



RESEARCH ARTICLE

HEPATOPROTECTIVE ACTIVITY OF AQUEOUS ROOT EXTRACT OF *CARICA PAPAYA* AGAINST PARACETAMOL-INDUCED HEPATOTOXICITY IN WISTAR RATS

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ABSTRACT

Background: Liver is prone to many diseases due to its role in metabolism and detoxification of various exogenous and endogenous compounds. Drug-induced liver damage represents a serious clinical problem in the world. **Objective:** To evaluate the potential hepatoprotective activity of the aqueous root extract of *Carica papaya* against paracetamol-induced hepatotoxicity in Wistar rats. **Methods:** Animals were pre-treated once daily for seven days before induction of hepatotoxicity. Five groups of rats were used. Groups 1 (normal control) and group 2 (negative control) received orally distilled water for seven days. Group 3 (positive control) received orally silymarin at 50 mg/kg body weight for 7 days. Groups 4 and 5 were treated orally with aqueous root extract of *Carica papaya* (100 and 200 mg/kg body weight, respectively) for seven days. Hepatotoxicity was induced on the seventh day in all the group animal except group 1, by oral administration of paracetamol, 500 mg/kg body weight. On the eighth day, blood was collected and serum markers such as aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, total bilirubin and total protein were measured. The liver from rat was also collected and subjected to histopathological analysis. **Results:** Hepatotoxicity induced with paracetamol resulted in a significant increase in aminotransferase, alanine aminotransferase and alkaline phosphatase levels, and a decrease in total protein level. Rats pre-treated with *Carica papaya* extract and silymarin exhibited decrease in serum enzymes and total bilirubin levels, and increase in total protein level. However, these changes were not significant. Histopathological analysis of liver sections of paracetamol-intoxicated rats showed necrosis, significant steatosis and congestion, while those of pre-treated rats with *Carica papaya* extract and silymarin exhibited moderate steatosis, congestion and inflammation. **Conclusion:** The aqueous root extract of *Carica papaya* exhibits only moderate hepatoprotective effect against a high dose of paracetamol-induced hepatotoxicity.

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INTRODUCTION

The liver is the main organ responsible for metabolic and physiologic homeostasis in the body. It plays a major role in detoxification and excretion of many endogenous and exogenous compounds. Any damage to it or impairment of its functions could have a significant impact on a person's health and lead to many diseases. The main causes of liver disease, characterized by hepatocyte death, are excessive alcohol consumption, viral infections, autoimmune disorders, exposure to toxic substances and drugs (Wolf, 1999). Liver damage caused by ingestion of hepatotoxic substances such as drugs is increasing worldwide, and conventional drugs used to treat this condition are generally insufficient and show serious adverse effects.

One of the clinically important drug associated with liver damage is paracetamol. Paracetamol (acetaminophen) is widely used as an antipyretic and analgesic, and it becomes toxic if administrated in excess (Davidson, 1966; Black, 1984). Its toxicity is the second most common cause of liver transplantation worldwide. Several already approved drugs were withdrawn from the market because they caused liver damage. Therefore, it is necessary to explore the herbal drugs in the management of drug-induced liver damage, in order to replace the drugs of low safety and efficacy (Mohamed-Saleem et al., 2008). Natural resources such as medicinal plants are constantly being searched for new molecules that can be used as drugs. Plants are, in fact, a rich source of bioactive molecules that can be used to treat many diseases, including

those affecting the liver. In this context, we are interested in *Carica papaya*, a widely grown and significant fruit tree in tropical and subtropical regions. Different parts of this plant are used to treat various diseases. A decoction of the leaves is used to treat hernia, malaria, urogenital pain, gonorrhoea and cancer. The maceration of the roots is used orally against urethritis (painful urination), typhoid, fever and as a laxative. A decoction of unripe fruits is a remedy for jaundice, sickle cell anaemia and hepatitis (African Pharmacopoeia, 1985). The aim of this study is to evaluate the potential hepatoprotective activity of the aqueous root extract of *Carica papaya* against paracetamol-induced hepatotoxicity in Wistar rats. In order to assess the extent of liver damage, some serum biochemical markers were estimated and histopathological studies of rats' livers were performed.

MATERIALS AND METHODS

Plant material: The plant material consists of *Carica papaya* roots. Roots were harvested at Felix Houphouët-Boigny University of Abidjan and transferred to the laboratory, where they were washed and dried for three weeks at room temperature. Samples of the plant were sent to the National Floristic Centre, Felix Houphouët-Boigny University, and compared there with authentic specimens registered under the number UCJ002676.

Animals: Wistar albino rats of the species *Rattus norvegicus*, aged 10 to 12 weeks and weighing between 120 and 150 g were used in this study. These animals were bred at the animal house of the Normal High School of Abidjan. They were housed in plastic cages lined with wood shavings and had free access to water and food pellets. Rats were also kept at room temperature with 12 h of light during the day and 12 h of darkness in the night. The Health Sciences Ethics Committee of Felix Houphouët-Boigny University of Abidjan examined and approved the study's experimental procedures.

Chemicals: Paracetamol (acetaminophen) and silymarin, the reference hepatoprotective drug, were purchased from Sigma-Aldrich (USA). Standard assay kits of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), total bilirubin and total protein were obtained from General Medical (Abidjan). All other reagents were of analytical grade.

Extract preparation: The plant extract was prepared according the method described by Zirihi *et al.* (2003). The dried roots of *Carica papaya* were first pulverized using a grinder. Then, one hundred (100) grams of plant powder were dissolved in two litres of distilled water and homogenized using a blender. The homogenate obtained was filtered twice, first through cotton and then through Whatman filter paper (3 mm). The filtrate obtained was concentrated to dryness under reduced pressure at 30°C using a rotary evaporator (BÜCHI). The resulting extract was the aqueous root extract of *Carica papaya*. It was stored at 4°C for later use.

Phytochemical screening: Phytochemical screening was performed to detect the presence of certain chemicals in the plant extract. Chemical groups such as polyphenols, flavonoids, tannins, quinone compounds, alkaloids, saponins, sterols and polyterpenes were investigated. The qualitative

method in test tubes in the presence of specific reagents was used (Wagner and Bladt, 1996). Characterisation is based on the principle that compounds induce chemical reactions in the presence of appropriate reagents, resulting in specific colours.

Acute toxicity test: The acute toxicity of aqueous root extracts of *Carica papaya* was performed in accordance with Organisation for Economic Cooperation and Development (OECD) guideline no. 423 (OECD, 2001). This method uses predetermined doses (5, 50, 300 and 2000 mg/kg body weight) and allows for the determination of a range of values for the lethal dose 50 (LD₅₀). Thus, two groups of three rats were fasted overnight. The first group received orally the extract solution at the limit dose of 2000 mg/kg body weight (b.w.) in a single administration. Following treatment, the rats were deprived of food again for three hours before being given access to it. They were observed regularly for 24 hours, with a particular focus on the first four hours, and daily for 14 days in order to record clinical signs of toxicity. The second group of three rats, which served as a control group, received distilled water under the same conditions, and rats were observed as before.

Assessment of hepatoprotective activity: The hepatoprotective activity of aqueous root extract of *Carica papaya* was evaluated in rats according to the method of Zakaria *et al.* (2020), with few modifications. All animals were pre-treated before hepatotoxicity was induced.

Experimental protocol: Paracetamol induced hepatotoxicity model was used. Twenty-five (25) rats were divided into five groups of five animals each. Group 1 served as the normal control group and received orally distilled water daily for seven days. Group 2 constituted the negative control (hepatotoxic) group and received also distilled water for seven days. Group 3 (positive control group) received orally the reference hepatoprotective drug, silymarin (50 mg/kg b.w.), daily for seven days. Groups 4 and 5 were treated with aqueous root extract of *Carica papaya* (100 and 200 mg/kg b.w. per day, respectively) for seven days. On the seventh day, three (3) hours after the last treatment, paracetamol suspension (in distilled water) was given orally, 500 mg/kg b.w., to all the rats except those in Group 1, which received only distilled water. Twenty-four (24) hours after the administration of paracetamol, rats from each group were anaesthetized using ether and blood was collected in dry tubes for biochemical analysis. The animals were then euthanized and their livers were removed. These were washed with distilled water and preserved in a 10% formalin solution for histopathological studies.

Biochemical investigation: After collection of blood, the samples were centrifuged at 3,000 rpm for ten (10) minutes to separate the serum. Liver markers such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), total bilirubin and total protein were measured according to standard methods and using a biochemistry analyser Cobas C311 (Roche Hitachi, Japan).

Histopathological studies: Liver samples previously fixed in 10% formalin were first dissected into around 5 mm-thick fragments. Sections were dehydrated in gradual ethanol (95-100%), cleared in toluene and infiltrated in paraffin melted at 60°C. The dehydrated liver fragments were then embedded in

molten paraffin in Leuckart bars. After cooling, 7 µm sections were made using a microtome (Microm), processed in toluene-ethanol series and stained with haematoxylin and eosin (H-E) dye. Sections were finally observed under photonic microscope (Zeiss) adapted to a camera for histological changes.

Statistical analysis: Statistical analysis of the data was performed using Graph Pad Prism software (version 7.00, Microsoft, USA). Results were expressed as means $\pm$ standard errors of the mean (SEM). Difference between means was determinate using one-way analysis of variance (ANOVA), followed by Tukey's multiple comparison test. The limit of significance was set at 5%, i.e. the difference between the means was significant for a p-value less than 0.05 ($p < 0.05$).

RESULTS

Phytochemical screening: Phytochemical screening of aqueous root extract of *Carica papaya* revealed the presence of the following secondary metabolites: polyphenols, flavonoids, catechic tannins, quinones, alkaloids, saponins, sterols and polyterpenes. Only gallic tannins were not found (Table 1).

Table 1. Phytochemical compounds of aqueous root extract of *Carica papaya*

Chemical groups		Extract
Polyphenols		+
Flavonoids		+
Tannins	Gallic	-
	Catechic	+
Quinones		+
Alkaloids		+
Saponins		+
Sterols and polyterpenes		+

(+) chemical group present; (-) chemical group absent.

Acute toxicity: The oral administration of aqueous root extract of *Carica papaya* at a maximum dose of 2000 mg/kg b.w. did not cause any changes in the general physical appearance or somato-motor activity of the rats during the observation period. No signs of toxicity such as agitation, tremors, convulsion, salivation, diarrhoea or coma were observed. Moreover, no deaths were recorded among the animals during the 14-day study period. These observations suggest that the lethal dose 50 (LD₅₀) of the aqueous root extract of *Carica papaya* is greater than 2000 mg/kg bw.

Effect of aqueous root extract of *Carica papaya* on the biochemical parameters: The effect of different treatments on the serum biochemical parameters of rats is shown in table 2. Oral administration of paracetamol (500 mg/kg b.w.) after 24 h resulted in a significant ($p < 0.05$) increase in AST, ALT and ALP levels, and a decrease in total protein level of the negative control rats (Group 2) compared to those of the normal control rats (Group 1). However, there was an insignificant increase in GGT and total bilirubin levels. Pre-treatment of animals with silymarin and aqueous root extract of *Carica papaya* decreased serum enzymes and total bilirubin levels, and increased total protein level in groups 3, 4 and 5 compared to those of hepatotoxic group (Group 2). However, these variations were not significant. Although none of the treatments restored biochemical parameters (including AST, ALT, ALP and total protein) to normal levels, the extract at 200 mg/kg bw showed slightly better results than the extract at 100 mg/kg b.w. and silymarin (50 mg/kg b.w.).

Histopathological observations: The effect of aqueous root extract of *Carica papaya* on the liver architecture of PCM-intoxicated rats is presented in Figure 1. Histopathological observations of liver sections from the normal control group (Group 1) showed normal cellular architecture with distinct hepatic lobules, well-organized rows of hepatocytes, open sinusoids, and an identifiable portal space with venules, arterioles and bile ducts (Figure 1a). In contrast, the hepatotoxic group (Group 2) showed severe damage of the cellular architecture with significant steatosis, focal areas of hepatocyte necrosis and congestion (Figure 1b). The liver sections of rats pre-treated with the standard drug silymarin (Group 3) exhibited moderate damage to the cellular architecture, characterized by dilated and congested sinusoids, as well as hepatic congestion and portal and centrilobular inflammation (Figure 1c). In the group of rats pre-treated with a 100 mg/kg b.w. dose of *Carica papaya* aqueous root extract (Group 4), the histological architecture of the liver sections showed slightly altered lobular organization with moderate hepatic steatosis associated with diffuse inflammation (Figure 1d). In the group of rats pre-treated with *Carica papaya* aqueous root extract at 200 mg/kg b.w. (Group 5), the liver architecture was generally preserved, although there were dilated sinusoids and areas of moderate congestion with mild steatosis (Figure 1e).

DISCUSSION

The liver plays an essential role in life because of its vital metabolic and detoxification abilities (Muriel, 2017). It is therefore a primary target for potentially toxic endogenous and exogenous substances. Exposure to these toxic substances leads to the production of many intermediate and end products that can cause hepatocellular death and liver disease (Lee, 2003). In this study, the aqueous root extract of *Carica papaya* was tested for its ability to protect rats' livers against paracetamol-induced hepatotoxicity. The phytochemical screening of this plant extract was first performed using specific reagents. The results showed the presence of polyphenols, flavonoids, catechic tannins, quinones, alkaloids, saponins, sterols and polyterpenes in this extract. Pokhrel and Karki (2021) also demonstrated the presence of these compounds in *Carica papaya* seeds and leaves' extracts. It is well known that natural phenolic compounds including flavonoids, tannins, phenolic acids exhibit hepatoprotective properties (Saha *et al.*, 2019). Steroidal alkaloids isolated from plants can also have anti-inflammatory and hepatoprotective effects, and act as antioxidants and free radical scavengers (Ali *et al.*, 2015). The acute oral toxicity study of aqueous root extract of *Carica papaya*, administrated at the maximum dose of 2000 mg/kg b.w., revealed no signs of toxicity and no mortality in rats during the 14-day observation period. The lethal dose 50 (LD₅₀) is estimated to be greater than 2000 mg/kg b.w. This plant extract is therefore classified as a substance of low toxicity (category 5) according the globally harmonized system of classification of chemicals (OECD, 2001). These results are in accordance with those of Halim *et al.* (2011), who demonstrated that a single oral dose of 2000 mg/kg b.w. of *Carica papaya* leaf aqueous extract did not cause mortality or significant changes in body weight, food and water consumption in rats. In the hepatoprotective study, Wistar rats were pre-treated with *Carica papaya* root extract and silymarin prior to the induction of hepatotoxicity by paracetamol (PCM). Paracetamol-intoxication model is a widely used model to study the

Table 2. Effect of aqueous root extract of *Carica papaya* on the serum biochemical parameters in paracetamol-intoxicated rats

Treatment	Biochemical parameters					
	AST (IU/L)	ALT (IU/L)	ALP (IU/L)	GGT (IU/L)	Total bilirubin (mg/L)	Total protein (g/L)
Group 1 Distilled water	129.9 ± 6.33 ^a	26.66 ± 1.63 ^a	104.3 ± 0.64 ^a	1.94 ± 0.26 ^a	9.15 ± 0.03 ^a	74.37 ± 0.41 ^a
Group 2 Distilled water + PCM	192.7 ± 9.68 ^b	45.83 ± 2.51 ^b	199.6 ± 17.41 ^b	2.66 ± 0.8 ^a	9.5 ± 0.04 ^a	61.3 ± 2.96 ^b
Group 3 Silymarin (50 mg/kg) + PCM ₄	172.1 ± 7.85 ^b	35.16 ± 1.94 ^b	150.4 ± 7.86 ^{ab}	1.47 ± 0.34 ^a	9.35 ± 0.09 ^a	62.99 ± 1.59 ^b
Group 4 AECp (100 mg/kg) + PCM	178.02 ± 7.64 ^b	36.72 ± 3.02 ^b	170.0 ± 18.93 ^b	2.5 ± 0.64 ^a	9.5 ± 0.17 ^a	62.67 ± 3.98 ^b
Group 5 AECp (200 mg/kg) + PCM	161.9 ± 6.19 ^{ab}	34.14 ± 1.24 ^b	133.4 ± 10.7 ^a	1.77 ± 0.42 ^a	9.53 ± 0.07 ^a	62.93 ± 2.52 ^b

AECp: aqueous root extract of *Carica papaya*; PCM: paracetamol. Values are expressed as means ± SEM (n = 5).

Letters represent statistical significance. Means in the same column with different superscript letters are significantly different (p < 0.05).

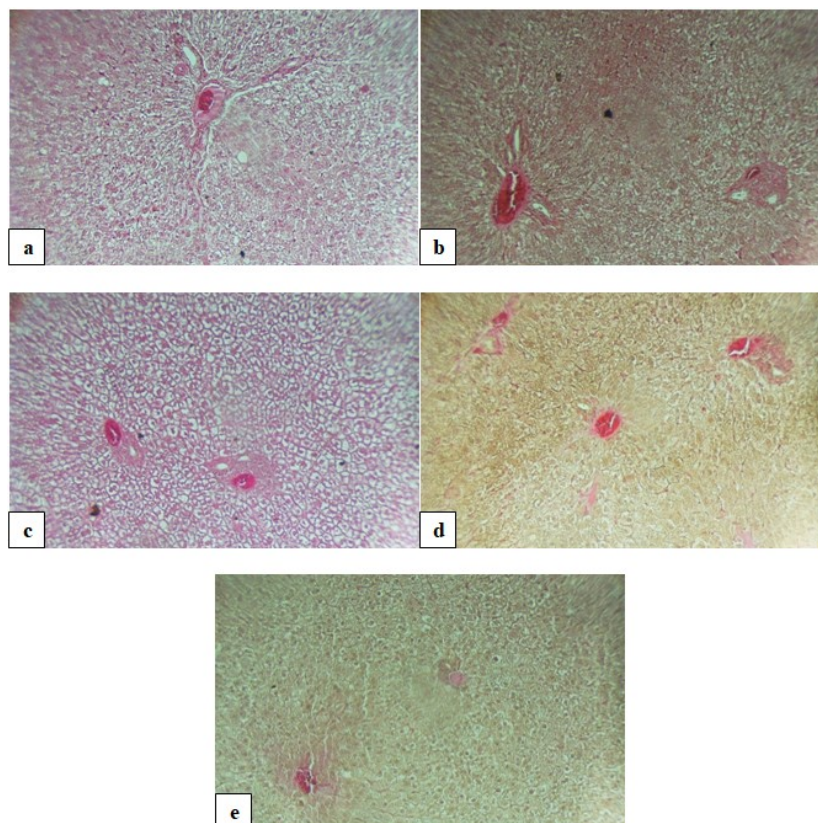


Figure 1: Histology of liver section of rats. (a) Liver section of normal control group rats (H-E ×200); (b) Liver section of PCM-intoxicated group rats (H-E ×200); (c) Liver section of Silymarin pre-treated group rats (H-E ×200); (d) Liver section of AECp (100 mg/kg) pre-treated group rats (H-E ×200); (e) Liver section of AECp (200 mg/kg) pre-treated group rats (H-E ×200)

potential hepatoprotective activity of extracts and compounds. It is a common antipyretic and analgesic drug that can be purchased freely without a prescription in a pharmacy. An over dosage administration can result in hepatic damage. In fact, when taken in high doses, it is oxidized by cytochrome P450 monooxygenase to form N-acetyl-p-benzoquinoneimine (NAPQI), a harmful and highly reactive metabolite, responsible for the PCM toxic effect to the liver (Hazai, 2002; Katzung, 2004). This metabolite is normally conjugated with glutathione (GSH) and excreted in urine (Mazaleuskaya, 2015). When the level of NAPQI formed exceeds that of GSH available for conjugation, unbound NAPQI becomes toxic and reacts with cellular macromolecules, resulting in cell damage such as necrosis (Hinson, 2010). The toxicity of paracetamol was assessed by determining biochemical parameters such as AST, ALT, ALP, GGT, total bilirubin, total protein, and histopathological analysis of the rats' livers. AST and ALT are the most commonly measured biochemical parameters for detecting hepatocyte damage. ALT is considered a more specific indicator of cytolysis and liver inflammation, since AST is also present in other organs such as the heart and skeletal muscles. The total protein level is an indicator of liver

function. As for ALP, GGT and total bilirubin, their high level in serum indicates a disruption in bile flow due to impaired bile formation or the appearance of an obstruction in the bile ducts, causing cholestasis and jaundice (Martin, 1992). In this study, a significant increase in serum transaminase (AST and ALT) and ALP levels, and a decrease in total protein levels, was observed in rats intoxicated with PCM and untreated. This increase in enzyme levels could be due to a disruption in liver function and hepatocyte damage, which leads to cytolysis and the release of intracellular enzymes into the blood. However, GGT and total bilirubin levels did not increase significantly in intoxicated and untreated rats. The preventive treatment of rats with the aqueous root extract of *Carica papaya* and silymarin led to a decrease in AST, ALT, ALP, GGT and total bilirubin levels and an increase in total protein levels. Although these changes were not significant, they could indicate slight stabilization of the cell membrane and the start of repairing liver tissue damage caused by PCM. Histopathological analysis of liver sections of rats corroborated the results of the biochemical investigation, indicating minimal attenuation of the hepatic toxicity of PCM by the plant extract. In fact, hepatocyte lesions (necrosis), significant steatosis and

congestion were observed in livers of PCM-intoxicated and untreated rats, while those of pre-treated rats with *Carica papaya* extract and silymarin exhibited moderate steatosis, congestion and inflammation.

CONCLUSION

This study found that the aqueous root extract of *Carica papaya* can reduce the hepatotoxic effects of a high dose of paracetamol. While its hepatoprotective effect is only moderate, this plant extract could still be considered a natural alternative to pharmaceutical treatments.

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Abbreviations

AECp: Aqueous root extract of *Carica papaya*

ALP: Alkaline phosphatase

ALT: Alanine aminotransferase

ANOVA: Analysis of variance

AST: Aspartate aminotransferase

b.w.: body weight

GGT: Gamma-glutamyl transferase

GSH: Glutathione

H-E: Haematoxylin and eosin

NAPQI: N-acetyl-p-benzoquinoneimine

OECD: Organisation for Economic Cooperation and Development

PCM: Paracetamol

SEM: Standard errors of the mean

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