HEPATOPROTECTIVE ACTIVITY OF AQUEOUS EXTRACT OF CASHEW APPLE CAKE (*Anacardium occidentale* L.) IN RATS AND MICE

ABSTRACT

Aims: The aqueous extract of cashew apple cakes, rich in molecules of pharmacological interest, could be used against many diseases. Thus, the aim of the present work is to evaluate its hepatoprotective activity in rats and mice.
Methodology: Two batches of rats weighing between 200 and 300 grams, with five rats per batch, were pretreated for eleven days with the aqueous extract of cashew apple cakes at concentrations ranging from 150 to 300 $mg.Kg^{-1}$ bw, then intoxicated with paracetamol at 2 $g.Kg^{-1}$ bw, for three days. The blood of these rats was collected and submitted to biochemical analyses.
Two batches of mice weighing between 20 and 30 grams, with five mice per batch, were pretreated with the same test substance at concentrations also ranging from 150 to 300 $mg.Kg^{-1}$ bw, then intoxicated with paracetamol before receiving phenobarbital. Afterwards, their sleep time was evaluated
Results: In rats, paracetamol intoxication materialized by the increase in serum ALT activity ranging from 109±5.19 to 571±20.28 $IU.L^{-1}$ and that of AST ranging from 144±5.77 to 428±14.19 $IU.L^{-1}$. Similarly, direct bilirubin increased from 0 to 1.08± 0.58 $mg.dl^{-1}$. These increases in transaminase activity and bilirubin levels were significantly decreased in rats pretreated with the aqueous extract of cashew apple cake. In mice, the phenobarbital test showed a 29.82 to 38.59% decrease in sleep time in mice pretreated with the aqueous extract of cashew apple cakes.
Conclusion: The aqueous extract of cashew apple cakes influencing biochemical parameters such as ALT, AST, bilirubin and sleep time, could therefore be used in the prevention of liver diseases, in traditional medicine.

Keywords: hepatoprotective- Anacrdium Occidentale L *-mouse-rat- transaminase - phenobarbital*

1. INTRODUCTION

The liver is an essential organ because of its multiple functions. In addition to regulating blood sugar, remodeling chylomicrons to meet the body's needs, it plays a fundamental role in the detoxification of ammonia, cholesterol and exogenous substances. During these biotransformation processes, the liver is exposed to aggressions that can lead to hepatopathies impacting its physiology and thus engaging the vital prognosis of the subject. According to studies carried out on the etiology of chronic hepatopathies diagnosed at the University Hospital of Cocody-Abidjan on 300 patients, 46% suffered from cirrhosis, 43% from chronic hepatitis and 11% from liver cancer. The first place of drug intoxications was taken by antituberculosis drugs, with 82.35%. Alcohol and viruses occupy an increasingly important place in this pathogenesis [1]. These epidemiological data revealing a diverse etiology of hepatopathies sound an alarm.

To protect this vital organ, synthetic hepatoprotective drugs are used, as well as natural substances (plants and agro-resources) with similar effects with the advantage of price and access [2, 3]. The cashew apple cake, containing pharmacological molecules of interest ncluding vitamin C and polyphenols [4, 5], could be an asset in the search for this protection. *Aanacardium Occidentale* is a tree of 8 to 10 meters high, belonging to the Anacardiaceae family, which also includes mango (*Mangifera indica* L.) and pistachio (*Pistacia vera* L.) trees. With a diameter of up to 12 to 15 meters, it has simple, alternate, leathery leaves that are rounded at the top and narrowed at the base [6].The fruit, the cashew nut, hangs from a fleshy, juicy stalk, red or yellow in color when ripe, called the cashew apple [4].

In traditional medicine, the cashew apple, is used against many ailments. The decoction of the bark of *Aanacardium Occidentale* L., is used as an antihypertensive and anti-dysenteric. The caustic oil of walnuts, treats scabs. The fruit relieves ulcers and toothache [6].

Studies carried out on the cashew apple indicate that its aqueous extract has a self-regulating glycemic effect [5]. It is also said to be analgesic, anti-inflammatory and antipyretic [7].
To enrich these pharmacological data, this work was conducted to evaluate the hepatoprotective effects of the cashew apple cake aqueous extract in rats and mice intoxicated with paracetamol.

2. MATERIALS AND METHODS

2.1 Material

2.1.1 Plant material

Cashew apples of red or yellow color, without dents were selected for this study, from Korhogo community in Far North of the Ivory Coast. They were harvested from the trees while some were picked after they fell in December, 2021.

2.1.2 Animal material

Wistar albino rats were used for hepatoprotective testing. They weigh between 200 and 300 grams. They come from the Pasteur Institute of Adiopodoumé, and were raised at the Felix Houphouët Boigny University animal house.
Male and female mice of the species *Mus musculus* weighing between 20 and 30 g were used in the sleep tests using phenobarbital. They also came from the animal house of the Pasteur Institute of Adiopodoumé located on the road to Dabou (Ivory Coast). Transported to the animal house of the University Peleforo GON COULIBALY, they were raised at an average temperature of 28°C with a relative humidity of 70% and fed with pellets from IVOGRAIN.

2.1.3 Chemicals and physiological fluid

- Glibenclamide arrow: (SANOFI-AVENTS (France).
- D (+) Glucose anhydrous: E. MERCK, Darmstadt (Germany).
- Nacl 0,9%:

2.2 Methods

2.2.1 Preparation of the cashew apple cake aqueous extract

The preparation of the aqueous extract of cashew apple was conducted according to the method of [8].
The apples collected were cleaned, washed and then disinfected for 30 min with 100 ppm of active chlorine in tanks. They were then rinsed with water before being squeezed. Pressing and spinning were done manually. The cakes, separated from the juice, were dried in the shade between 25 and 28°C. Dried, these cakes are crushed and reduced to powder. This powder was used in the preparation of the aqueous extract of cashew apple. Fifty grams (50) of crushed cashew apple cake were mixed on a magnetic stirrer of the AGIMATIC-N type for 24 hours in a liter of distilled water. The resulting solution was filtered through cotton wool and Wattman paper. The same operation was repeated. Distilled water was added to the pellet, then mixed for 2 hours and also filtered. The filtrates were collected in a flask and dried in the study at 60° C. The powder obtained, perfectly soluble in water, was used as the aqueous extract of cashew apple.

2.2.2 Effect of aqueous extract of cashew apple cake on biochemical parameters of rats intoxicated with paracetamol.

For the determination of the hepatoprotective properties of the aqueous extract of cashew apple cake (CAJ), was recommended among other methodological approaches that of [9] slightly modified. For this purpose, fifteen (15) rats were used for the study. These rats were weighed and deprived of food for 18 hours, with free access to water only one hour before the administration. Then, they were divided into 5 batches of three rats, as follows:

Batch 1 (negative control): received only distilled water (10 ml.Kg^{-1} bw) orally for 14 days
Batch 2: Distilled water (10 ml.Kg^{-1} bw) administered orally for 11 days, followed by the oral administration of paracetamol at 2 g.Kg^{-1} bw for 3 days
Batch 3: Silymarin 100 mg.Kg^{-1} bw administered orally for 11 days, followed by oral administration of paracetamol 2 g.Kg^{-1} bw for 3 days
Batch 4: CAJ 150 mg.Kg^{-1} bw administered orally for 11 days, followed by oral administration of paracetamol 2 g.Kg^{-1} bw for 3 days.
Batch 5: CAJ 300 mg.Kg^{-1} bw administered orally for 11 days, followed by oral administration of paracetamol 2 g.Kg^{-1} bw for 3 days.

2.2.3. Blood sampling technique for biochemical parameters analysis

Twenty-four hours after the end of the treatments, the animals were weighed and anesthetized with ether. Then, their blood collected from the retro orbital sinus of the animals' eyes was transported in dry tubes to the laboratory for biological analysis. The blood from the dry tubes was centrifuged at 3000 rpm and the supernatant was used for biochemical analysis.

2.2.4. Transaminase assay

The determination of aspartate aminotransferase (AST/GOT) and alanine aminotransferase (ALT/GPT) was performed in the biochemistry laboratory of the Faculty of Medicine of Abidjan-Cocody. It was performed with commercial Cobas kits bearing technical information ALTL: ACN 685; ALTPL: ACN 684 for ALT/GPT and ASTL: ACN 687; ASTPL: ACN 686 for AST/GOT. The Cobas C111 analyzer was used for the different determinations, according to the manufacturer's recommendations. The concentration of these enzymes is expressed in international units per liter of substrate (IU/L).

2.2.5 Conjugated bilirubin assay

The analyses were carried out according to the Malloy-Evelyn principle [10], with the commercial cobas kit bearing the technical name BILD2: ACN 734. Cobas C111 was the analyzer used for the assays.

2.2.6 Liver sampling

At the end of all treatments, the liver was harvested and weighed. The relative weight (RW) of the liver was calculated in relation to the body weight according to the formula given by [11]:

$$RW = \frac{\text{Liver weight (LW)}}{\text{Body weight (BW)}} \times 100$$

2.2.7 Study of the effect of the cashew apple cake aqueous extract (CAJ) on the sleep time of mice intoxicated with paracetamol and given phenobarbital

This study was performed according to the method of [12]. After 12 hours of fasting, 30 mice were divided into five batches of six. They were then treated as follows:
Batch 1 (negative control): received only distilled water (0.1 ml.Kg^{-1} bw)
Batch 2: distilled water (0.1 ml.Kg^{-1} bw) administered orally for 11 days, followed by intraperitoneal (IP) administration of paracetamol at 200 mg.Kg-1 PC for 3 days
Batch 3: Silymarin 100 mg.Kg^{-1} bw administered orally for 11 days, followed by IP administration of paracetamol 200 mg.Kg^{-1} PC for 3 days
Batch 4: CAJ 100 mg.Kg^{-1} bw administered orally for 11 days, followed by IP administration of paracetamol 200 mg.Kg^{-1} bw for 3 days.
Batch 5: CAJ 200 mg.Kg^{-1} administered orally for 11 days, followed by IP administration of paracetamol 200 mg.Kg^{-1} bw for 3 days.
24 hours after these different treatments, 80 mg.Kg^{-1} bw of phenobarbital was administered orally to the mice in order to evaluate the effect of aqueous extract of cashew apple cake on the sleep time of the animal.

The biological tests were carried out in accordance with the internationally accepted principles of the European Community Directive (Council Directive 86/609/EEC of 24 November 1986).

2.3 Statistical analysis

Statistical data expressed as means ± standard error were obtained from the (n=5) separate experiments. The averages calculated were compared from Student's test (t). When $p \leq 0.05$, the difference is said to be significant. The curves and statistical analysis were performed using Graph Pad Prism 5.1 San Diego, CA, USA.

3. RESULTS

3.1 Effect of aqueous extract of cashew apple cake on biochemical parameters of rats intoxicated with paracetamol.

Table 1, presents the results on the effect of aqueous extract of cashew apple cake on biochemical parameters of rats intoxicated with paracetamol.

In the control rat given only distilled water as treatment, ALT and AST activities were 109 and 144 $IU.L^{-1}$, respectively. The bilirubin level is zero (0) $mg.dL^{-1}$. AST activity is 428 $IU.L^{-1}$ ($P < 0.0001$) and ALT activity is 571 $IU.L^{-1}$ ($P < 0.0001$) in the control rat intoxicated with paracetamol. In the latter, the bilirubin level was 1, 08 ± 0.5 $mg.dL^{-1}$ ($P < 0.0001$). Paracetamol at 2 $g.Kg^{-1}$ bw, therefore, caused a very significant increase in serum transaminase activity, and in direct bilirubin level. In animals pretreated with silymarin followed by intoxication with paracetamol, serum transaminase activities decreased significantly, they are now 173 ± 11.55 $IU.L^{-1}$ for ALT and 198 ± 4.56 $IU.L^{-1}$ for AST ($P < 0.01$). Those pretreated with CAJ followed by paracetamol intoxication, show serum transaminase activities reminiscent of the normal control. The bilirubin level is at its initial value of 0 $mg.dL^{-1}$ in all rats treated with silymarin or aqueous extract of cashew apple cake.

Table 1 Effect of aqueous extract of cashew apple cake (CAJ) on biochemical parameters of rats intoxicated with paracetamol

Treatment		AST (IU/L)	ALT (IU/L)	DBil (mg/dL)
Batch 1: normal (distilled water)		144 ± 5.77	109± 5.19	0
Batch 2: PCM (2 g/Kg bw)		428 ±14.19****	571 ±20.28****	1,08 ± 0.58****
Batch 3: silymarin + PCM (2 g/Kg bw)		198 ± 4.56**	173± 11.55**	0
Batch 4 and 5: CAJ + PCM (2 g/Kg bw)	Batch 4: CAJ (150 $mg.Kg^{-1}$ bw)	132 ± 17.32	94± 5.25	0
	Batch 5: CAJ (300 $mg.Kg^{-1}$ bw)	157 ± 11.55	99± 8.33	0

The AST/ALT ratio (428/571) in rats intoxicate with paracetamol is 0.74. Lower than 1, this ratio indicates a hepatic cytolytis. Values are given as means ± standard deviation (N=3). Student's t test: **P < 0.01; ***P <0.0001 compared to normal control values. PCM: paracetamol. CAJ: cashew apple aqueous extract

3.2. Effect of aqueous extract of cashew apple cake on body weight, liver weight and relative weight of paracetamol intoxicated rats.

Table 2 shows the results of the effect of aqueous extract of cashew apple cake on body weight, liver weight and relative liver weight of rats.

During treatment, all animals, including the normal control (treated only with distilled water), experienced decreases in live weight. The control intoxicated with paracetamol and untreated had the greatest weight loss of 30±6.33 grams ($P < 0.05$). Animals pretreated for 11 days with silymarin followed by intoxication with paracetamol have a less significant weight loss of seven (07) grams. In

animals pretreated with aqueous extract of cashew apple cake and then intoxicated with paracetamol, this weight loss varied between eleven (11) and thirteen (13) grams.
The relative liver weight of the control animal treated with distilled water was 4.19 ± 0.35 grams. In the control rat intoxicated with paracetamol and not treated, the relative liver weight of 3.09 ± 1.25 grams, shows a decrease. In rats treated with silymarin or aqueous extract of cashew apple cake and then intoxicated with paracetamol, the relative liver weight increased and was close to that of the normal control.

Table 2. Effect of aqueous extract of cashew apple cake on body weight, liver weight and relative weight of rats intoxicated with paracetamol

groups	Weight (g)	Weight of liver (g)	Relative liver weight (%)
batch 1: Normal (distilled water)	05±3.15	8.189±2,35	4.19±0.35
Batch 2: PCM	30±6.33*	7.046±2,89	3.06±1.25
Batch 3: Sily + PCM	07±5.01	8.086±1,68	4.07±0.89
Batch 4: CAJ (150 mg/Kg bw) + PCM	13±4.15	7.655±2,67	3.73±1.23
Batch 5: CAJ (300 mg/Kg bw) + PCM	11±4.15	7.700±3,89	3.88±0.95

Values are given as means ± standard deviation (N=3). Student's t test: *P <0.05; compared with normal control values. PCM: paracetamol (2 g/Kg bw). CAJ: cashew apple aqueous extract. Sily: Silymarin

3.3. Sleep test in mice intoxicated with paracetamol and given phenobarbital

Table 3 shows the results of sleep time of mice intoxicated with paracetamol and given phenobarbital. The non-intoxicated mouse (normal control), having received only water and phenobarbital at 80 $mg.kg^{-1}$ bw was put into a sleep that lasted 160 minutes. The mouse intoxicated (intoxicated control) with paracetamol a 200 $mg.kg^{-1}$ bw and not treated, was plunged into a sleep of longer duration, 250 minutes ($P < 0.01$). The paracetamol-intoxicated mouse treated with silymarin had a sleep duration of 165 minutes, approximately equal to that of the normal control. Indeed, this sleep time was shortened by 85 minutes compared to that of the intoxicated control. The mouse intoxicated with paracetamol and treated with the aqueous extract of cashew apple cake at 300 $mg.Kg^{-1}$ bw followed by intraperitoneal administration of phenobarbital, was plunged into a sleep whose duration was 175 minutes, a value close to those of the normal mouse and the mouse intoxicated and treated with silymarin. The reduction in sleep time under these conditions was 38.59%. The mouse of lot 4, treated with the aqueous extract of cashew apple cake at 150 $mg.Kg^{-1}$ bw had a relatively long sleep time of 200 minutes, which corresponds to a reduction of 29.82% compared to the sleep time of the mouse of lot 2 (intoxicated and untreated control).

Table 3. Effect of aqueous extract of cashew apple cake on sleep time of mice intoxicated with paracetamol and given phenobarbital

Treatment ($mg.Kg^{-1}$ bw)	Batch 1 Water + PHE	Batch 2 Water + PCM + PHE	Batch 3 Silymarin 100 mg/Kg bw + PCM + PHE	Batch 4 CAJ 150 mg/Kg bw + PCM + PHE	Batch 5 CAJ 300 mg/Kg bw + PCM + PHE
Sleep time (minutes)	160±33.09	285± 23.09**	165± 18.78	200± 20.56	175± 19.84
Percentage reduction in sleep time (%)	-	-	42.10	29.82	38.59

Values are given as means ± standard deviation (N=3). Student's t test: **P < 0.01 compared with normal control values. PCM: paracetamol **(200 mg/Kg bw)**; PHE: phenobarbital **(80 mg/Kg bw)**; CAJ: cashew apple water extract.

4. DISCUSSION

The objective of this work was to evaluate the hepatoprotective activity of an aqueous extract of cashew apple cake in rats and mice intoxicated with paracetamol.
The liver has a metabolic function of protein, partly characterized by transaminations reactions, producing precursors of gluconeogenesis from amino acids. These reactions are mainly catalyzed by ALT and AST, which are found in the liver and muscle, more precisely in the cytosol, but also in the mitochondria in the case of AST. The increase in serum activity of these enzymes, in the level of direct bilirubin associated with the decrease in live weight of the animal and in the relative weight of the liver in rats intoxicated with paracetamol at 2 $g.Kg^{-1}$ bw, indicates that hepatolysis is taking place since the ASAT/ALAT ratio is less than one [13].

The toxicity of paracetamol is explained by its hepatic biotransformation during which a reactive metabolite N-acetyl-p-benzoquinone-imine is produced by the cytochrome P450 system [14]. This reactive molecule leads to hepatic necrosis due to a depletion of glutathion, an endogenous antioxidant whose role is to protect the hepatocyte membranes from the risks of peroxidation. This peroxidation of hepatocyte membranes leads to the release of transaminases into the bloodstream, resulting in increased activity. Moreover, this dysfunction can justify the increase in the level of direct bilirubin not transformed into conjugated bilirubin, which cannot be produced in a damaged hepatocyte. Finally, the decrease in protein synthesis due to the disturbance of the physiology of a necrotic liver would be the cause of the decrease in the weight of the animal and the relative weight of the liver.
In animals pretreated with silymarin and then intoxicated with paracetamol, the decrease in serum transaminase activity and the increase in the weight of the animal and its relative weight, although less formal, indicates that this reference molecule has a hepatoprotective power. These same remarks being observed in animals pretreated with the aqueous extract of cashew apple cake for concentrations ranging from 150 to 300 $mg.Kg^{-1}$ bw and intoxicated, suggest that this vegetable substance would also be endowed with a hepatoprotective activity in the same way as the silymarin.
This hepatoprotective activity of the aqueous extract of cashew apple could be attributed to its molecular content indicating the presence of vitamin C and polyphenols [4, 5]. These molecules, some of which have potential antioxidant effects [15], could therefore suppress glutathion depletion and deactivate N-acetyl-p-benzoquinone imine, or inhibit cytochrome P450, as does silymarin. Similar results have been observed with *Rhamnus alaternus* L., and Ananas comosus, plant substances considered as hepatotropic [16, 17].

Phenobarbital is an antiepileptic drug that increases the sleep time of mice intoxicated with paracetamol, as shown by the results. This increase, could be attributed to a dysfunction of the liver and the life span of this antiepileptic molecule. In the presence of CAJ for concentrations ranging from 150 to 300 $mg.Kg^{-1}$ bw, this sleep time decreases from 28.82 to 38.59%. This decrease is synonymous with an improvement of the liver physiology and thus a confirmation of the hepatoprotective effect of this natural substance. Similar results were obtained with *Terminalia superba* in rats [18]. However, the rat would be more resistant to the toxic effect of paracetamol than the mouse in view of the sleep times recorded and the toxic doses of paracetamol used.

5. CONCLUSION

This study showed that the aqueous extract of cashew apple cakes reduced the increase in serum transaminase activity (ALT and AST) and direct bilirubin levels in rats intoxicated with paracetamol. Similarly, it reduced the sleep time of mice intoxicated with paracetamol and given phenobarbital. The aqueous extract of cashew apple cakes influencing these biochemical parameters and the sleep time of mice subjected to the phenobarbital test, could therefore be of use in the treatment of hepatitis in traditional medicine.

Ethical Approval

Animal Ethic committee approval has been taken to carry out this study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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