

Antiatherosclerotic Activities of *Raphionacme brownii* (Apocynaceae) Elliot-Scott on Rats

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Abstract Our study consisted of evaluating the antiatherosclerotic activity of *Raphionacme brownii* tubers. The antiatherosclerotic activities were evaluated on rats, subdivided into two phases including the induction of hypercholesterolemia for 30 days and the treatment of hypercholesterolemia for 15 days. The evaluation of the antiatherosclerotic activity revealed a significant decrease in TC to 44.28% in females and 47.98% in males; TG to 34.48% in females and 26.66% in males; LDL to 45.16% in females and 41.30% in males and conversely an increase in HDL to 14.58% in females and 20.75% in males. The atherogenic index showed a better activity of the effect of *Raphionacme brownii* tubers on atherosclerosis. The richness in bioactive compounds could justify the traditional use of *Raphionacme brownii* as a hypolipidemic agent treating cardiovascular diseases.

Keywords: *Raphionacme brownii*, secondary metabolites and atherosclerosis

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1. Introduction

Cardiovascular diseases (CVD) are the leading cause of death and disability worldwide. An estimated 17.9 million deaths are attributable to cardiovascular diseases, accounting for 32% of total global mortality [1] WHO estimates that cardiovascular morbidity in African countries will double; the socioeconomic repercussions are likely to negatively impact the development of these countries, making them poorer as a result [2].

The increase in the frequency of these cardiovascular diseases is due to certain risk factors such as smoking, poor diet and obesity, sedentary lifestyle and harmful use of alcohol, diabetes, high blood pressure, and dyslipidemia [3,4]. Dyslipidemia constitutes a major risk factor for the occurrence of atherosclerosis and cardiovascular diseases [3]. Atherosclerosis is an inflammatory phenomenon initiated and maintained by excess cholesterol [5]. Lipid assessment allows the determination of total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides which are parameters recognized as risk factors for cardiovascular diseases (Hokanson, 1999) [6]. The management of dyslipidemia is based on hygiene and dietary measures supplemented by lipid-lowering treatment [5].

In Chad, hospital mortality from CVD was 15.4%, mortality related to hypertension and its complications

represented 55% [7]. There was an increasing trend in the prevalence of dyslipidemia over the five years [8].

Considering the adverse effects and inaccessibility of conventional medicines treating cardiovascular diseases, WHO recommends the evaluation of the safety and efficacy of herbal medicines with a view to standardizing their use and integrating them into conventional care [9], given that more than 80% of African populations use pharmacopoeia and traditional medicine [10]. This is why *Raphionacme Brownii*, which has therapeutic properties for cardiovascular diseases [11], is chosen for our study.

2. Materials and Methods

Preparation of the aqueous extract of the plant.

The tubers of *R. brownii* were harvested, cleaned, dried, crushed and then a quantity of 100 g of powder of the plant was introduced into a beaker containing 1 L of distilled water [12]. The whole was macerated for 24 hours. After maceration, the mixture was sieved and then filtered using Wattman paper No. 3. The filtrate obtained, the volume of which was measured, collected and evaporated in an oven (80°C) for one day. We obtained dry extract of the plant. This filtrate (stock solution) of concentration was diluted with distilled water at 1/8, 1/4, 1/2, and 1/1. The administration volume being 10 ml / kg, the different doses were thus obtained [13].

Induction of hypercholesterolemia (HC).

The 38 normocholesterolemic (NC) male and female rats were divided into 12 groups including two negative control (NC) groups of 8 rats and 10 test groups (TC):

- A group of 4 NC males were fed the NC diet for 30 days;
- A group of 4 NC females were fed the NC diet for 30 days;
- 5 groups of 3 rats were fed for 30 days with a diet rich in cholesterol (HC);
- 5 groups of 3 rats were fed for 30 days with a diet rich in cholesterol (HC).

The composition of the diet in percentage (%) for one kg of feed is carried out according to the table described by Alam *et al.*, in 2011. The nutrient content of this diet (g/100g of feed): total lipid (19.70 ± 0.28); Protein (32.95 ± 2.4); ash (0.02 ± 0.005); Fiber (12.33 ± 1.50); Carbohydrates (35 ± 2.3) (Alam *et al.*, 2011). [13]

Treatment of high cholesterol.

After induction, the rats were gavaged using a gastroesophageal tube. The extract was administered orally every day for up to 2 weeks of treatment. Body weight, food intake, and water consumption of the test groups were determined and compared to the control groups (positive and negative). The treatment was carried out as follows:

- 2 male and female NC groups received only distilled water by gavage (negative control);
- 2 male and female HC groups received Atorvastatin (1 mg/kg), (positive control);
- 2 male and female HC groups received 225 mg/kg of plant extract (Trial 1);
- 2 male and female HC groups received 300 mg/kg of plant extract (Trial 2);
- 2 male and female HC groups received 375 mg/kg of plant extract (Trial 3).

Evaluation of biochemical parameters.

After treatment, all animals were fasted for 12 hours and then sacrificed. Blood collected through the jugular vein of each animal was centrifuged at 800 rpm/10 ml and kept at -20°C for determination of biochemical parameters. Total cholesterol (TC) and triglycerides (TG) by the method described by Bonnefont, [14], High density lipoproteins (HDL), [10]. The Friedewald formula was

used to calculate low density lipoproteins (LDL), [10]. These parameters are measured by commercial assay kit (Trinder, 1969) [15].

Determination of the atherogenicity index.

The plasma atherogenicity index is a predictive parameter of cardiovascular risk, particularly in certain categories of patients. The atherogenicity index is the ratio between plasma cholesterol levels of atherosclerotic and antiatherosclerotic lipoproteins [16]:

Ratio: $\text{CT/C-HDL} < 4.5$ and $\text{LDL/HDL} < 3.55$ (men) and < 3.22 (women).

3. Results

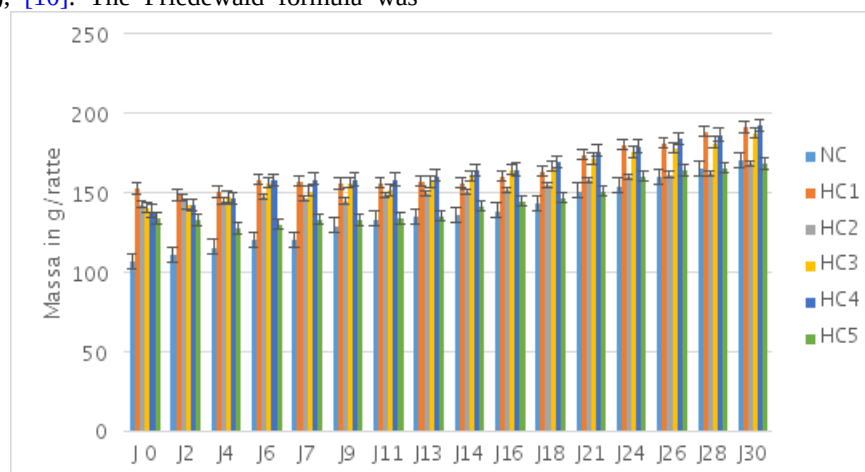
Induction of hypercholesterolemia

Body mass during induction of hypercholesterolemia

Figure 1 and Figure 2 below indicated the body weight variation of male and female rats during 30 days of hypercholesterolemia induction. Body weight was expressed in g/rat/2 days.

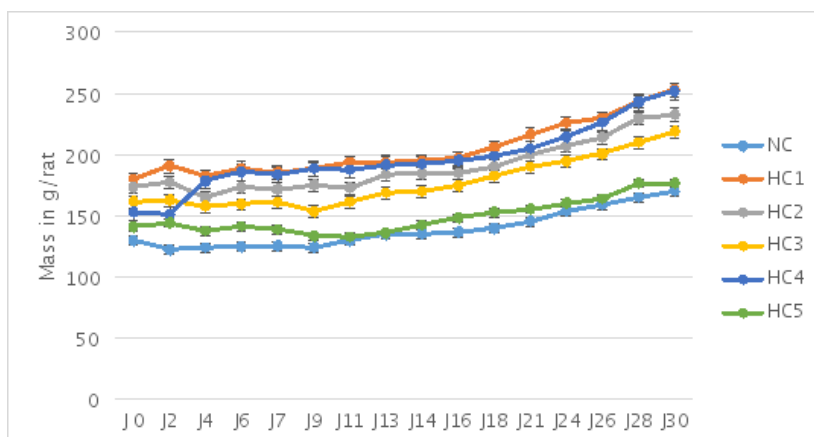
These results show that the body weight of the NC rats decreased gradually until the 9th day before increasing until the last day. This weight was from 129.66g/rat to 124.33g/rat then to 164.75g/rat, an increase of 21.49%. In the rats fed the cholesterol-enriched diet, we also observed a slight drop in body weight up to one week in the HC2 and HC3 groups. This weight had increased from 173.33g/rat to 171.67g/rat and 161.67g/rat to 161.33g/rat, respectively. After one week, the rats in these groups mentioned above began to gradually gain weight until the last day. This increase in weight was 25.54% for HC2 and 26.06% for HC3. For batches HC1, HC4 and HC5, we observed only a significant increase in body weight which was 28.89%, 39.33% and 20.37% respectively.

In females fed the HC diet, we noted a linear increase in almost all batches except batch HC5 which experienced a decrease in body weight at one week of 2.49% before resuming growth until the 30th day. Compared to the initial weight of the animals, this increase was 20.20% for HC1, 15.24% for HC2, 25.04% for HC3, 27.89% for HC4 and 20.59% for HC5.



NC: Normocholesterolemic batch; HC: Hypercholesterolemic batch; n= 2 for normal batches and n= 2 for hypercholesterolemic batches; each point corresponds to the mean $\pm$ standard error of the mean.

Figure 1. Weight mass of rats during induction of hypercholesterolemia



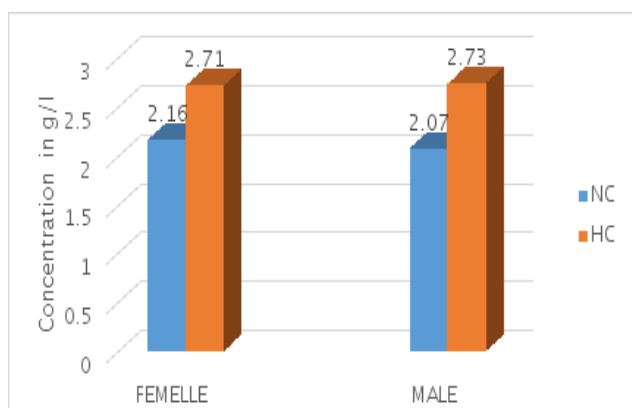
NC: Normocholesterolemic batch; HC: Hypercholesterolemic batch; n= 3 for normal batches and n= 3 for hypercholesterolemic batches; each point corresponds to the mean $\pm$ standard error of the mean.

Figure 2. Weight of rats during induction of hypercholesterolemia

Plasma CT content in hypercholesterolemic rats

Figure 3 below showed us the plasma CT content in hypercholesterolemic rats and expressed in g/l.

It appears from this result that the total blood cholesterol level of hypercholesterolemic rats was 2.71g/l and 2.73g/l respectively in females and males. This showed an increase of 0.55g/l or 20.29% and 0.66g/l or 24.17% respectively in females and males compared to the NC group.



NC: Normocholesterolemic group; HC: Hypercholesterolemic group; n= 2 for females and n= 3 for males; each point corresponds to the mean $\pm$ standard error of the mean.

Figure 3. Plasma CT content in hypercholesterolemic rats

Plasma TG content in hypercholesterolemic rats

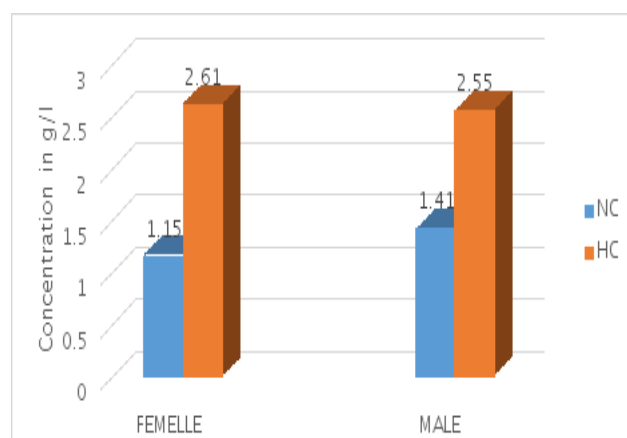
Plasma TG content in hypercholesterolemic rats is shown in Figure 4 and expressed in g/l/rat.

This result showed us an increase in blood triglyceride levels in HC rats compared to the NC group. This increase was 1.46g/l or 44.44% and 1.14g/l or 44.70% respectively in females and males.

Plasma HDL content in hypercholesterolemic rats

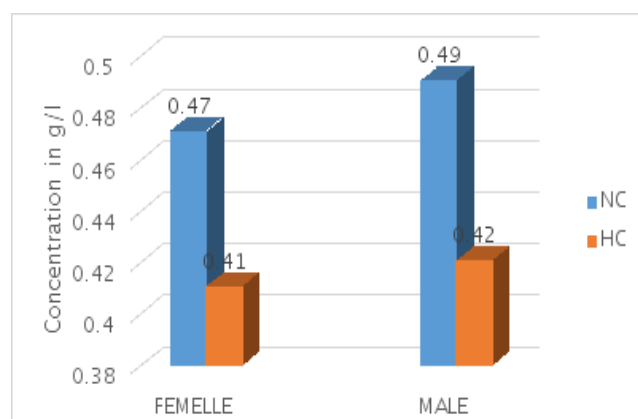
Figure 5 below shows the plasma HDL cholesterol content of hypercholesterolemic rats which was expressed g/l/rat.

This result indicated that the blood HDL level in hypercholesterolemic rats decreased slightly. This level is 0.41g/l or 12.76% and 0.42g/l or 14.28% respectively in females and males.



NC: Normocholesterolemic group; HC: Hypercholesterolemic group; n= 2 for females and n= 3 for males; each point corresponds to the mean $\pm$ standard error of the mean.

Figure 4. Plasma TG content in hypercholesterolemic rats



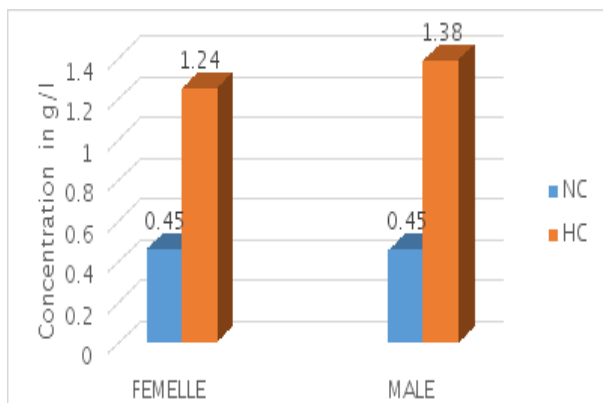
NC: Normocholesterolemic group; HC: Hypercholesterolemic group; n= 2 for females and n= 3 for males; each point corresponds to the mean $\pm$ standard error of the mean.

Figure 5. Plasma HDL-C content in hypercholesterolemic rats

Plasma LDL content in hypercholesterolemic rats

Figure 6 below showed us the plasma LDL cholesterol content of hypercholesterolemic rats which was expressed in g/l/rat.

This result showed us an increase in the plasma LDL level in rats made hypercholesterolemic compared to the NC group. We noted an increase of 0.79g/l or 63.70% and 0.93g/l or 67.39% respectively in females and males.



NC: Normocholesterolemic group; HC: Hypercholesterolemic group; n= 2 for females and n= 3 for males; each point corresponds to the mean $\pm$ standard error of the mean.

Figure 6. Plasma LDL-C content in hypercholesterolemic rats

Atherogenicity index

The atherogenic index is calculated from the plastic content of total cholesterol, LDL-cholesterol and HDL-cholesterol: TC/c-HDL and c-LDL/c-HDL

Table 1. Atherogenicity index after induction

Sex	Reports	NC	HC5
Female	LDL/HDL	0.95	3.02
	CT/HDL	4.59	6.60
Male	LDL/HDL	0.91	3.28
	CT/HDL	4.22	6.5

NC: Normocholesterolemic group; HC: Hypercholesterolemic group; n= 2 for females and n= 3 for males; each point corresponds to the mean $\pm$ standard error of the mean.

Treatment of high cholesterol

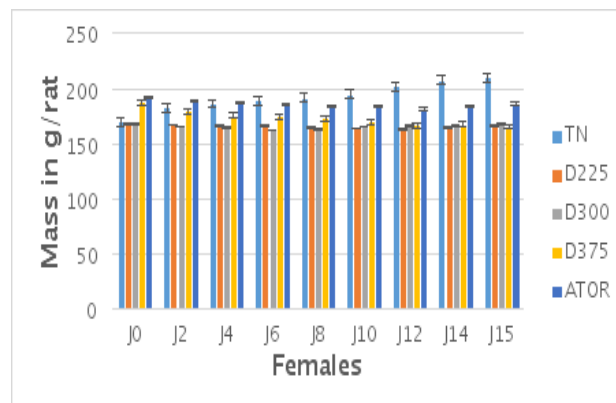
Effect of aqueous extract of *R. brownii* tubers on weight gain

Figure 7 and Figure 8 below indicated the effect of aqueous extract of *R. brownii* tubers (EATRB) on body weight gain of male and female rats during 15 days of treatment. Body weight was expressed in g/rat/2 days.

The results of the effect of the aqueous extract of *R. brownii* tubers on weight gain showed us that in rats treated at the dose of 375mg/kg, the initial weight which was 187.5g/rat decreased to 174.5g/rat, a decrease of 6.93% in the first week. After the second week of treatment, the weight was 165.5g/rat, a decrease of 11.73%. For the doses of 225mg/kg and 300mg/kg, a slight non-significant decrease in the weight of the rats was noted. Treated with atorvastatin, the rats showed a significant decrease in their weight which was from 191.5g/rat to 181.5g/rat on the twelfth day, a decrease of 5.22%, then a slight increase to 186.5g/rat, still a decrease of 5g/rat after 15 days of treatment.

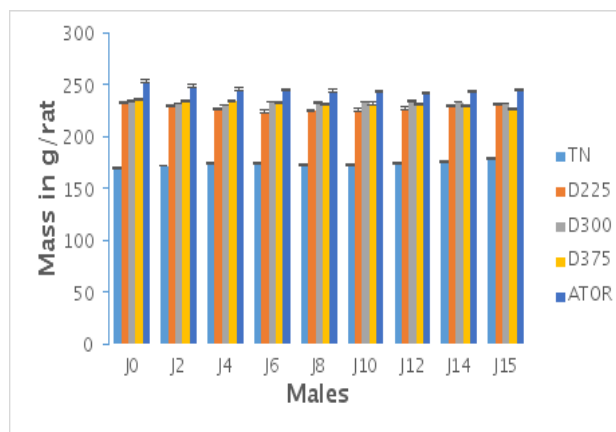
For males treated with atorvastatin, a decrease in weight was observed from 252.67g/rat to 241.33g/rat on day 12, i.e., 11.34g/rat (4.48%). On day 15 of treatment, the weight was 244.33g/rat, a decrease of 8.34g/rat. In rats treated at the 375mg/kg dose, the weight decreased from

234.67g/rat to 231.67g/rat, i.e., 3g/rat, in the first week and to 226.67g/rat, i.e., a decrease of 8g/rat (3.40%). In males treated at the 225mg/kg and 300mg doses, a slight decrease in body weight was also noted.



TN: Negative control; D: Dose; ATOR: Atorvastatin; EATRB: aqueous extract of *Raphionacme brownii* tubers; n= 2 for females; each point corresponds to the mean $\pm$ standard error of the mean.

Figure 7. Effect of EATRB on weight gain in rats



TN: Negative control; D: Dose; ATOR: Atorvastatin; EATRB: aqueous extract of *Raphionacme brownii* tubers; n= 3 for males; each point corresponds to the mean $\pm$ standard error of the mean.

Figure 8. Effect of EATRB on weight gain in rats

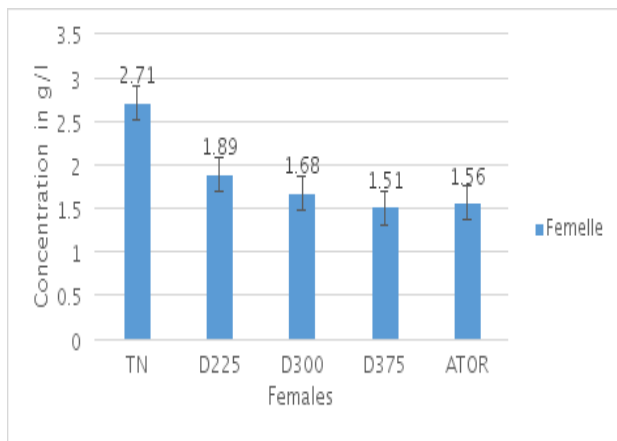
Effect of aqueous extract of *R. brownii* tubers on total cholesterol in rats

The results of the effect of the aqueous extract of *R. brownii* tubers on the total cholesterol level of male and female rats during 15 days of treatment are shown in Figure 9 and Figure 10 below. The plasma level was expressed in g/l/rat.

These results showed us that the aqueous extract of *R. brownii* tubers caused a significant decrease in the blood level of total cholesterol in rats treated with the three doses 225mg/kg, 300mg/kg and 375mg/kg. The rate had decreased from 2.71g/l to 1.89g/l, a decrease of 30.25% at the 225mg/kg dose. At the 300mg/kg dose, the rate had decreased from 2.71g/l to 1.68g/l/rat, a decrease of 38%. This rate was 1.51g/l/ratte in rats treated at the 375mg/kg dose, a decrease of 44.28%. Treated with atorvastatin, the rats showed a decrease in the TC rate to 1.56g/l, a decrease of 42.43%.

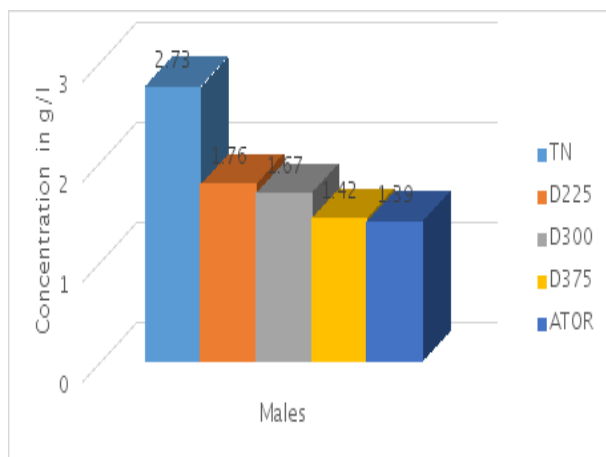
In males, we observed through these results, a significant decrease in the CT rate. In rats treated with

different doses of the aqueous extract of *R. brownii* tubers, the CT rate had decreased from 2.73g/l to 1.76g/l, i.e. a 35.53% decrease, to 1.67g/l, i.e. a 38.82% decrease, and to 1.42g/l, i.e. a 47.98% decrease, respectively, at doses of 225mg/kg, 300mg/kg, and 375mg/kg. For rats treated with atorvastatin, the CT rate had decreased from 2.73g/l to 1.39g/l, i.e. a decrease of 49.08%.



TN: Negative control; D: Dose; ATOR: Atorvastatin; EATRB: aqueous extract of *Raphionacme brownii* tubers; n= 2 for females; each point corresponds to the mean $\pm$ standard error of the mean.

Figure 9. Effect of EATRB on the CT rate of rats



TN: Negative control; D: Dose; ATOR: Atorvastatin; EATRB: aqueous extract of *Raphionacme brownii* tubers; n= 3 for males; each point corresponds to the mean $\pm$ standard error of the mean.

Figure 10. Effect of EATRB on the CT rate of rats

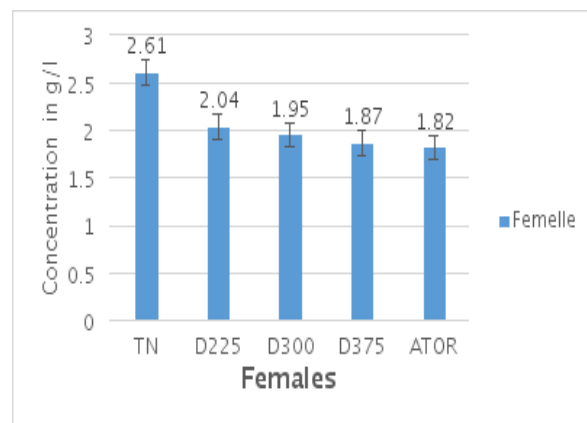
Effect of aqueous extract of *R. brownii* tubers on triglycerides of rats

Figure 11 and Figure 12 below show the effect of the aqueous extract of *R. brownii* tubers on the plasma triglyceride content of hypercholesterolemic rats. The content was expressed in g/l/rat.

These results show that the effect of EATRB caused a decrease in plasma TG levels in rats made hypercholesterolemic compared to the NC group. The level which was 2.61g/l decreased to 1.87g/l, a decrease of 28.35%, to 0.72g/l, a decrease of 27.58%, and to 0.90g/l, a decrease of 34.48%, respectively, at doses of 225mg/kg, 300mg/kg, and 375mg/kg in rats. This level also decreased from 2.61g/l to 1.74g/l in rats treated with atorvastatin, a decrease of 33.33%.

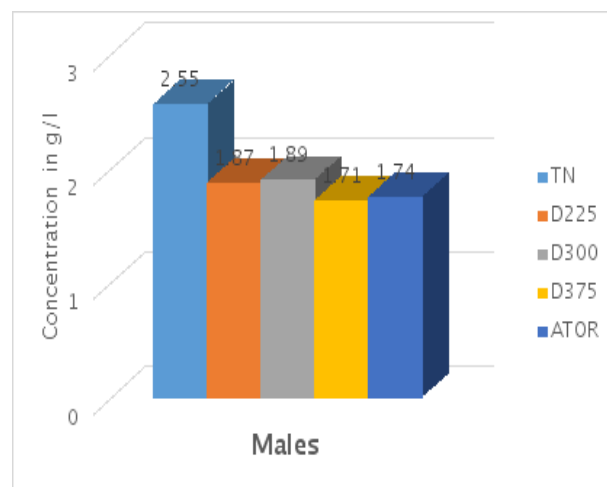
In males treated with the different doses of the aqueous extract of *R. brownii* tubers, a decrease in blood TG levels was also observed, which was from 2.55g/l to 2.04g/l at the 225g/l dose, i.e. a 20% decrease, to 0.60g/l at the 300mg/kg dose, i.e. a decrease of 23.52%, and to 0.68g/l, i.e. a 26.66% decrease, at the 375mg/kg dose. Treated with atorvastatin, the plasma TG level in rats decreased to 0.73g/l, i.e. a decrease of 28.62%.

We noticed that plasma TG level was significantly decreased in male rats than in female rats.



TN: Negative control; D: Dose; ATOR: Atorvastatin; EATRB: aqueous extract of *Raphionacme brownii* tubers; n= 2 for females; each point corresponds to the mean $\pm$ standard error of the mean.

Figure 11. Effect of EATRB on blood TG levels in rats



TN: Negative control; D: Dose; ATOR: Atorvastatin; EATRB: aqueous extract of *Raphionacme brownii* tubers; n= 3 for males; each point corresponds to the mean $\pm$ standard error of the mean.

Figure 12. Effect of EATRB on blood TG levels in rats

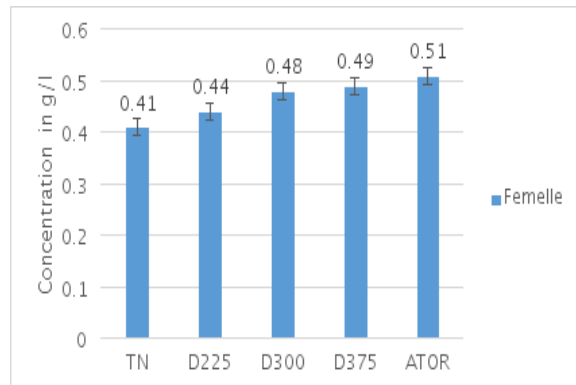
Effect of aqueous extract of *R. brownii* tubers on c-HDL of rats

The results of the effect of the aqueous extract of *R. brownii* tubers on the c-HDL level of male and female rats during 15 days of treatment are shown in Figures 13 and 14 below. The level was expressed in g/l/rat.

Plasma HDL levels in rats treated with atorvastatin increased significantly compared to TN rats. This level was 0.51g/l/rat, an increase of 19.60%. For rats treated with EATRB, a slight increase was observed at doses of 225mg/kg and 300mg/kg, respectively, at 0.44g/l, or 6.81%, and 0.48g/l, or 14.58%. In rats treated at the dose

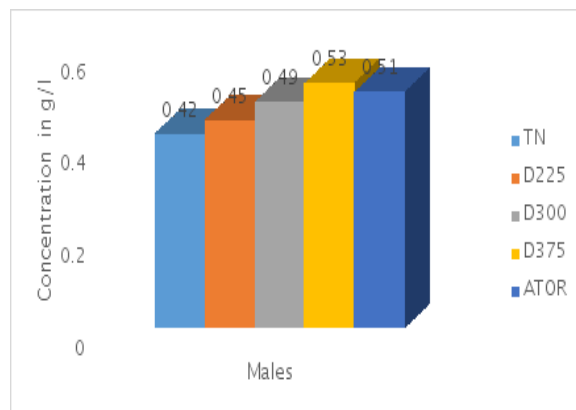
of 375mg/kg, the increase in blood HDL levels was significant at 0.49g/l, or 16.32%.

In males treated with atorvastatin, plasma HDL levels increased slightly to 0.51g/l, an increase of 17.64%. This non-significant increase in HDL levels was also observed in rats treated with the 225g/l dose, or 6.66%. For the 300mg/kg and 375mg/kg doses, plasma HDL levels increased significantly in rats, respectively, to 0.49g/l, or 14.28%, and 0.53g/l, or an increase of 20.75%.



TN: Negative control; D: Dose; ATOR: Atorvastatin; EATRB: aqueous extract of *Raphionacme brownii* tubers; n= 2 for females; each point corresponds to the mean $\pm$ standard error of the mean.

Figure 13. Effect of EATRB on plasma HDL content of rats



TN: Negative control; D: Dose; ATOR: Atorvastatin; EATRB: aqueous extract of *Raphionacme brownii* tubers; n= 3 for males; each point corresponds to the mean $\pm$ standard error of the mean.

Figure 14. Effect of EATRB on plasma HDL content of rats

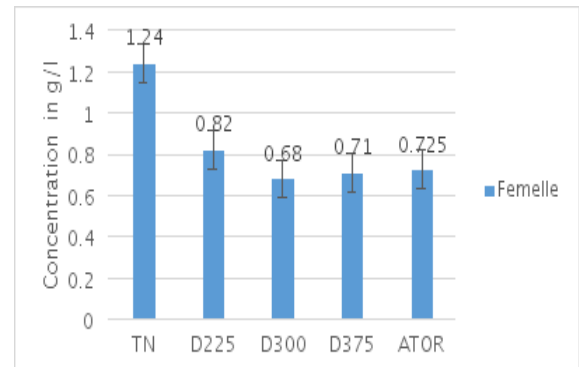
Effect of aqueous extract of *R. brownii* tubers on c-LDL of rats

Figure 15 and Figure 16 below showed us the effect of the aqueous extract of *R. brownii* tubers on the plasma c-LDL content of hypercholesterolemic rats which is expressed in g/l/rat.

We observed through these results that the plasma LDL level in rats made hypercholesterolemic compared to the NC group, decreased very significantly in rats treated at doses of 300mg/kg, 375mg/kg and atorvastatin respectively to 0.68g/l or 45.16%, to 0.71g/l or 42.74% and to 0.725g/l or 41.53%. In rats treated at the dose of 225mg/kg, the decrease in the LDL level was also significant at 0.82g/l or 33.87%.

Rats treated with different doses of EARB showed a significant decrease in LDL levels after treatment. This decrease in blood LDL levels was 0.88g/l or 36.23%;

0.83g/l or 39.85% and 0.81g/l or 41.30% respectively at doses of 225mg/kg, 300mg/kg and 375mg/kg. The same was true for rats treated with atorvastatin, whose decrease was 0.79g/l or 42.75%.



TN: Negative control; D: Dose; ATOR: Atorvastatin; EATRB: aqueous extract of *Raphionacme brownii* tubers; n= 2 for females; each point corresponds to the mean $\pm$ standard error of the mean.

Figure 15. Effect of EATRB on plasma LDL levels in rats

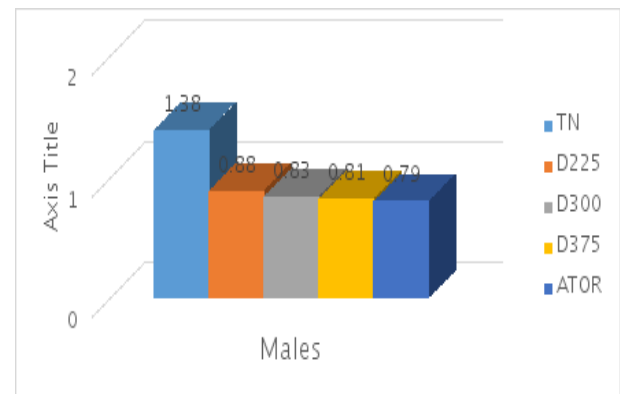


Figure 16. Effect of EATRB on plasma LDL levels in rats

TN: Negative control; D: Dose; ATOR: Atorvastatin; EATRB: aqueous extract of *Raphionacme brownii* tubers; n= 3 for males; each point corresponds to the mean $\pm$ standard error of the mean.

EATRB Atherogenicity Index

The antiatherogenic index is a parameter that indicates the activity of EARB on atherosclerosis in rats. The atherogenic index is determined by calculation based on the effect of the aqueous extract of *R. brownii* tubers on the plastic content of total cholesterol, LDL-cholesterol and HDL-cholesterol. The results are shown in Table 2 below.

Table 2. Atherogenicity index of the EATRB effect

Doses	Reports	TN	D225	D300	D375	ATOR
Female	CT/HDL	6.60	4.29	3.5	3.08	3.05
	LDL/HDL	3.02	1.86	1.41	1.44	1.42
Male	CT/HDL	6.5	3.91	3.40	2.67	2.72
	LDL/HDL	3.28	1.95	1.69	1.52	1.54

TN: Negative control group; D: dose; ATOR: atorvastatin; n= 2 for females and n= 3 for males; each point corresponds to the mean $\pm$ standard error of the mean.

4. Discussion

The study of the antiatherosclerotic activity of

Raphionacme brownii tubers in rats, it appears that during the induction of hypercholesterolemia in 30 days, the rats showed a significant increase in body weight. This increase was 25.54% for HC2 and 26.06% for HC3. For batches HC1, HC4 and HC5, we observed only a significant increase in body weight which was respectively 28.89%, 39.33% and 20.37%. The increase in body weight in rats is correlated with the consumption of cholesterol-enriched foods, particularly egg yolks and pork oil. However, in our study, food consumption is low in rats. This low consumption could be explained by the disgust of lipids whose quantity is higher than normal, because the consumption of a meal enriched with lipid can cause nausea or stomach aches [17]. Our results corroborate with the work carried out in Algeria by Mir who induced the increase in the weight of rats by the consumption of sardine proteins supplemented with cholesterol [18]. The increase in the rates of overweight and obesity could be due to the increase in the intake of total lipids (total fats), mainly through an increased consumption of animal fats and vegetable oils [19]. Because the overconsumption of lipids induces a low oxidation of lipids, and therefore leads to storage. The form of energy storage in mammals is almost exclusively in the form of triglycerides in adipose tissue and this is expansive and, above all, the metabolic pathways they use are more oriented towards storage than towards oxidation [20]. Higher fat intakes can increase total energy intake, which can then lead to an energy imbalance and excessive weight gain [19]. Since fat is the most energetic nutrient, an excess of fat in general and saturated fat in particular is the main cause of cardiovascular diseases or overweight [21]. The occurrence of cardiovascular diseases is strongly correlated with an unbalanced diet, particularly if it is rich in saturated fatty acids and cholesterol. Abnormally high levels of LDL cholesterol and triglycerides cause a progressive deposition of fat in the arteries [22].

After the 30 days of induction of hypercholesterolemia in rats, blood was collected by sacrificing these animals from where the blood dosage revealed an increase in the total cholesterol level of 20.29% in females and 24.17% in males, triglycerides of 44.44% in females and 44.70% in males, LDL of 63.70% in females and 67.39 in males compared to the negative control group. Conversely, a decrease in the HDL level was observed but within the norm of 12.76% in females and 14.28% in males. A 1% decrease in HDL-c levels increases the risk of CVD by 2-3%, comparable to the change in risk associated with an increase in LDL-c by 1% [23]. Obesity is associated with elevated triglycerides, sometimes LDL-cholesterol, and decreased HDL-cholesterol. Dyslipidemia is found in 30-60% of overweight or obese cases, partly explaining the increased risk of cardiometabolic complications in obesity combined with low-grade inflammatory state and insulin resistance [24]. Obesity is a risk factor for hypercholesterolemia and certain foods consumed rich in saturated fat can increase LDL-c and lead to weight gain [25]. Cholesterol, being a lipid substance, is necessary for the formation of cell membranes, sex hormones, vitamin D and bile acid. It can be synthesized in the liver and intestine or provided by the consumption of foods of animal origin. Excess cholesterol in the blood can cause cardiovascular diseases [21]. Studies have shown that

hypercholesterolemia is not only a risk factor, but a real cause of mortality from coronary heart disease. The higher the cholesterol level, the greater the risk (**Kahn et al., 2005**) [26]. Triglycerides are one of the major components of triglyceride-rich lipoproteins, which include very low-density lipoproteins (VLDL) and chylomicrons, synthesized and secreted by the liver and enterocytes, respectively. The key enzyme in the regulation of triglyceride-rich lipoproteins is lipoprotein lipase, which ensures the hydrolysis of the triglyceride content of VLDL and chylomicrons to produce cholesterol-enriched remnants. These remnants participate in the development of atherosclerosis by their ability to penetrate the arterial intima with induction of vascular inflammation. In all these clinical situations, a high triglyceride level is associated with a decrease in HDL and a preponderance of small and dense LDL, constituting the classic atherogenic lipid triad [27]. The decrease in c-HDL level associated with hypercholesterolemia, hypertriglyceridemia with an increase in c-LDL correspond to an atherogenic dyslipidemia leading to the development of atherosclerosis [28]. Rather high triglyceride levels are often associated with excess weight because the metabolism of triglyceride-rich lipoproteins (VLDL, chylomicrons) and that of HDL are strongly and inversely correlated [23].

The determination of the atherogenicity index revealed that the TC/HDL ratio is 6.5 in males and 6.60 in females and the LDL/HDL ratio is 3.28 in males and 3.02 in females. However, according to the Framingham TC/HDL and LDL/HDL ratio, they are considered high if they are respectively greater than 4.85 and 3.55 [29]. The inclusion of total cholesterol in the formula would partly take into account VLDL cholesterol and triglycerides which are parameters linked to the metabolic syndrome [30].

Furthermore, our results show a decrease in body weight in the hypercholesterolemic group treated with the aqueous extract of *Raphionacme brownii tubers* compared to the TN group. The decrease in body weight was 11.73% in female rats treated at the 375mg/kg dose versus 5.22% in female rats treated with atorvastatin. In males, the aqueous extract of *Raphionacme brownii tubers* induced a non-significant decrease of 3.40% in animals treated at the 375mk/kg dose versus 4.48% of atorvastatin. These results are in agreement with those of Mir who observed a weight loss in rats [18]. Body weight loss is not correlated with food consumption in animals. We observed rather an increase in the quantity of food consumed which was 42.99% and 63.80% respectively in the rats treated with doses 225mk/kg and 375mg/kg. It is the same in the rats treated with atorvastatin, i.e. 41.39% decrease. A slight decrease in food consumption was observed at 300mg/kg. The same observation was made in the males with; 21.15% at the dose 375mg/kg and 34.14% at atorvastatin. So much so that a non-significant decrease in food consumption at the end of the treatment was noted, respectively 20.14% and 22.95%. This increase in food consumption in rats in general, would justify the effect of the aqueous extract of the tubers of *Raphionacme brownii* on the loss of body weight. Subjects who lost weight regardless of the level of weight loss represented very satisfactory values of BP and blood lipid profile indices [31]. Weight loss reduces cholesterol levels and a weight loss of more than 10%

significantly improves LDL-c levels [25].

Thus, the effect of the aqueous extract of *Raphionacme brownii tubers* caused a decrease in lipid parameters in rats. The decrease in total cholesterol was 35.53%; 38.82% and 47.98% respectively at doses of 225mg/kg, 300mg/kg and 375mg/kg. For rats treated with atorvastatin, the decrease in TC was 49.08%. In females, the decrease in total cholesterol was 30.25% at the 225mg/kg dose. At the 300mg/kg dose, it was 38%. This decrease in female rats treated at the 375mg/kg dose was 44.28%. Treated with atorvastatin, female rats showed a decrease in TC to 42.43%. The treatment of pure hypercholesterolemia (elevation of blood LDL-cholesterol) or mixed hyperlipidemia (elevation of LDL-cholesterol and triglycerides) consists of the implementation of hygiene and dietary rules accompanied by drug treatment mainly by statins [32]. Statins inhibit cholesterol biosynthesis by competitive and reversible inhibition of HMGCoA reductase. This inhibition is due to a structural analogy with HMGCoA, the natural substrate of the enzyme. HMGCoA reductase allows the transformation of HMGCoA into mevalonate, this is the limiting step in the endogenous synthesis of cholesterol. They reduce the level of c-LDL by increasing the hepatic capture of LDL and by increasing their hepatic degradation. This hepatic purification reduces the lifespan of LDL in the plasma and therefore reduces their concentration [33]. Statins are all indicated in the treatment of pure hypercholesterolemia or mixed hyperlipidemia. They are effective in secondary prevention but also in primary prevention in subjects at high cardiovascular risk [34]. According to American recommendations, statins are lipid-lowering drugs that should reduce c-LDL by 30 to 49% [35].

Triglyceride levels decreased with the aqueous extract of *Raphionacme brownii tubers*. The decrease was 28.35%; 27.58% and 34.48% respectively at doses of 225mg/kg, 300mg/kg and 375mg/kg in female rats. In female rats treated with atorvastatin, a decrease of 33.33% was observed. Similarly, in males, the decrease was 20% at the 225mg/kg dose. At the 300mg/kg dose, it was 23.52% and 26.66% at the 375mg/kg dose. Treated with atorvastatin, plasma TG levels decreased by 28.62%. Management is based primarily on lifestyle modification with the target of weight reduction, simple carbohydrates and alcohol. In case of moderate HTG (<5g/kg), the priority lipid target to reduce cardiovascular risk remains LDL with the introduction of a statin [36]. Thus, the aqueous extract of *Raphionacme brownii tubers*, which reduced weight mass, must also have reduced triglycerides.

The aqueous extract of *Raphionacme brownii tubers* induced a decrease in LDL cholesterol of 45.16%; 42.74% and 41.53% respectively in rats treated at doses of 300mg/kg, 375mg/kg and atorvastatin. In rats treated at a dose of 225mg/kg, the decrease in LDL levels was also significant at 33.87%. In males, the decrease in blood c-LDL levels was 36.23%; 39.85% and 41.30% respectively at doses of 225mg/kg, 300mg/kg and 375mg/kg. The same was true in rats treated with atorvastatin, whose decrease was 42.75%. The decrease in LDL cholesterol would be due to the presence of phenolic compounds contained in the plant. Phenolic compounds can act on many processes

involved in the development of CVD, for example by inhibiting LDL oxidation that causes atherosclerosis [37]. These phenolic compounds could also act by modifying lipemia or cholesterolemia, well-known risk factors responsible for the onset of cardiovascular diseases (inhibition of the activity of several enzymes involved in the synthesis and regulation of plasma cholesterol), reduction of the availability of exogenous cholesterol [38], decrease in plasma LDL concentrations [39]. Statins have different efficacies on the reduction of c-LDL. Atorvastatin shows a better reduction of c-LDL than pravastatin, simvastatin, and lovastatin [33]. Using atorvastatin as a reference drug in our study, we obtained substantially the same results with our plant. So we could say that the aqueous extract of the tubers of *Raphionacme brownii* would act like atorvastatin.

Conversely, rats treated with atorvastatin experienced an increase in HDL levels of 19.60%. For rats treated with EATR, an increase in blood HDL levels was observed at the 375mg/kg dose, which was significant at 16.32%. In males, atorvastatin induced a slight increase of 17.64% in plasma HDL levels. This non-significant increase in HDL levels was also observed in rats treated at the 225g/l dose, i.e., 6.66%. For the 300mg/kg and 375mg/kg doses, plasma HDL levels increased significantly in rats by 14.28% and 20.75%, respectively. The elevation of HDL had reduced carotid intima-media thickness in patients with cardiovascular disease who already had a fairly low LDL level. It has been shown that raising HDL levels reverses atherosclerosis in the presence of an already well-controlled LDL level [40]. HDL is secreted (liver 80%, intestine 20%) in an immature form, consisting of apolipoprotein AI surrounded by phospholipids. There is a maturation period in the circulation where these nascent HDL acquire cholesterol and phospholipids and enlarge, becoming the mature forms of small (HDL-3) and large (HDL-2). This increase in size prevents the overly rapid non-specific catabolism by the kidneys of very small HDL [23]. The main function of HDL is reverse cholesterol transport (RCT) which allows the transfer of cholesterol from peripheral cells and tissues to the liver. RCT is likely the main function of HDL and gives it an atheroprotective effect [41]. Statins can increase HDL-c levels by 5-15% [23]. Thus, the aqueous extract of *Raphionacme brownii tubers*, which promoted an increase in HDL levels to approximately this value, would act as a statin.

Conflicts of Interest

The authors declare that there is no conflict of interest for this work.

Authors' Contributions

NRL researched and ensured the field sample collection, assisted with laboratory handling, and wrote the first manuscript. AH contributed to data processing. KM contributed to editing and improving the work. BBO coordinated the entire work.

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