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Hypolipidemic Potentials of Methanolic Extract of *Rauvolfia vomitoria* Leaves in Rats Fed with High Cholesterol

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

The study was aimed to investigate the hypolipidemic potential of methanolic extract *Rauvolfia vomitoria* leaves in high cholesterol-fed rats. The preliminary study showed that *R. vomitoria* leaves were able to scavenge the 2,2-azino-bis (3-ethylbenzthiazoline-6-sufonic acid) (ABTS) and 2-Diphenyl-1- picrylhydrazyl (DPPH) radicals and these radicals scavenging abilities were found to be dose-dependent. Administration of cholesterol to rats for 45 days induced a significant increase in the activities of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and increase lipids levels in the plasma and tissues while HDL cholesterol was decreased. It also elevated the levels of malondialdehyde (MDA) and decreased superoxide dismutase (SOD) activities in the tissues. However, co-administration of high cholesterol-fed rats with *R. vomitoria* extract at doses of 100 and 200 mg/kg significantly reversed lipids levels to near

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normal with cholesterol in the plasma, liver, heart, kidney and lung reduced by (23.13% and 56.43%), (30.09% and 20.90%), (38.21% and 74.53%), (12.61% and 32.49%) and (37.11% and 29.90%) respectively while HDL cholesterol level was increased by (225.44% and 110.39%). The levels of AST, ALT and ALP in the plasma and MDA in the tissues were also decreased while SOD activities in the liver, heart, kidney and lung were elevated by (89.35% and 149.21%), (74.91% and 68.35%), (56.76% and 114.77%), and (204.91% and 274.62%) respectively. The extract of *R. vomitoria* was found to be rich in phenolic content and was proved to have no toxic effects on rats when administered alone to normal rats at a dose level of 200mg/kg/day. The results obtained in this study demonstrated the antioxidant and lipid-lowering effects of *R. vomitoria* and, suggests that the plant could serve as a new potential natural product for the treatment of hyperlipidemia.

Keywords: Rauvolfia vomitoria; scavenge; malondialdehyde; high cholesterol; hyperlipidemia.

1. INTRODUCTION

Hyperlipidemia and oxidative stress are major risk factors for atherosclerosis, and all three are among the most important risk factors for cardiovascular diseases and conditions [1,2]. Cardiovascular diseases (CVD) such as atherosclerosis and myocardial infarction, are a common cause of mortality and morbidity responsible for more than 17 million deaths annually [3,4]. Many cardio-metabolic risk factors such as hypercholesterolemia, diabetes, high blood pressure, obesity and sedentary lifestyle are associated with cardiovascular diseases [5]. It is well documented that hypercholesterolemia contributes to the development of atherosclerosis, with hypertension and renal failure [6]. Hypercholesterolemia has also been shown in the previous study to enhance oxidative stress and increase lipid peroxidation [7]. Therefore, controlling oxidative stress in hypercholesterolemic conditions is a practical strategy to manage the damaging effects of the conditions [8]. Synthetic drugs with cholesterollowering effects are known to have a high prevalence of adverse effects [9]. Therefore, the search for natural products with lipid-lowering potential and antioxidant properties with minimal or no side effects is on the increased, and plants are known to be a good source of useful drugs with less toxic effects than synthetic drugs. One plant that has attracted much attention over the vears for its medicinal value is Rauvolfia vomitoria.

Rauvolfia vomitoria is a medicinal plant that is widely distributed in Africa and Asia [10]. It belongs to the family Apocynaceae and grow to a height of about 15 m. It is commonly known as a Swizzle stick and known locally among Yorubas as "Asofeyeje", Igbos as "Ira" and Hausas as "Wadda" [11]. Traditionally, the plant is used in the treatment of high blood pressure, fever, general weakness, intestinal diseases, liver problems, mental illness, impotency, haemorrhoids and rheumatisms [12,13]. Rauwolfia vomitoria is a good source of therapeutically active alkaloids and about 200 alkaloids have so far been reported from [14]; Rauwolfia species alkaloids of pharmacological interests include aimaline and ajmalicine [15] while reserpine which is another alkaloid has been known to be its active principle [15]. Although pharmacological properties of R. vomitoria extracts such as its anticancer, hepatoprotective, anticonvulsant, anti-psychotic and anti-diabetic have been demonstrated in previous studies [13,16], there is a dearth of scientific data to support the folkloric use of this plant in the treatment of hypertension or related vascular diseases in Nigerian herbal homes. Therefore, the present work was designed to provide scientific validation for the use of R. vomitoria in the treatment of hypertension or related vascular Nigerian diseases by herbal medicine practitioners.

2. MATERIALS AND METHODS

2.1 Reagents

Folin-Ciocalteu reagent, dinitro salicylic acid reagent, 2,2-Diphenyl-1-picrylhydrazyl (DPPH), Trolox Equivalent Antioxidant Capacity Assay (ABTS), ethanol, Trichloroacetic acid (TCA), thiobarbituric acid, sodium carbonate, sodium chloride, glacial acetic acid and potassium hexacyanoferrate were obtained from Sigma– Aldrich Chemical Co. Ltd. (England). All other chemicals used were of analytical grade.

2.2 Plant materials and Extract Preparation

The leaves of *R. vomitoria* were obtained from a local farm at Ibadan, Oyo State. The plant identification and authentication were carried out at the Department of Pure and Applied Biology,

Ladoke Akintola University of Technology, Ogbomoso, by Prof A.J. Ogunkunle. The leaves were air-dried for two weeks at room temperature and pounded into powder. 100g of the powdered *R. vomitoria* leaves were soaked in 500ml of methanol and shaken for 72 hours, afterwards, it was filtered and the supernatant was concentrated using a rotatory evaporator.

2.3 The in-vitro Antioxidant Assays and Total Phenolic Content of *R. vomitoria*

The in-vitro antioxidant potentials of *R. vomitoria* methanolic extract was carried out using 2,2-Diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity as previously described by Schlesier et al., [17]. Trolox Equivalent Antioxidant Capacity Assay (ABTS) as described by Re et al., [18]. Total phenolics of *R. vomitoria* were determined by the Folin-Ciocalteu method as described by [19].

2.4 Animals

Thirty-six male Wistar rats with an average weight of 200g were obtained from the Experimental Animal Unit of Faculty of Agriculture, Ladoke Akintola University of Technology, Ogbomosho, Nigeria. All rats had free access to feed and water and were maintained under standard environmental conditions. The animals were acclimatized for 3 weeks before the commencement of the study. All the ethical protocols laid by the committee in line with ARRIVE guidelines, and the national institutes of health guide for the care and use of laboratory animals (NIH Publications No. 8023, revised 1978) were followed.

2.5 Experimental Design

Three weeks after acclimatization the animals were divided into six groups of six animals per group.

- Group I received distilled water only
- Group II received 200mg/kg body weight R. vomitoria only
- Group III received 30 mg/animal of cholesterol only,
- Groups IV received 30mg/animal of cholesterol and 100mg/kg body weight of R. vomitoria

- Group V received 30mg/animal of cholesterol and 200mg/Kg body weight of R. vomitoria
- Group VI received 30mg/animal of cholesterol and 0.26 g/kg body weight of Questran.

The animals were administered with cholesterol, the extract and Questran through an oral route for 45 days after which the rats were sacrificed by cardiac puncture under light ether anaesthesia. Blood, liver, kidney, heart and lung samples were removed from the animals and stored for biochemical analyses.

2.6 Determination of Biochemical Parameters in Plasma

The concentrations of aspartate aminotransferase (AST), alanine aminotransferase (ALT), total protein, cholesterol and total triglycerides were determined in the plasma using enzymatic kits.

2.7 Preparation of Tissues Homogenates

The liver. Heart, kidney and lung samples are homogenized in phosphate buffer saline (PBS) to give 10% (w/v) tissues homogenate. The supernatant obtained after the homogenates were centrifuged at 12,000 rpm for 15 min was used for biochemical assay.

2.8 Determination of Antioxidant Enzyme Activities and MDA Levels

The concentration of superoxide dismutase (SOD), thiobarbituric acid-reactive product and malondialdehyde (MDA) in the liver and kidney homogenates were measured, as described by Misra and Fridovish [20] and Buege and Aust [21] respectively. All enzyme activities were expressed as per mg of protein.

2.9 Statistical Analysis

The results of this study were expressed as mean ± S.E.M. One-way Analysis of Variance (ANOVA) followed by Turkey's test was used for statistical analysis and pvalue<0.05 were considered statistically significant.

3. RESULTS

3.1 The in-vitro Antioxidant Potential and Total Phenolic Compounds

The *R. vomitoria* demonstrated a concentration and time-dependent scavenging activity by quenching DPPH radicals (Fig. 1) and was compared with gallic acid, as a positive control. The IC50 values (defined as the concentration of test compound required to produce 50% inhibition) for DPPH scavenging by *R. vomitoria* and gallic acid are 401.61 ± 7.82 µg/dL and 16.32 ± 1.50 µg/dL respectively (Table 1). In the TEAC assay, the TEAC value of Trolox is 1.00. Gallic acid responded as the strongest with a TEAC value of 4.25 ± 0.12 while *R. vomitoria* responded lowest with a TEAC value of 0.85 ± 0.11 (Table 1 & Fig. 1). The phenolic content of *R. vomitoria* was determined using Folin-Ciocalteu assay and was found to be 32.07 \pm 1.24 mg/g in Gallic acid equivalent (Table 1).

3.2 Effects of the Extract on Plasma and HDL Lipids of Rats

Results of plasma and HDL lipids analyses are presented in Figs. 2 and 3. Administration of 200 mg/kg body weight of *R. vomitoria* alone did not produce any significant changes in lipid

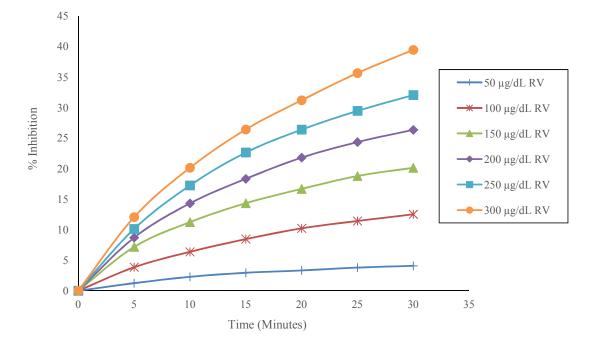




Table 1. Total phenolic content, DPPH radical scavenging value and Trolox equivalent
antioxidant capacity (TEAC) of <i>R. vomitoria</i>

Sample	Total phenol	DPPH scavenging activity (IC 50) ^b	Trolox equivalent antioxidant capacities (TEAC) ^c
Trolox	ND	ND	1
Gallic	ND	16.32 ± 1.50	4.25 ± 0.12
R. vomitoria	32.07 ± 1.24	401.61 ± 7.82	0.85 ± 0.11

Each value represents the mean \pm SEM (n=3).

a Total phenolic content was expressed as mg gallic acid equivalents/g dried extract.

b Expressed as μg/mL

c Expressed as mmol/L

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parameters in plasma and HDL when compared with control animals. However, administration of cholesterol alone significantly increased plasma cholesterol and triglyceride concentrations by 39.81% and 26.55% respectively while it reduced HDL cholesterol by 66.42% and increased HDL triglyceride by 36.95% when compared with the control animals. However, co-administration of rats with cholesterol and *R. vomitoria* extract or Questran, prevented the induction of hypercholesterolemia such that 100 mg/kg and

200 mg/kg body weight of R. vomitoria reduced plasma cholesterol concentration by 23.13% and 56.43% respectively, reduced plasma triglyceride 36.76% and concentration by 21.39% respectively, cholesterol increased HDL concentration 110.39% by 225.44% and respectively and reduced HDL triglyceride 48.52% concentration by and 24.42% respectively when compared with the rats fed with high cholesterol only.

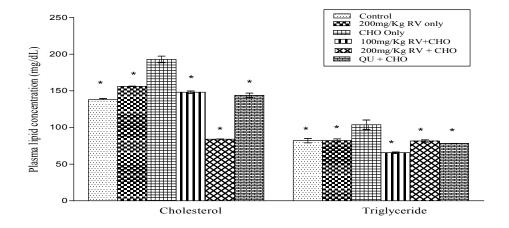


Fig. 2. Effects of methanolic leaf extract of *R. vomitoria* on plasma lipids in rats. Values are means ± SEM (n=6); *Significantly different from CHO group at p < 0.05

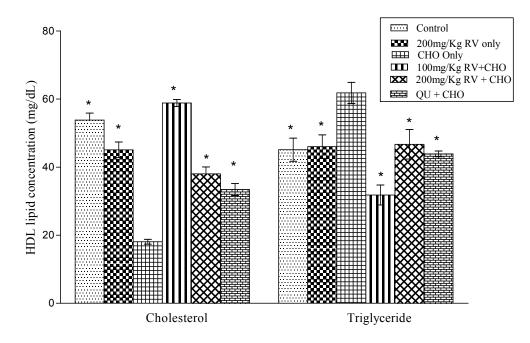


Fig. 3. Effects of methanolic leaf extract of *R. vomitoria* on HDL lipids in rats. Values are means ± SEM (n=6); *Significantly different from CHO group at p < 0.05

Group	Liver	Heart	Kidney	Lung
Cholesterol				
Control	2.94 ± 0.02*	3.77 ± 0.51*	2.14 ± 0.09*	2.37 ± 0.10*
R. vomitoria only	1.94 ± 0.02*	2.71 ± 0.36*	2.30 ± 0.09*	2.48 ± 0.09*
Cholesterol only	4.02 ± 0.03	6.36 ± 0.67	3.57 ± 0.12	3.88 ± 0.07
100mg/kg R. vomitoria+Cholestrrol	2.81 ± 0.30*	3.93 ± 0.32*	3.12 ± 0.04*	2.44 ± 0.01*
200mg/kg R. vomitoria+Cholestrrol	3.18 ± 0.11*	1.62 ± 0.13*	2.41 ± 0.14*	2.72 ± 0.12*
Questran+Cholesterol	3.59 ± 0.06	2.24 ± 0.02*	2.97 ± 0.06*	3.18 ± 0.08*
Triglycride				
Control	2.61 ± 0.08*	2.90 ± 0.01*	2.59 ± 0.12*	3.29 ± 0.03*
R. vomitoria only	2.02 ± 0.17*	2.78 ± 0.24*	2.11 ± 0.01*	3.37 ± 0.06*
Cholesterol only	3.77 ± 0.06	3.83 ± 0.14	3.50 ± 0.03	9.35 ± 0.29
100mg/kg R. vomitoria+Cholestrrol	2.43 ± 0.02*	3.14 ± 0.21	2.83 ± 0.05*	4.57 ± 0.12*
200mg/kg R. vomitoria+Cholestrrol	2.53 ± 0.09*	3.14 ± 0.11	2.07 ± 0.02*	4.78 ± 0.23*
Questran+Cholesterol	3.08 ± 0.06*	3.14 ± 0.21	3.07 ± 0.04*	5.71 ± 0.13*
Phospholipid				
Control	22.33 ± 0.98	19.00 ± 0.62	12.23 ± 0.28*	31.12 ± 0.93*
R. vomitoria only	20.05 ± 1.18	21.10 ± 0.80	12.14 ± 0.17*	30.79 ± 0.35*
Cholesterol only	21.82 ± 0.16	23.47 ± 0.10	23.37 ± 0.51	35.68 ± 0.42
100mg/kg R. vomitoria+Cholestrrol	18.91 ± 0.03	20.70 ± 1.84	13.02 ± 0.24*	23.39 ± 0.51*
200mg/kg R. vomitoria+Cholestrrol	17.48 ± 0.92*	20.26 ± 1.59	13.05 ± 0.49*	30.94 ± 0.78*
Questran+Cholesterol	21.20 ± 0.42	23.63 ±0.54	15.01 ± 0.77*	29.50 ± 0.40*

Table 2. Effects of methanolic leaf extract of *R. vomitoria* on lipids of the tissues

Values are means \pm SEM (n=6); *Significantly different from CHO group at p < 0.05

3.3 Effects of the Extract on Lipids of the Tissues

Results of tissues lipids analyses are presented in Table 1. Administration of cholesterol alone significantly increased hepatic, cardiac, renal and pulmonary cholesterol concentrations by 36.73%, 68.70%, 66.82% and 63.71% respectively when with compared the control animals. Administration of cholesterol alone also significantly increased triglycerides concentrations the tissues in all while concentrations phospholipids were only significantly increased in the kidney and lung when compared with the control animals. The coadministration of rats with cholesterol and 100 mg/kg and 200 mg/kg body weight of R. vomitoria extract resulted in the reduction of lipids with hepatic tissues triglyceride concentration reduced by 35.54% and 32.89% respectively, cardiac triglyceride concentration

reduced by 18.02 % and 18.02 % respectively, renal triglyceride concentration reduced by 19.14 % and 40.86 % respectively and pulmonary triglyceride concentration reduced by 51.12% and 48.88% respectively when compared with the rats treated with high cholesterol only.

3.4 Effect of Extract on Activities of ALP, ALT and AST

Administration of cholesterol only significantly increased enzymatic activity of ALP, ALT and AST by 20.52 %, 44.65 % and 18.90 % respectively when compared with the normal rats (Table 3). However, co-administration of 100 mg/kg and 200 mg/kg body weight of *R. vomitoria* extract and Questran to cholesterol treated rats caused a reduction in plasma ALP, ALT and AST activity when compared with the rats fed with high cholesterol only.

Blood Enzymes	Alkaline phosphatase	Alanine aminotransferase	Aspartate aminotransferase
Control	196.40 ± 9.33	14.49 ± 0.68*	81.35 ± 4.29
R. vomitoria only	170.20 ± 9.67*	18.17 ± 0.66*	69.42 ± 1.29*
Cholesterol only	236.70 ± 4.22	20.96 ± 0.26	96.73 ± 1.35
100mg/kg R. vomitoria+Cholestrrol	207.00 ± 15.77	16.43 ± 0.67*	83.13 ± 5.12
200mg/kg R. vomitoria+Cholestrrol	210.60 ± 5.07	16.78 ± 0.21*	65.41 ± 6.33*
Questran+Cholesterol	183.10 ± 13.68*	11.57 ± 0.57*	43.00 ± 0.42*

Table 3. Effect of methanolic extract of Rauvolfia vomitoria on activities of ALP, ALT and AST in rats fed with high cholesterol

Values are means \pm SEM (n=6); *Significantly different from CHO group at p < 0.05.

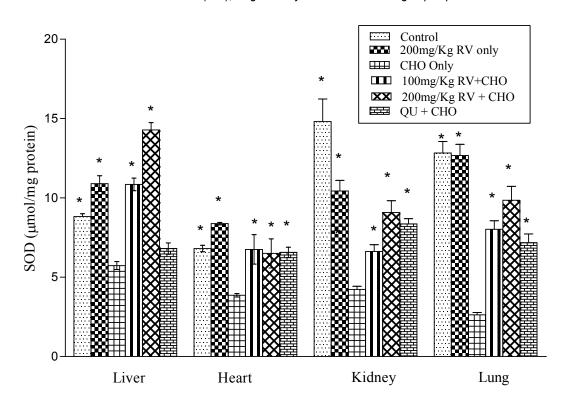


Fig. 4. Effects of methanolic leaf extract of *R. vomitoria* on SOD activity of cholesterol-fed rats. Values are means \pm SEM (n=6); *Significantly different from CHO group at p < 0.05

3.5 Effect of Rauvolfia vomitoria Extract on Tissue SOD Activity

The tissues SOD levels of rats fed with high cholesterol only were significantly reduced in the liver, heart, kidney and lung by 35.03 %, 43.29 %, 71.47 % and 79.51 % respectively when compared with the normal rats while administration of 200 mg/kg of R. vomitoria alone did not produce any significant change in SOD levels. However, co-administration of 100 mg/kg and 200 mg/kg body weight of Rauvolfia vomitoria extract to cholesterol-fed rats increased hepatic SOD level by 89.35% and 149.21% respectively, increased cardiac SOD level by 74.91 % and 68.35 % respectively, increased renal SOD level by 56.76% and 114.77% respectively and increased pulmonary SOD level by 204.91% and 274.62% respectively when compared with the rats fed with high cholesterol only.

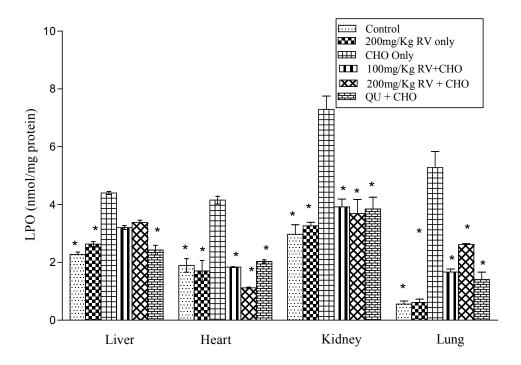


Fig. 5. Effects of methanolic leaf extract of *R. vomitoria* **on MDA level of cholesterol-fed rats** Values are means ± SEM (n=6); *Significantly different from CHO group at p < 0.05

3.6 Effect of *Rauvolfia vomitoria* Extract on Tissues Malonaldehyde Levels

Hepatic, cardiac, renal and pulmonary MDA levels of rats fed with high cholesterol only were significantly increased when compared with the normal rats while administration of 200 mg/kg body weight of R. vomitoria alone did not produce any significant change in MDA levels. However, co-administration of 100 mg/kg and 200 mg/kg body weight of R. vomitoria extract to cholesterol-fed rats caused a reduction in hepatic MDA level by 27.20 % and 23.29 % respectively, reduction in cardiac MDA level by 55.76 % and 73.04 % respectively, reduction in renal MDA level by 46.23 % and 49.36 % respectively and reduction in pulmonary MDA level by 68.38 % and 50. 46 % respectively when compared with the rats treated with cholesterol only.

4. DISCUSSION

The levels of various lipids in the plasma of animals have been shown to serve as indices of hypertension, atherosclerosis and coronary heart disease [3]. Several studies have indicated that diet treatment or drug therapy to regulate cholesterol can reduce subsequent CVDassociated mortality and morbidity [22]. The synthetic lipid-lowering drugs have been reported to be toxic in previous studies [8] therefore screening of medicinal plants for lipid-lowering properties with the less toxic effect would present an avenue for the discovery of new drugs [8].

Free radical levels have been reported to increase in hypercholesterolemia conditions [7], therefore this study determined the antioxidant potential of *R. vomitoria* using the ABTS⁺⁺ and DPPH radical scavenging assays. These two assays are among the common assays used to evaluate the total antioxidant activity of vegetables or other plants [23,24]. In the present study, *R. vomitoria* showed DPPH radical scavenging activity which is attributed to its hydrogen donating ability. The extract also showed a strong ABTS radical scavenging ability in a concentration-dependent manner suggesting that *R. vomitoria* extract has strong antioxidant potential.

Administration of high cholesterol to rats significantly increases plasma cholesterol level and decrease HDL cholesterol level when compared with the control group a strong indication of disturbances in cholesterol metabolism, a result that is in agreement with a similar study [8]. Administration of cholesterol also leads to the significant accumulation of cholesterol in the tissues which is in support of a previous study [25]. In all the compartments, there was a reduction in cholesterol levels of rats co-administered with high cholesterol and *R*. *vomitoria* extract when compared with the cholesterol group only. Although it is not clear how *R. vomitoria* leaf extract reduced the levels of cholesterol, it may be due to its ability to modulate cholesterol metabolism by the liver or lipoprotein lipase activity [26]. The chemical constituents in *R. vomitoria* leaf extracts probably downregulate cholesterol biosynthesis or inactivate the enzymatic pathways or both.

Rats fed with high cholesterol in this study have their liver enzymes (ALT, ALP and AST) activities increased in the plasma, this finding is in agreement with earlier work by Panchal et al. [27] which reported increased liver weight, fat deposition, inflammation, and fibrosis with increased plasma activity of liver enzymes in rats on high fat/high cholesterol diets. The elevation of these liver enzymes values may be indicative of some liver impairment, or possibly damage. Liver damage resulting from underlying cellular death is often associated with cholestasis, druginduced injury and obesity [28]. There was a reduction in the elevated levels of these enzymes in rats co-administered with R. vomitoria extract cholesterol when compared to the and cholesterol group only which is an indication of the stabilization of plasma membrane as well as repair of liver damage caused by cholesterol. This observation is in agreement with the commonly accepted view that serum levels of transaminases return to normal with the healing of hepatic parenchyma and the regeneration of hepatocytes [29].

The level of lipid peroxidation in the tissues of animals treated with cholesterol alone was elevated, this is in agreement with a previous study that conclude that a cholesterol-rich diet results in increased lipid peroxidation, followed by hypercholesterolemia [7]. The increase in MDA (malonaldehyde) level suggests the failure of an antioxidant defence system to prevent the formation of excessive free radicals [30]. However, co-administration of cholesterol and 100 and 200mg of Rauvolfia vomitoria leaves or standard drug (Questran) to the animals shows a reduction in the level of lipid peroxidation when compared to rats treated with cholesterol only. Hence, it may be possible that the mechanism of protection by R. vomitoria methanolic extract is due to its antioxidant potentials.

The activity of the antioxidant enzyme SOD was significantly decreased in the tissues of rats fed with high cholesterol in this study. The decreased activity of SOD in the tissues of cholesterol-fed rats may be due to increased utilisation of the enzyme against reactive oxygen species [31]. However, co-administration of rats with *R. vomitoria* extract and cholesterol reversed the reduction in SOD levels when compared to the cholesterol group only, which demonstrates that *R. vomitoria* leaf extract protects the tissues from oxidative damage.

Our present study revealed that R. vomitoria contains a considerable amount of phenolic compounds and exhibited strong free radical scavenging properties. Many researchers have reported that phenolic compounds in plant extract have antioxidant properties in various experimental models [32,33]. Therefore, the ability of R. vomitoria to protect against induction hypercholesterolemia of in cholesterol administered rats may be attributed to the presence of phenolic compounds in the extract. The phenolic substances are known to possess the ability to reduce oxidative damage and acts as an antioxidant. They can trap the free radicals directly or scavenge them through a series of coupled reactions with antioxidant enzymes [34]. The finding in this study justifies the use of *R*. vomitoria in folks medicine, in the management of hypertension and cardiovascular diseases.

5. CONCLUSION

The results obtained in this study confirm the lipid-lowering effects of *R. vomitoria* in rats fed on high cholesterol diet. *R. vomitoria* at 100 and 200 mg/kg was effective in reducing the levels of lipids in the plasma, liver, heart, kidney and lung while it increased the cholesterol in the HDL. The health benefit associated with *R. vomitoria* may be related to its antioxidants potentials which were demonstrated in this study through *in-vitro* radicals scavenging ability, prevention of lipid peroxidation and preservation of the endogenous antioxidant system. This makes the plant to be effective in the management of free radical-mediated diseases and cardiovascular diseases.

DISCLAIMER

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVALS

The faculty of basic medical science, Ladoke Akintola University of Technology, Ogbomoso, research ethics committee gave ethical approval for the study (FBMS2018/09).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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