Research Article

Evaluation of the anti-hypercholesterolemic activity of the aqueous extract of the leaves of *Hura crepitans* L. (Euphorbiaceae) in wistar rats

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Abstract

Hypercholesterolemia is an excess of cholesterol in the blood, responsible for around 4,4 million deaths (7,9%) worldwide. It is a risk factor for cardiovascular disease, which accounts for 17,7 million deaths worldwide, representing a global mortality rate of 31 %. The aim of the present study was to evaluate the anti-hypercholesterolemic effect of aqueous extract of *Hura crepitans* L. (Euphorbiaceae) leaves in Wistar rats. The aqueous extract of *Hura crepitans* L. leaves was prepared by decoction. The effect of this extract on hypercholesterolemia induced by 4 % cholesterol was evaluated according to the standard protocol. To this end, six (6) batches of five (5) rats each were formed and treated for eight (8) weeks by gavage with the different products. Results showed that the aqueous extract of *Hura crepitans* L. significantly reduced ALAT, ASAT, creatinine, total cholesterol, LDL-cholesterol, triglycerides and the atherogenicity index, and increased HDL-cholesterol levels, compared to rats in the induction batch given 4% cholesterol alone. Chemical screening revealed the presence of metabolites such as flavonoids, alkaloids, tannins, anthraquinones, terpenoids, oses and holosides. This would justify the effects observed and its use in traditional medicine.

Keywords: Anti-hypercholesterolemic, cholesterol, *Hura crepitans* L.

Introduction

Hypercholesterolemia is more precisely due to an increase in the level of total cholesterol found in large quantities in the blood, causing the formation of plaques on the inner lining of blood vessels (Thanassoulis et *al*., 2022). In view of the inaccessibility of conventional medicines and their exorbitant prices, which do not facilitate access for all, their side effects and the scarcity of certain products, African populations in general, and the Congolese in particular, turn to traditional medicine for treatment. Nowadays, many researchers and pharmaceutical laboratories around the world are turning to medicinal plants thanks to the virtues of their various organs and also the different remedies developed from them, which constitute the most widely used therapeutic means in Africa (Mouanda Ngouadi, 2023 ; Mashi et *al*., 2019). Consequently, the present study proposes to evaluate the anti-hypercholesterolemic effect of the aqueous extract of *Hura crepitans* L. leaves in Wistar rats.

Materials and methods

Plant material

Leaves of *Hura crepitans* L., collected in the Bouenza department precisely at Mienge-Mienge (April 28, 2023) were used and identified at the National Herbarium at the National Institute of Exact and Natural Sciences (IRSEN) in Brazzaville by comparison with a reference specimen registered under number (concession I.R.S.C., Brazzaville, coll: P. Sita n°874 Date: 26-1-1963). These leaves were dried at room temperature (27 ± 2°C), protected from sunlight and then pulverized.

Animal material

Female rats of Wistar strain with body weight between 140 and 150 g were used. These rats were supplied by the animal

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house of the Faculty of Science and Technology of the Marien N'GOUABI University. These rats had free access to standard food and drinking water.

Preparation of *Hura crepitans* aqueous extract

The aqueous extract of *Hura crepitans* L. leaves was prepared by decoction at 10%. The resulting decoction was evaporated in an oven at 70°C, and the dry extract obtained was used for the various tests.

Preparation of the coconut oil solution

The cholesterol solution was prepared by mixing 0.4 g of cholesterol powder in 10 mL of coconut oil until it was completely dissolved. This was freshly prepared for each administration.

Evaluation of the effects of aqueous extract of *Hura crepitans* leaves on 4% cholesterol-induced hypercholesterolemia and obesity in Wistar rats

The effect of the aqueous extract of *Hura crepitans* leaves on 4% cholesterol-induced hypercholesterolemia was evaluated according to the protocol described by Innih et *al*. (2021).

Six (6) batches of five (5) rats each were formed and treated for eight (8) weeks per os as follows:

- batch 1 received distilled water (1 mL/100 g/d, b.w.);
- batch 2 received coconut oil (1 mL/100 g/d, b.w.);
- batch 3 received 4% cholesterol solution (30 mg/kg/d, b.w.);
- batch 4 received 4% cholesterol solution (30 mg/kg/d, b.w.) + Atorvastatin (20 mg/kg/d, b.w.);
- batches 5 and 6 received 4% cholesterol solution (30 mg/kg/d, b.w.) + aqueous extract of *Hura crepitans* leaves at doses of 250 and 500 mg/kg/d, b.w. respectively.

During treatment, the effect of the aqueous extract of *Hura crepitans* leaves was assessed on weight evolution by recording the body weight of each batch of rats at the end of each week, for the eight (8) weeks.

At the end of treatment, rats were fasted for eighteen hours (18 h) and then sedated with diethyl ether. Blood samples were taken by puncture from the retro-orbital sinus of the eye. Blood was collected in dry tubes and centrifuged (TD4A-WS DEESK) at 3,000 rpm for 15 minutes, and the serum obtained was used for biochemical analyses: Alanine aminotransferase (ALAT), Aspartate aminotransferase (ASAT), High Density Lipoprotein cholesterol (HDL-C), Total cholesterol (TC), Triglycerides (TG), Creatinine and Glucose using a branded reader (BioMate 3S). The Plasma Atherogenicity Index (PAI) and VLDL levels were deduced according to the following formulas:

PAI= TC/HDL-C and VLDL = TG/5. (Guenzet et *al*., 2017; Mikolo et *al*., 2020)

After blood sampling, the rats were sacrificed, and macroscopic observation of the liver and gynoid fat distribution was made.

Results

Evaluation of the effects of aqueous extract of *Hura crepitans* L. leaves on 4% cholesterol-induced hypercholesterolemia and obesity in Wistar rats

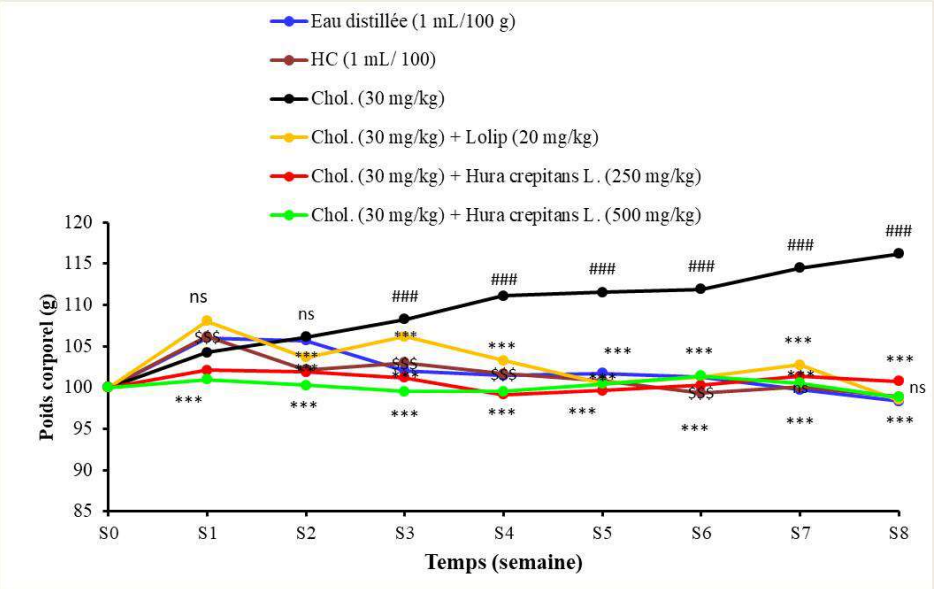

Figure 1: Weight gain in rats treated with aqueous *Hura crepitans* extract. ED: Distilled water; HC: Coconut oil; HC-Chl: Coconut oil + Cholesterol; Extract: *Hura crepitans* L. Results are expressed as mean ± mean standard error, n= 5 Rats per batch, *p<0.05, **p<0.01, ***p<0.001 significant difference, compared with cholesterol control ;#p<0.05, ##p<0.01, ###p<0.001 significant difference, compared with coconut oil control; $p<0.05, $$p<0.01, $$$p<0.001 significant difference, compared with distilled water control and ns: not significant Legend of abbreviations.

Effect on body weight

Figure 1 shows the weight evolution of the rats over the eight (8) weeks of the experiment. The results show that the 4% cholesterol solution alone resulted in a highly significant increase ($p<0.001$) in the body weight of the rats compared with the control batch (distilled water). However, the aqueous extract of *Hura crepitans* leaves at doses of 250 and 500 mg/Kg respectively resulted in a highly significant ($p<0.001$) decrease in body weight. The same observation was made in rats given the cholesterol solution with the reference molecule (Atorvastatin 20 mg/kg).

Effect on biochemical parameters

Table 1 shows the results of the effect of *Hura crepitans* aqueous extract on biochemical parameters. The table shows that administration of the 4 % cholesterol solution caused an increase in biochemical parameters (ALAT, ASAT, TC, LDL-C and creatinine), a decrease in HDL and no significant change in VLDL. Aqueous extract at doses of 250 and 500 mg/kg, on the other hand, significantly reduced the levels of these parameters, with an increase in HDL.

Effect on the liver

Figure 2 shows the effect of *Hura crepitans* aqueous extract on rat liver after treatment. Macroscopic observation of the livers of rats treated with the cholesterol solution (30 mg/kg) reveals the presence of lesions with a complete change in coloration compared with the control batch (distilled water). However, as with the reference batch, no apparent changes were observed in rats treated concomitantly with both doses of aqueous extract with cholesterol (30 mg/kg).

Effect on gynoid fat distribution

Table 2 shows the effect of aqueous extract of *Hura crepitans* L. leaves on abdominal fat mass in rats. The table shows a highly significant ($p<0.001$) reduction in fat mass in rats treated with 250 mg/kg and 500 mg/kg of aqueous extract of *Hura crepitans* L. leaves respectively, and a significant ($p<0.01$) reduction in rats treated with the reference batch (Atorvastatin) compared with the positive control batch treated with cholesterol solution (30 mg/kg) alone. This phenomenon is clearly illustrated in figure 3.

Effect on indexes

Table 3 shows the effect of aqueous extract of *Hura crepitans* L. on hepatic and adipose indexes in rats. The table shows that the aqueous extract at doses of 250 mg/kg

Table 1: Effect of aqueous extract of *Hura crepitans* leaves on biochemical parameters in rats. Results are expressed as mean ± standard mean error, with n = 5. *p<0.05, **p<0.01, ***p<0.001 significant difference from cholesterol control; ns: not significant ; # p<0.05, ##p<0.01, ###p<0.001 significant difference from coconut oil control; $p<0.05, $$$p<0.01, $$$p<0.001 significant difference from distilled water control.

	Treatment					
Biochemical parameters	**ED 1mL/100g**	**HC 1mL/100g**	**Chol. (30 mg/kg)**	**Chol. (30 mg/kg) + + l'Atorvastatine 20mg/kg**	**Chol. (30 mg/kg) + *Hura crepitans* (250mg/kg)**	**Chol. (30 mg/kg) + *Hura crepitans* (500mg/kg)**
ALAT (UI/L)	32,66 ± 4,08	57,31 ±8,81$$$	50,46 ± 12,18###	33,10 ± 4,32***	46,66 ± 12,22*	34,61 ± 2,14***
ASAT (UI/L)	95,22 ± 6,69	81,65± 22,98$$$	111,57± 28,7###	91,14± 6,07***	103,98 ±14,16**	82,05 ± 10,76***
CREAT (mg/dL)	557,5 ± 51,05	114,5 ± 42,27$$$	362,5 ±111,68###	255 ± 79,00***	165 ± 88,24***	183,33±58,11***
HDL (mg/dL)	30,52 ± 16,59	23,65± 5,7ns	24,26 ± 6,78ns	26,85±13,11ns	33,76 ± 6,58**	34,59 ±29,45***
LDL (mg/dL)	9,44 ± 15,48	57,96 ± 12,84$$$	38,99 ±8,31###	20,03±15,97***	20,50 ± 19,03***	8,92 ± 28,80***
CT (mg/dL)	30,21 ± 2,91	91,47 ± 16,87$$$	73,46 ± 1,53##	54,94 ± 5,82***	42,63 ± 0,58***	59,52 ±1,20***
TG (mg/dL)	54,62 ± 6,64	49,24±11,86ns	51,04± 7,50#	40,28 ± 6,69***	50,09 ± 10,35ns	49,56 ± 9,13***
VLDL (mg/dL)	10,92±0,32	9,84 ± 0,44ns	10,20 ±19,26ns	8,05 ±0,21ns	10,01 ± 0,18ns	9,912 ±0,20ns
Glucose (g/L)	0,85 ± 0,34	0,97 ± 0,30ns	0,30 ± 0,10###	0,72 ± 0,19*	0,96 ± 0,06*	0,70 ± 0,12*
IAP	2,86 ± 1,56	4,65 ± 1,13$	4,68 ± 2,16 ns	4,27 ± 1,73ns	0,86 ± 0,51*	1,60 ± 0,61*

ED: Distilled water; HC: Coconut oil; HC-Chl: Coconut oil + Cholesterol; Extract: *Hura crepitans* L.; CREAT: Creatinine; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; TG: Triglycerides; ALAT: Alanine aminotransferase; ASAT: Asparate aminotransferase; TC: Total cholesterol.

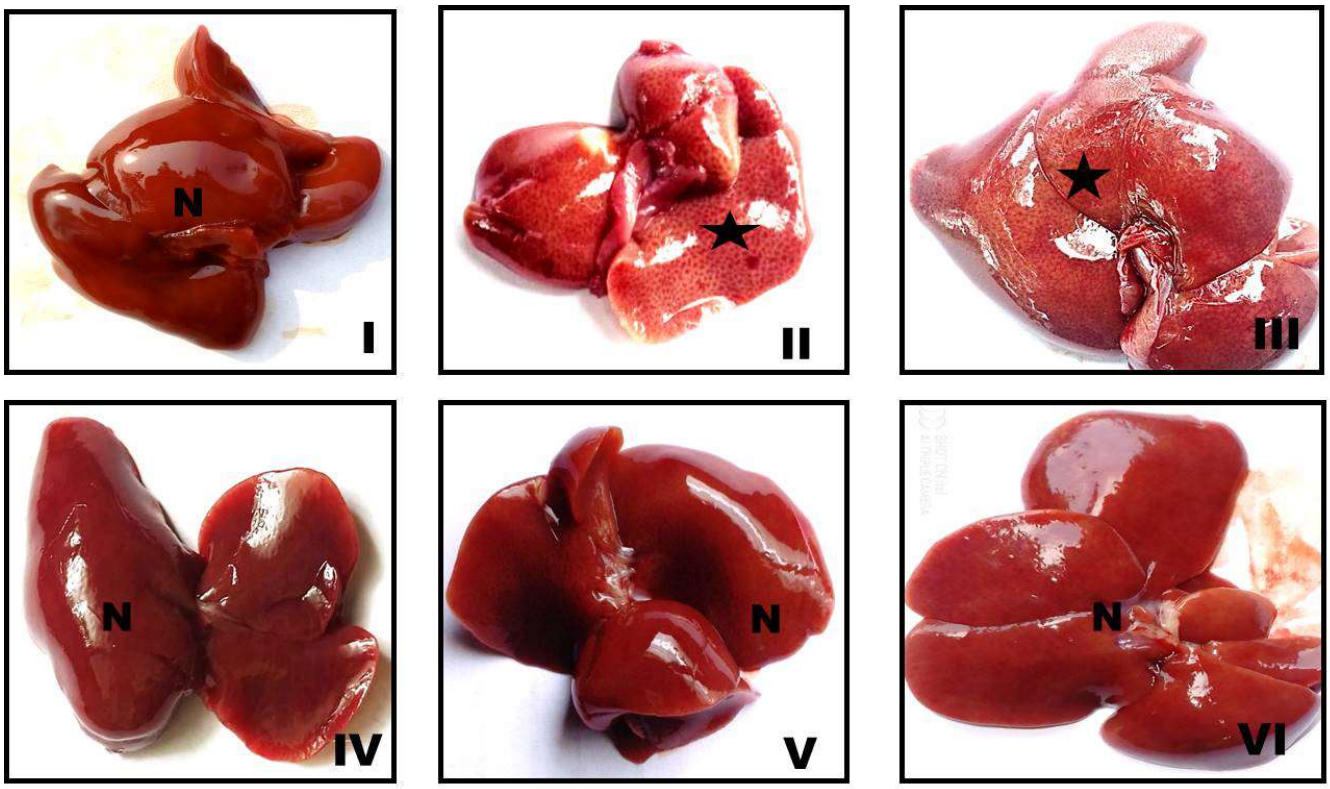

Figure 2: Macroscopic observation of the livers of rats from each batch after treatment**.** I : distilled water (1mL/100g), II : coconut oil (1mL/100g), III : cholesterol solution (30mg/kg), IV : cholestérol solution (30mg/kg) + Atorvastatine (20mg/kg), V : cholestérol solution (30mg/kg) + *Hura crepitans* (250 mg/Kg) VI: cholestérol solution (30mg/kg) + *Hura crepitans* (500mg/Kg) N : normal ;

Table 2: Effect of aqueous extract of *Hura crepitans* L. leaves on abdominal fat mass in rats

Treatment	Abdominal fat (g)
ED 1 mL/100g	3,29 ±0,14
HC (1 mL/100g)	**10,31**±0,16$$$
Chol. (30 mg/kg)	8,99 ± 0,18ns
Chol. + l'Atorvastatine (20 mg/kg)	5,10 ± 0,00**
Chol. + *Hura crepitans* L. (250 mg/kg)	5,39 ± 0,05**
Chol. + *Hura crepitans* L. (500 mg/kg)	2,06 ± 0,09***

ED: Distilled water; HC: Coconut oil; HC-Chl: Coconut oil + Cholesterol; Extract: *Hura crepitans* L. Results are expressed as mean ± standard mean error, with n = 5. *p<0.05, **p<0.01, ***p<0.001 significant difference, compared with cholesterol control; ns: not significant ;# p<0.05, ## p<0.01, ###p<0.001 significant difference, compared with coconut oil control; $p<0.05, $$$p<0.01, $$$p<0.001 significant difference, compared with distilled water control.

and 500 mg/kg respectively did not cause any significant change in the hepatic index compared with the control batch. However, it did result in a highly significant (p<0.001) decrease in adipose index compared to rats fed cholesterol solution alone. This decrease was also observed in rats treated with the reference molecule.

Chemical profile of *Hura crepitans* L. leaves

Table 4 shows the results of the chemical screening (tube reaction) of the aqueous extract of *Hura crepitans* L. leaves. It appears from this table that the aqueous extract of *Hura crepitans* L. leaves contains several secondary metabolites as shown in the table.

Discussion

This study evaluated the anti-hypercholesterolemic activity of the aqueous extract of *Hura crepitans* L. leaves in Wistar rats. The eight (8)-week weight trend of rats treated with the aqueous extract of *Hura crepitans* L. leaves on 4% cholesterol-induced hypercholesterolemia revealed a highly significant reduction in body weight in rats treated with 250 and 500 mg/kg aqueous extract of *Hura crepitans* L. leaves respectively, compared with those given only 4%

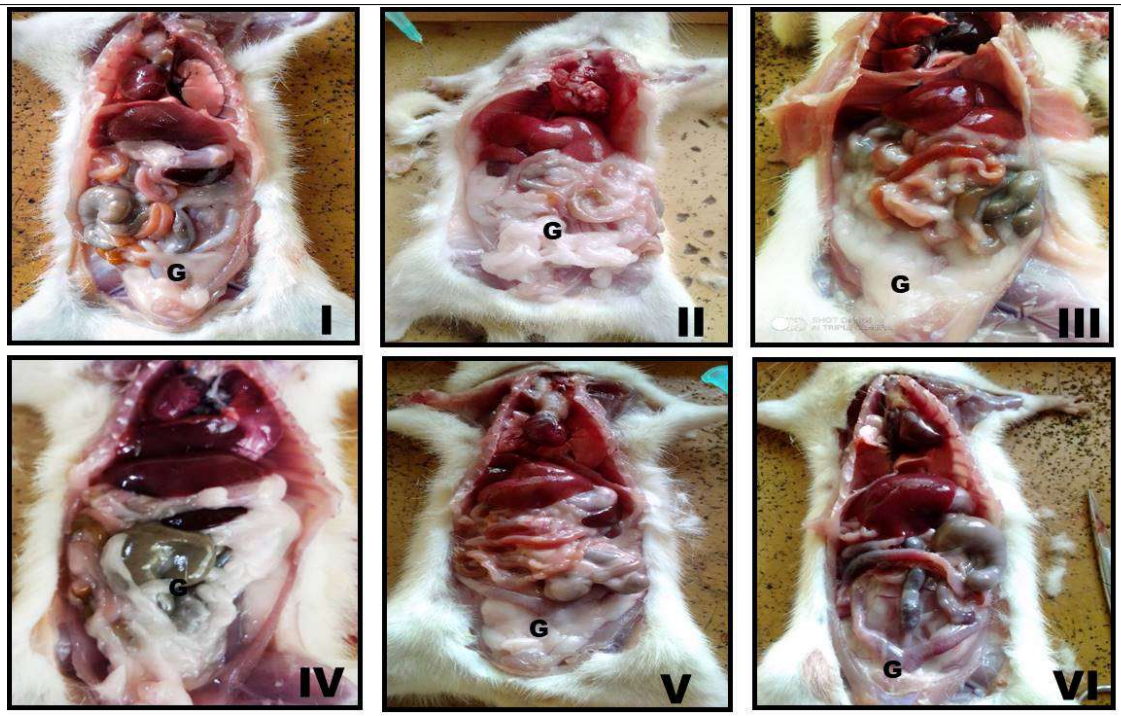

Figure 3 : Macroscopic observation of the amount of fat in the abdominal cavity of rats from each batch after treatment. NB : I : Distilled water (1 mL/100g), II : coconut oil (1 mL/100g), III : cholesterol solution (30 mg/kg), IV : cholesterol solution (30 mg/kg) + Atorvastatine (20 mg/kg), V : cholesterol solution (30 mg/kg) + *Hura crepitans L.* (250 mg/Kg) VI : cholesterol solution (30 mg/kg) *Hura crepitans L.* (500 mg/Kg), G : Fat

Table 3 : Effect of aqueous extract of *Hura crepitans* L. leaves on liver and adipose indices in rats

Index	ED 1mL/100g	HC 1mL/100g	Chol. (30 mg/kg)	Chol. (30 mg/kg) + l'Atorvastatine (20mg/kg)	Chol. (30 mg/kg) + *Hura crepitans* L. (250mg/kg)	Chol. (30 mg/kg) + *Hura crepitans* L. (500mg/kg)
P. C. (g)	196±9,63	201,15±3,88ns	236,4±12,13	202,27±8,22	227,5 ±14,62	230,9 ±13,34
Foie (g)	5,57±0,39	6,11±0,16ns	6,02±0,57ns	4,98±0,16ns	5,80± 0,51ns	6,41±0,08ns
TA (g)	3,29±0,14	10,31±0,16$$$	8,99±0,18ns	5,10±0,0**	5,39±0,05**	2,06±0,09***
IH (%)	2,83 ±0,08	3,04 ± 0,12ns	2,53±0,14ns	2,46 ± 0,05ns	2,38 ± 0,10ns	2,79 ± 0,15ns
IA (%)	1,69 ±0,21	5,08±0,68$$	3,77±0,51ns	2,49±0,34**	2,29±0,50***	0,90±0,09***

Liver Index (HI): organ weight/body weight on last day×100; Adipose Index (AI) = fat weight/body weight *100, Adipose Tissue (AT). ED: Distilled water; HC: Coconut oil; HC-Chl: Coconut oil + Cholesterol; Extract: *Hura crepitans* L. Results are expressed as mean ± standard mean error, with n = 5. *p<0.05, **p<0.01, ***p<0.001 significant difference, compared with cholesterol control; ns: not significant ;# p<0.05, ##p<0.01, ###p<0.001 significant difference, compared with coconut oil control; $p<0.05, $$$p<0.01, $$$p<0.001 significant difference, compared with distilled water control.

Table 4 : Chemical screening results

Métabolites secondaires	Extrait aqueux des feuilles de *Hura crepitans* L.
Alcaloïdes	++
Tannins	+++
Flavonoïdes	++
Anthraquinones libres	++
Mucilages	++
Anthocyanes	++
Oses, holosides	+
Stéroïdes et terpénoïdes	+

+++ : Réaction positive ; ++ : Réaction moyennement positive ; + : Réaction louche

cholesterol. These results suggest that the aqueous extract of *Hura crepitans* leaves contains secondary metabolites that counteract the increase in body weight. Indeed, according to Kotagale et *al*, (2014), alkaloids are endowed with anorexigenic properties. These results corroborate those obtained by Abbas et *al,* (2015) who studied the effect of Portulaca oleracea aqueous extract on obesity in Wistar rats. The results of biochemical parameters after eight (8) weeks of experimentation, show a significant decrease in transaminases (ALAT and ASAT) in rats given the 4% cholesterol solution and then treated with respective doses of 250 mg/kg and 500 mg/kg of the aqueous extract of *Hura crepitans* L. leaves compared to those given only the 4%

cholesterol. This result suggests that the aqueous extract protected the liver against cholesterol accumulation, and therefore did not promote liver damage. These effects were demonstrated by Owojuyigbe et *al* (2020) in a study on the hepatoprotective effect of *Hura crepitans* L. stem. At renal level, the aqueous extract led to a decrease in creatinine compared to the batch receiving only the cholesterol solution. This result suggests that the extract did not cause renal damage. The lipid profile measures the various lipid components present in the blood in order to assess atherogenic risks (Couderc et *al*., 2017). These results show that administration of the cholesterol solution concomitantly with the aqueous extract of *Hura crepitans* L. leaves significantly reduced total cholesterol, LDL-cholesterol, triglycerides and the atherogenicity index, and increased HDL levels compared with those who received the 4% cholesterol solution alone. The decrease in these parameters suggests that the aqueous extract of *Hura crepitans* L. leaves is a good indication of protection against risk factors for the development of atherosclerosis and hence cardiovascular disease. Chemical screening showed the presence of flavonoids. The anti-hypercholesterolemic activity observed is thought to be due to their presence in the plant's aqueous extract. In fact, flavonoids increase cholesterol uptake by cells, inhibiting cholesterol biosynthesis and reducing intestinal reabsorption of bile salts, thus lowering blood cholesterol levels (Kabsa et al., 2003). HDL also transports cholesterol from cells to the liver, where it is broken down into bile acids (Tang et al., 2006). The increase in HDL levels observed in this study would prevent the deposition of cholesterol in the arteries, as HDL has the function of cleaning the arteries, thus preventing the process of atherosclerosis. These results show that the aqueous extract of *Hura crepitans* L. leaves protects the arteries and therefore has a cardio-protective effect. This effect could be due to the presence of flavonoids, antioxidants that improve endothelial function by inhibiting or limiting the ability of free radicals to oxidize LDL lipoproteins, thereby reducing the risk of cardiovascular disease by preventing plaque aggregation and adhesion (Mulvihill et al., 2010). Abdominal fat was significantly reduced in rats treated with 250 and 500 mg/kg aqueous extract respectively. The same observation was made in the reference lot (Atorvastatin 20 mg/kg) compared with the lot receiving only the 30 mg/kg cholesterol solution. This result suggests that the aqueous extract of *Hura crepitans* L. leaves prevents fat accumulation, thereby reducing the risk of cardiovascular disease. Macroscopic observation of the livers of rats treated with the various doses of aqueous extract of *Hura crepitans* L. leaves showed no apparent lesions compared with the batch treated with cholesterol solution 30 mg/kg alone. This result is in agreement with that obtained by Owojuyigbe et al. (2020). As plants are home to a diversity of active substances and secondary metabolites responsible for various effects, a chemical screening was carried out to identify the secondary metabolites that could be responsible for the pharmacological effects observed. The results show that the aqueous extract of *Hura crepitans* L. leaves contains alkaloids, flavonoids, tannins, free anthraquinones, mucilages, oses, holosides, steroids and terpenoids. These results are in line with those obtained by Owojuyigbe et al, (2020).

Conclusion

The study on the evaluation of the anti-hypercholesterolemic activity of aqueous extract of *Hura crepitans* L. leaves in rats showed that aqueous extract of *Hura crepitans* L. leaves possesses anti-hypercholesterolemic properties, and contains secondary metabolites such as flavonoids and tannins which would be responsible for the effects observed.

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