glycerins **[21]**. One of the significant damages caused by paracetamol is the breakdown of membrane lipids. The oil with these fatty acids helps correct this lipid deficit, thus protecting the liver cells against cell lysis **[22]**. Oleic acid reduces oxidation in endothelial and liver cells **[23]**. **[24]** observed in their studies that palmitic acid had significant activity in liver function. All these actions of the fatty acids contained in *Carapa procera* oil could be responsible for inhibiting the action of paracetamol on the liver. *Carapa procera* oil could therefore have hepatoprotective activity.

Our results also revealed normal blood count values in rats. These results are significantly close to those obtained by **[25]**.

Paracetamol overdose has a double toxic action: on the one hand on liver cells through necrosis and on the other hand on cells such as red blood cells which struggle to transport oxygen **[26]**. Our results showed a decrease in red blood cells and hemoglobin. The hematocrit being the volume occupied by the red blood cells circulating in the blood in relation to the total volume of the blood also decreases. These results are consistent with those obtained by **[27]** who showed in their studies a reduction in these parameters in the face of liver intoxication. Our studies also showed a reduction in blood platelets. According to **[26]**, the liver is responsible for the production of most of the coagulation factors which constitute the main role of blood platelets. An infection therefore of the liver would lead to a drop in blood platelets.

Conversely, our results also showed an increase in white blood cells, lymphocytes, MHC and MCHC. These observations are identical to those of **[27]** who revealed an increase in these parameters following liver infection. Studies have also shown that during liver poisoning, the concentration of blood cells such as lymphocytes and white blood cells increase in the blood to strengthen the body's immunity **[26]**.

Studies carried out after administration of vitamin C or *Carapa procera* oil showed a significant increase in the levels of red blood cells, white blood cells, hematocrit, lymphocytes, and blood platelets compared to the control group. At the maximum dose of 200 mg/kg bw, the percentage increases are respectively 69.56; 52.48; 11.92; 57.27 and 76.13%. These results are consistent with those obtained by **[28]** who showed an increase in blood cell levels after administration of the aqueous extract of the mesocarp of the *Garcinia kola* fruit. Similar results were also obtained by **[29]** with the extract of *Ficus sycomorus* leaves, with a significantly high level of white blood cells and blood platelets in rats with hepatitis. The increase in white blood cells and lymphocytes in our studies could be due to a stabilization of the immune system by *Carapa procera* oil which would promote the production of immune cells **[29, 30, 31]** showed that palmitic acid which is a component of *Carapa procera* oil cleaned and purified the blood by renewing the body's defense cells. The high level of platelets blood stimulated by *Carapa procera* oil observed could be because the latter are sentinel cells and contribute significantly to anti-infectious immunity **[32]**. Hemoglobin remained significantly stable, and those of red blood cells and hematocrit increased compared to the control. These observations are like those of **[33]** who estimated that a decrease in these parameters could cause anemia. The levels of MCH and MCHC decreased after administration of *Carapa procera* oil. This drop could be explained by the fact that red blood cells are no longer destroyed by liver infection **[29]**.

CONCLUSION

The results of this study showed that total oil of *Carapa procera* could have a hepatoprotective activity by restoring the macroscopic characteristics of the liver which were damaged by the overdose of paracetamol. For this purpose, it stabilizes the weight of the liver, gradually restores the texture, consistency, and color of the liver.

Also, total vegetable oil inhibits the effects of excess paracetamol on blood cells. It especially increases the levels of defense cells such as white blood cells, lymphocytes, and blood platelets. *Carapa procera* vegetable oil could therefore have a stabilizing activity on blood parameters.

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Competing interests

Authors have declared that no competing interests exist.

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