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ANTIDIABETIC PROPENSITY OF *Tetracarpidium conophorum* (AFRICAN WALNUT) SEED IN ALLOXAN-INDUCED DIABETIC RATS

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ABSTRACT

Diabetes mellitus (DM) refers to a metabolic condition that could lead to high morbidity and mortality. Current therapies for DM are not without adverse effects and do not restore normal glucose balance. Consequently, this investigation aimed to assess the anti-diabetic propensity of *Tetracarpidium conophorum* seed on alloxan-induced diabetic rats. Thirty-six Wistar rats were split into six groups of six rats each. Rats in groups 2 to 6 were induced with 150 mg/kg of Alloxan monohydrate. Animals in groups 1 and 2 were untreated; those in group 3 were administered Glibenclamide, while animals in groups 4, 5, and 6 were treated with 100, 200, and 400 mg/kg body weight of *Tetracarpidium conophorum* for 21 days. Blood glucose level and lipid profile were evaluated at the end of the period in all studied groups. In comparison to the normal control group and the diabetic control group, *Tetracarpidium conophorum* seed-extract administration resulted in lower glucose, TC, TG, LDL-C, and VLDL levels, while also increasing HDL levels ($P \leq 0.05$). Therefore, it may be inferred that consumption *Tetracarpidium conophorum* seed extracts orally for 21 days at doses of 100, 200, and 400 mg/kg each had positive effects on hypoglycemia. Further evidence that it may be helpful in the management and prevention of diabetes came from its effects on blood lipids and glucose levels in diabetic rats.

Keywords: *Tetracarpidium conophorum* seed; diabetes; alloxan; blood sugar; plant extracts; lipid profile.

INTRODUCTION

Hyperglycemia has been reported to be one of the main factors that lead to diabetes mellitus (DM) [1]. The underlining complications of hyperglycemia are diabetic nephropathy, peripheral vascular

disturbances, delayed wound healing, neuropathy, retinopathy, diabetic ketoacidosis and heart attack [2]. DM has been reported to the most typical endocrine disorder which has affected 100 million or more people globally (about 6% of the world's population). It is a metabolic medical situation identified by a rise in blood glucose concentration owing to insulin non-secretion or insulin sensitivity. Its occurrence is traceable to lack of pancreas or a declined production of insulin, which unhinged the levels of sugar in the blood. It has been uncovered to harm diverse component of the body, specifically the blood vessels, eyes, kidneys, heart and nerves [3]. If left unattended to, DM become visible by elevated blood glucose levels emerging from malfunctioned metabolism of glucose, leading to atherosclerosis, obesity, cardiovascular disease, failure of different enzymes, organs, and pathways, and eventually death [4,5]. There are orthodox drugs available to address DM, but prolonged use may result in other severe negative consequences. Therefore, finding new, safe, and potent natural DM treatment alternatives is one of the most crucial things to look into, and this is why so many researchers are interested in it [6,7]. Numerous medicinal herbs have been shown to have hypoglycemic effects in recent investigations on experimental diabetes [8-12].

Tetracarpidium conophorum, frequently identified as African walnut, is a limb of the family of Euphorbiaceae [13]. It is found in the wet parts of Eastern and Western Nigeria and Western Africa in general. In Nigeria, it is identified as "Ukpa" by the Igbos, "Awusa or Asala" by the Yorubas, "Oghoya", "Okhue" or "Okwe" by the indigens of Edo state [13,14]. Previous research on this plant revealed that it included hypolipidemic, hepatoprotective, anti-oxidative, hypoglycemia, and anti-oxidative agents [15]. *Tetracarpidium conophorum* is a commercial plant that is extensively grown for its nuts, which are consumed as a delicacy. You can eat the nuts either raw or cooked [16,17]. Nut consumption, diabetes mellitus, and its consequences have been shown to be inversely correlated [18]. Antihyperglycemic substances have recently been found in African walnut seed [19]. Its method of controlling blood sugar levels may involve reducing intestinal absorption and promoting the use of glucose by cells [20]. Thus, this research was done to assess the possible antidiabetic propensity of *Tetracarpidium conophorum* nut in an alloxan-induced diabetic rat model.

MATERIALS AND METHODS

Collection and Extraction of Plant Materials

T. conophorum cooked seeds were obtained from a local market in the "Oja-Oba" area of Ibadan, Nigeria, and were identified by a botanist. The seeds were delicately taken out of their shells and allowed to air dry for seven days before being ground into powder. Using Soxhlet equipment and ethanol as the solvent, the extraction was carried out in accordance with the procedure previously reported by Airaodion et al. [21,22]. An extract yield of 3.04 g, representing a yield of 12.16%, was obtained after the solvent was evaporated using a rotary evaporator with a temperature setting of 35^{o}C. A refrigerator was used to keep the evaporated extract until it was needed for analysis.

Experimental Animals

For this investigation, 36 mature Wistar rats with body weight of 120 - 140 g were

utilized. Before the trial started, they had seven days to get used to the lab surroundings. The rats were fed conventional rat food and given access to fresh water during this time. Throughout the duration of the trial, they were housed in sterile cages that were kept in ventilated spaces (under humid tropical circumstances). All of the animals received humane treatment in accordance with the standards outlined in the National Academy of Science's "Guide for the Care and Use of Laboratory Animals," which was published by the National Institutes of Health [23]. Alloxan monohydrate was dissolved in sterile normal saline and administered intraperitoneally to the experimental rats after a seven-day acclimatisation period. The dosage was 150 mg/kg body weight [24,25]. After about 72 hours of the injection, diabetic rats were those with fasting blood glucose (FBG) levels of 126 mg/dL or higher (7.0 mmol/L).

Grouping of Animals

The animals were stochastically slit into six classes of six each. They were classified as follows:

Group 1: Normal control (non-diabetic rats)
Group 2: Negative control (diabetic without treatment)
Group 3: Positive control (diabetic + Glibenclamide)
Group 4: Diabetic + 100mg/kg body weight of *T. conophorum* seed
Group 5: Diabetic + 200mg/kg body weight of *T. conophorum* seed
Group 6: Diabetic + 400mg/g body weight of *T. conophorum* seed

N.B: Glibenclamide is a known medication used in the treatment of diabetes mellitus.

After twenty-one (21) days of treatment, the animals were fasted overnight and anesthetized using diethyl ether. Blood samples were collected by cardiac puncture.

Determination of Fasting Blood Glucose

In the course of this investigation, the fasting blood glucose (FBG) level was assessed five times. The first time was prior to the administration of alloxan to induce DM. The second occasion was following the administration of alloxan to induce DM. The results were also determined 7, 14, and 21 days respectively, following the start of treatment. The animal tails were sterilised with 10% alcohol, cut with scissors, and the blood was allowed to contact the test strip in following the procedures outlined by Airaodion et al. [26] to determine the FBG level. Next, a calibrated glucose metre (One-touch Glucometer, Acon Laboratory INC. San Diego, USA) was used to place the test strip. The straight result was shown after around 5 seconds.

Determination of Lipids

Lipid samples were extracted and quantified using techniques outlined by Owoade et al. [27,28].

Statistical Analysis

Graph Pad Prism was used to conduct a variance analysis on the data. Results were displayed using the formula Mean$\pm$Standard Error of the Mean (SEM). For the mean comparison, one-way analysis of variance (ANOVA) was used, followed by Tukey's post hoc test. At $P \leq 0.05$ (95% confidence level), differences between means were deemed significant.

RESULTS

Effect of *Tetracarpidium conophorum* Seed on Fasting Blood Glucose (FBG) Level

Figs. 1 and 2 respectively portrayed rats' FBG levels prior and after alloxan induction in the respective controls and treatment groups. Alloxan injection resulted in a noticeable ($P \leq 0.05$) upsurge in FBG level of alloxan-induced group compared with those in the normal control group. The effects of *Tetracarpidium conophorum* seed extract administration on the FBG level of alloxan-treated rats were displayed in Figs. 3-5. At the end of 7 days of treatment, a noticeable ($P \leq 0.05$) decline in the FBG levels was observed sequel to *Tetracarpidium conophorum* seed extract treatment. At the end of 14 and 21 days respectively, there was a further significant ($P \leq 0.05$) decline in the levels of FBG following the administration of *T. conophorum* seed extract. But in rats with uncontrolled diabetes, the situation was the exact opposite. Rats given a 400 mg/kg body weight ethanol extract of *Tetracarpidium conophorum* seed showed the largest decrease in FBG.

Effect of *Tetracarpidium conophorum* Seed Extract on serum Lipid Profile of Diabetic Rats

Figs. 6-11 shows the impact of *T. conophorum* seed extract on lipid profile indices. The induction of diabetes in the rats resulted in significant ($P \leq 0.05$) increases in LDL-cholesterol, VLDL, TG, and TC, whereas HDL-cholesterol and HDL/LDL ratio were reduced significantly ($P \leq 0.05$). Conversely, the administration of *T. conophorum* seed extracts markedly elevated ($P \leq 0.05$) HDL and HDL/LDL Ratio, but reduced LDL-cholesterol, VLDL, TG, and TC as the concentration of the extract increased, when respectively compared with those in the diabetic control animals. The decrease of blood lipid TC, TG, LDL-C, and VLDL levels in rats were dose-dependent.

4. DISCUSSION

With the upsurge in diabetes across the globe and the adverse implication of regularly used allopathic medications such as biguanides and sulfonylureas, quantum number of scientists has sifted attention to antidiabetic agents from plant extracts as an optional treatment. This study is to explore the antidiabetic propensity of *T. conophorum* nut in alloxan-induced diabetic Wistar rats. The findings alluded that the nut extract possesses a potent antidiabetic impact, which may be used to manage diabetes.

Alloxan is recognized as a toxin with the capability to damage pancreatic cells, resulting in a preliminary insulin shortage without destroying other classes of islets [4]. It is employed in the laboratory to influence both T_1DM and T_2DM in animals. The fundamental mechanism underlying alloxan-induced diabetes follows that alloxan's liberates free radicals which influence the destruction of the pancreatic β-cells, facilitating their mortality. Alloxan overran the pancreatic β-cells *via* the $GLUT_2$ transporter [24]. Alloxan is inhibited in the cytosol when several cellular reducing agents to dialuric acid are present. Alloxan suppression affected the formation of a redox cycle and the generation of superoxide radicals (O.). The generation of hydrogen peroxide (H_2O_2), which combines with ferrous (Fe^{2+}) to produce hydroxyl radical (OH), a strong oxidative agent, was impacted by the dismutation of superoxide radicals [8].

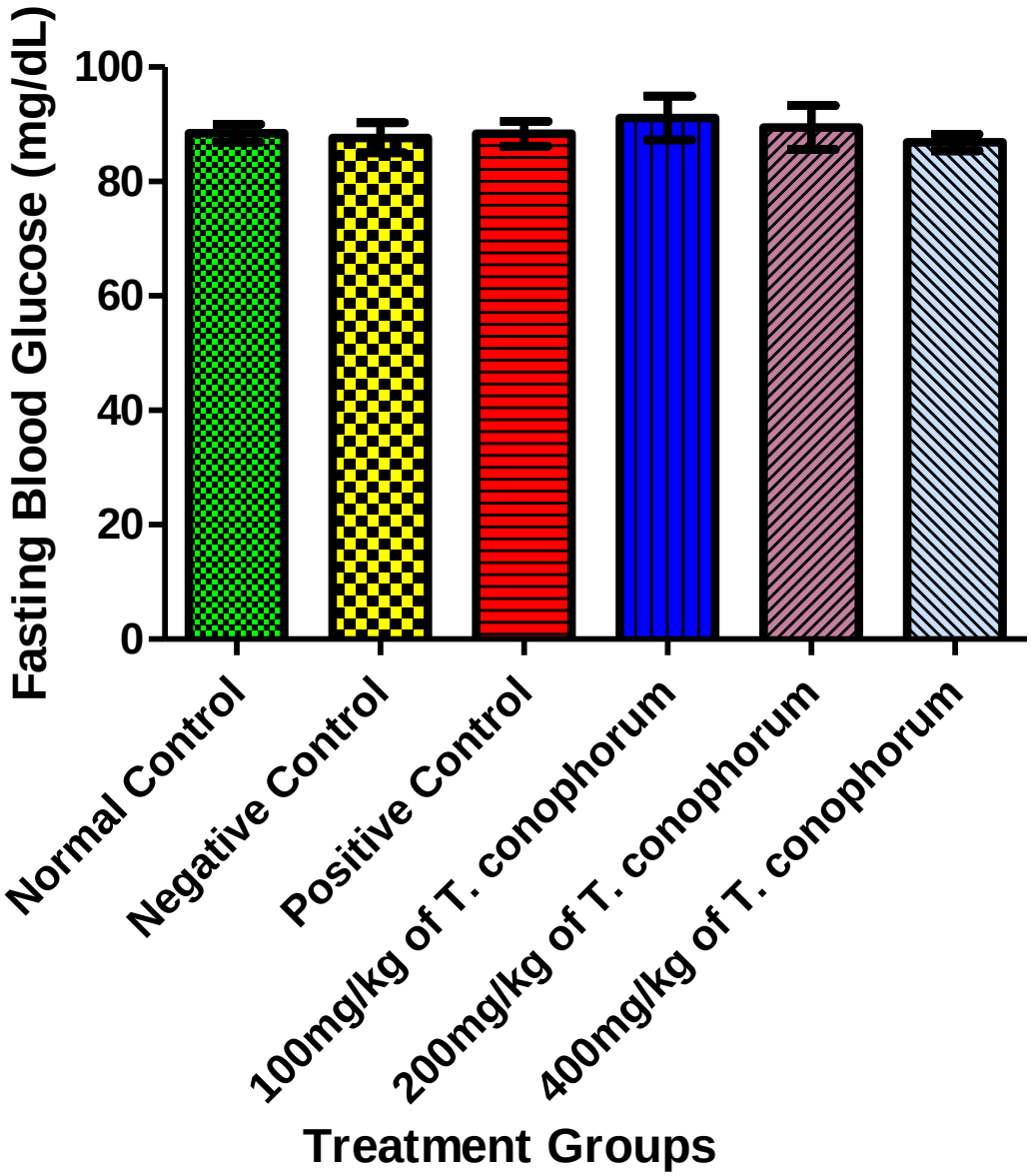

Fig. 1. Fasting blood glucose of animals before diabetes induction

Results are presented as mean ± SEM with n = 6. Bars with different letters are significantly different at P≤0.05

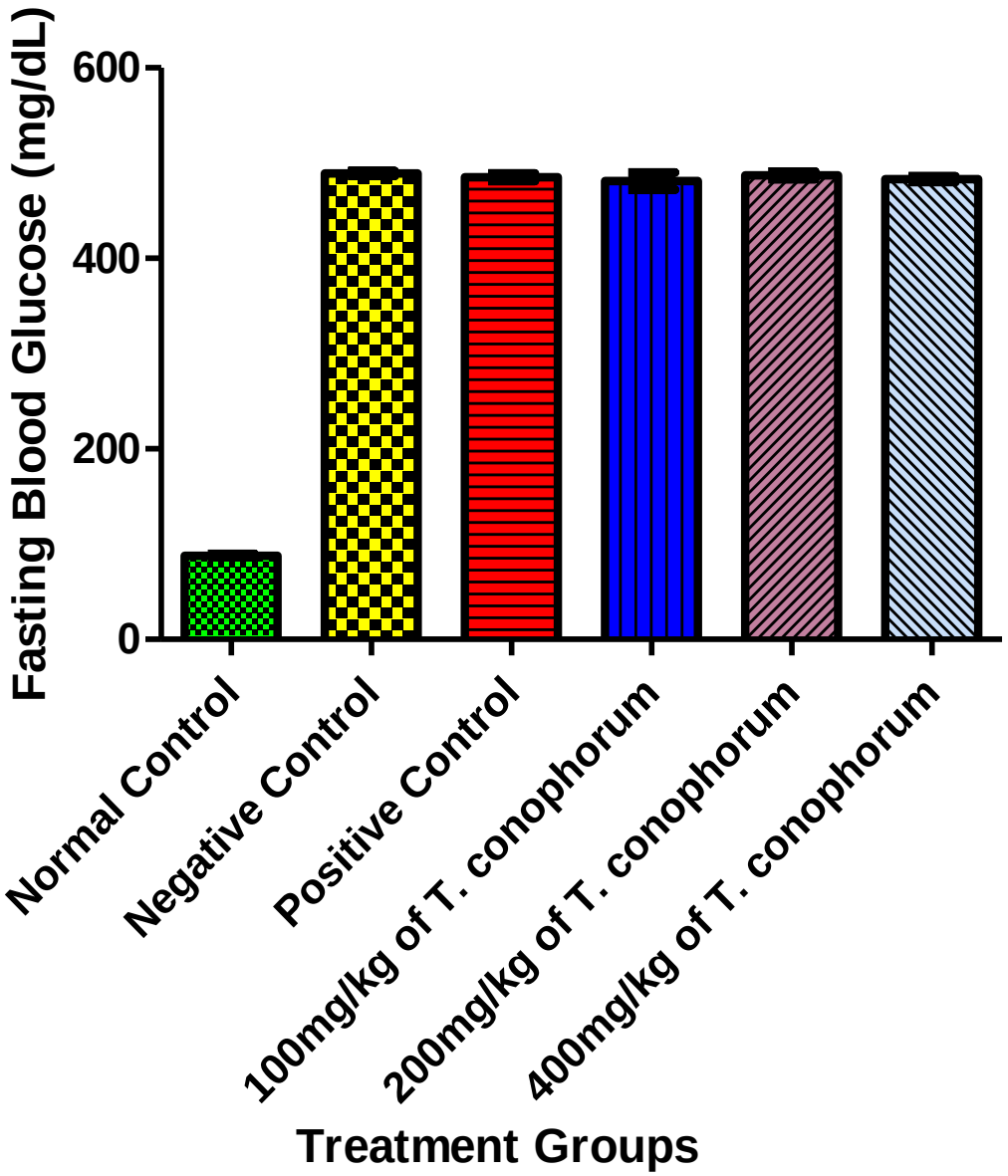

Fig. 2. Fasting blood glucose of animals after diabetes induction by alloxan
Results are presented as mean ± SEM with n = 6. Bars with different letters are significantly different at P≤0.05

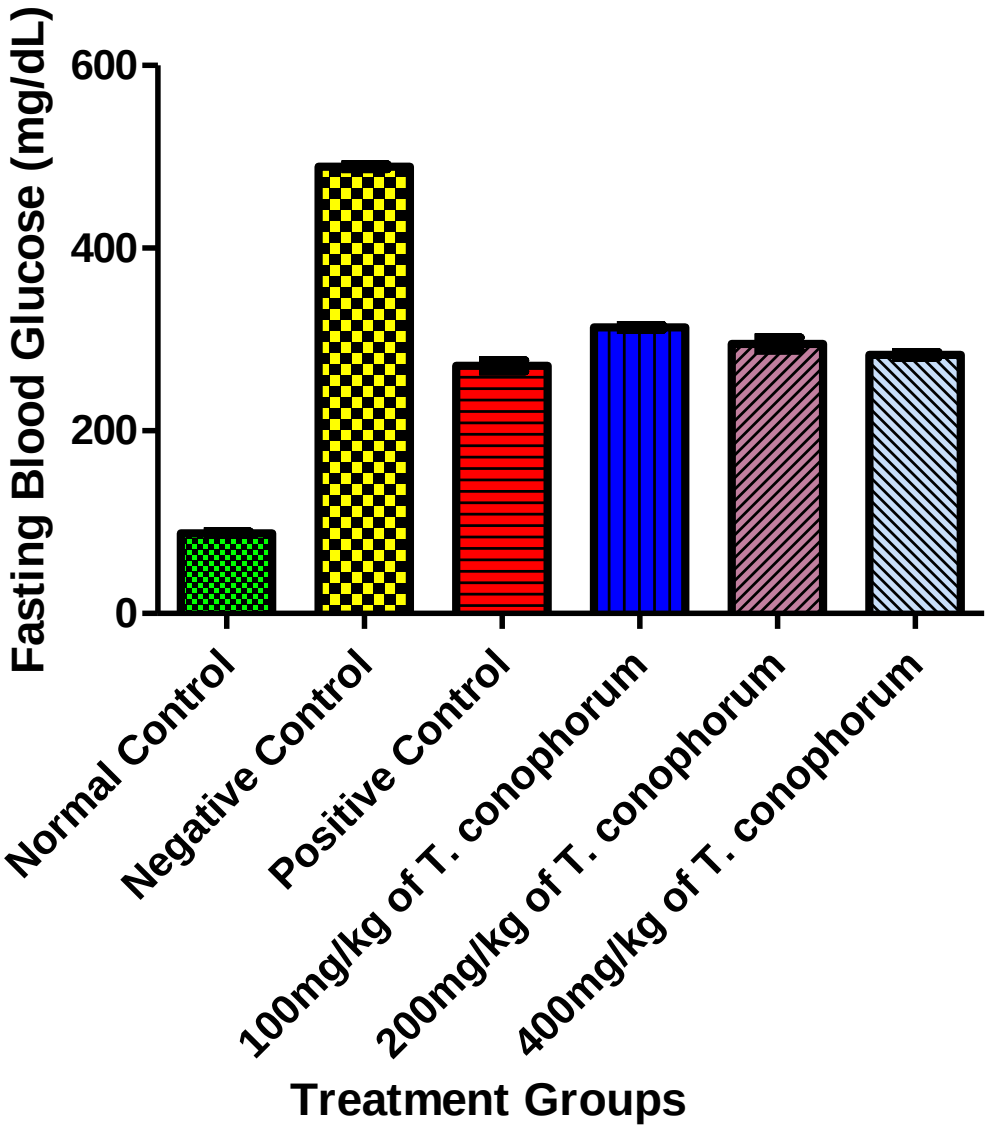

Fig. 3. Effect of different doses of *T. conophorum* seed administration on the fasting blood sugar of animals after 7 days of treatment

Results are presented as mean ± SEM with n = 6. Bars with different letters are significantly different at P≤0.05

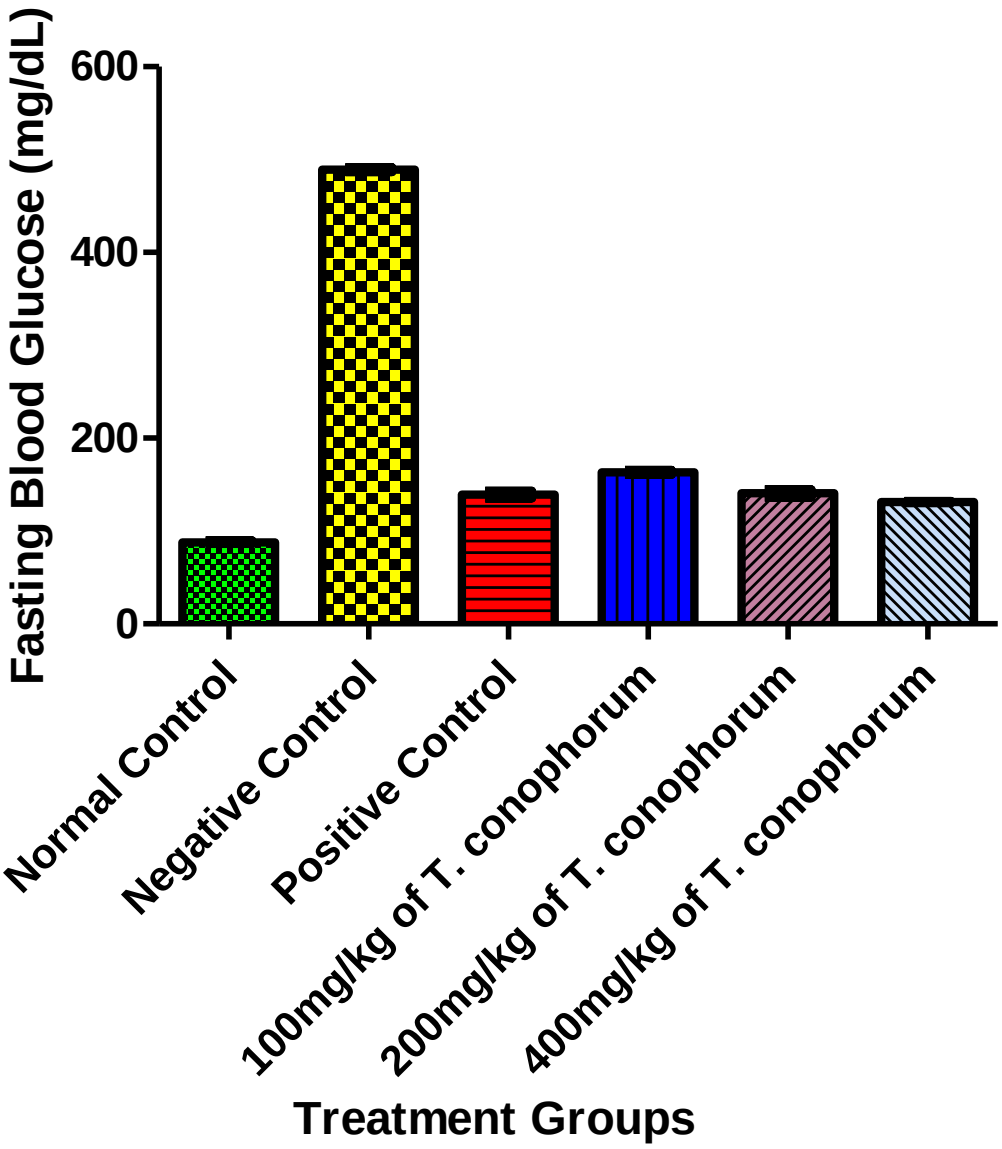

Fig. 4. Effect of different doses of *T. conophorum* seed administration on the fasting blood sugar of animals after 14 days of treatment

Results are presented as mean ± SEM with n = 6. Bars with different letters are significantly different at $P \leq 0.05$

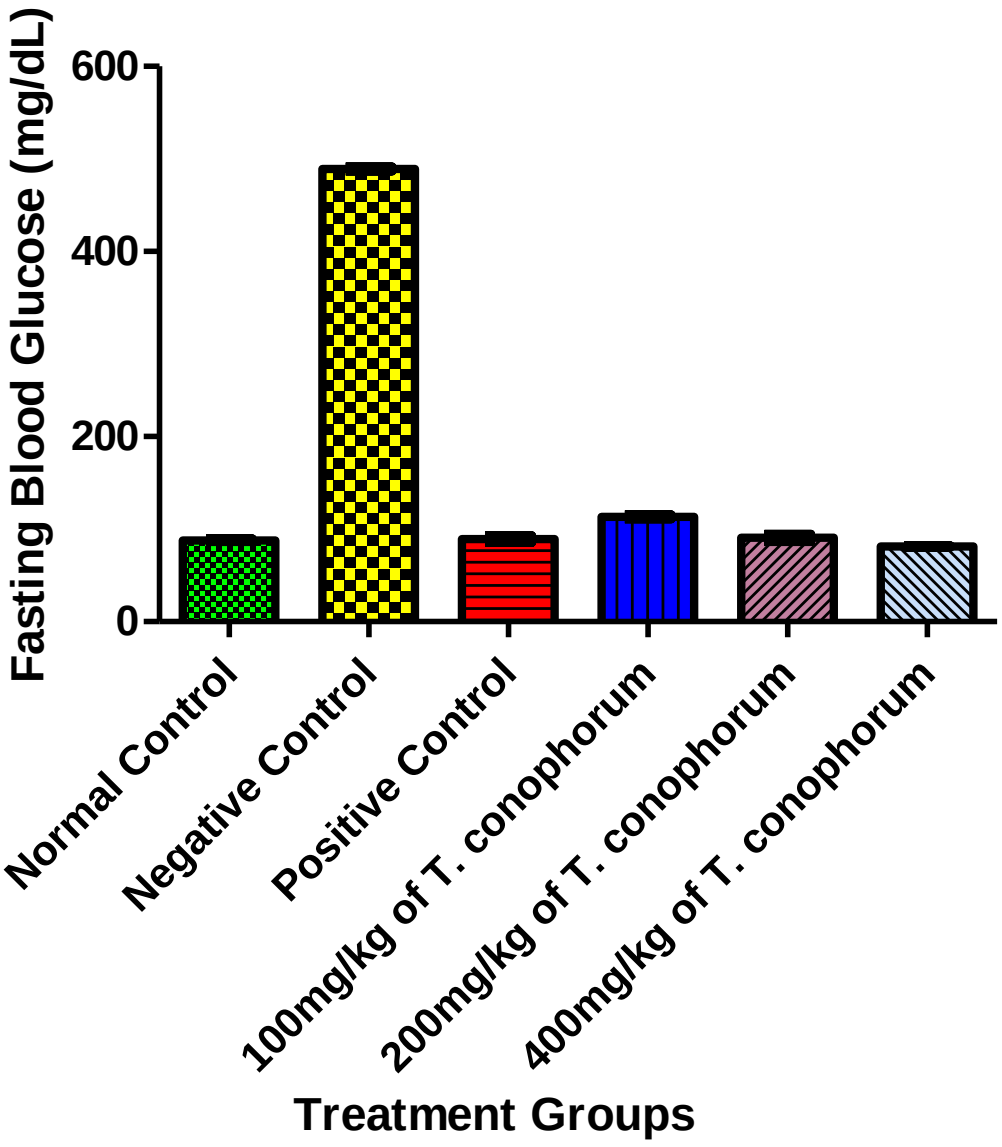

Fig. 5. Effect of different doses of *T. conophorum* seed administration on the fasting blood sugar of animals after 21 days of treatment

Results are presented as mean ± SEM with n = 6. Bars with different letters are significantly different at P≤0.05

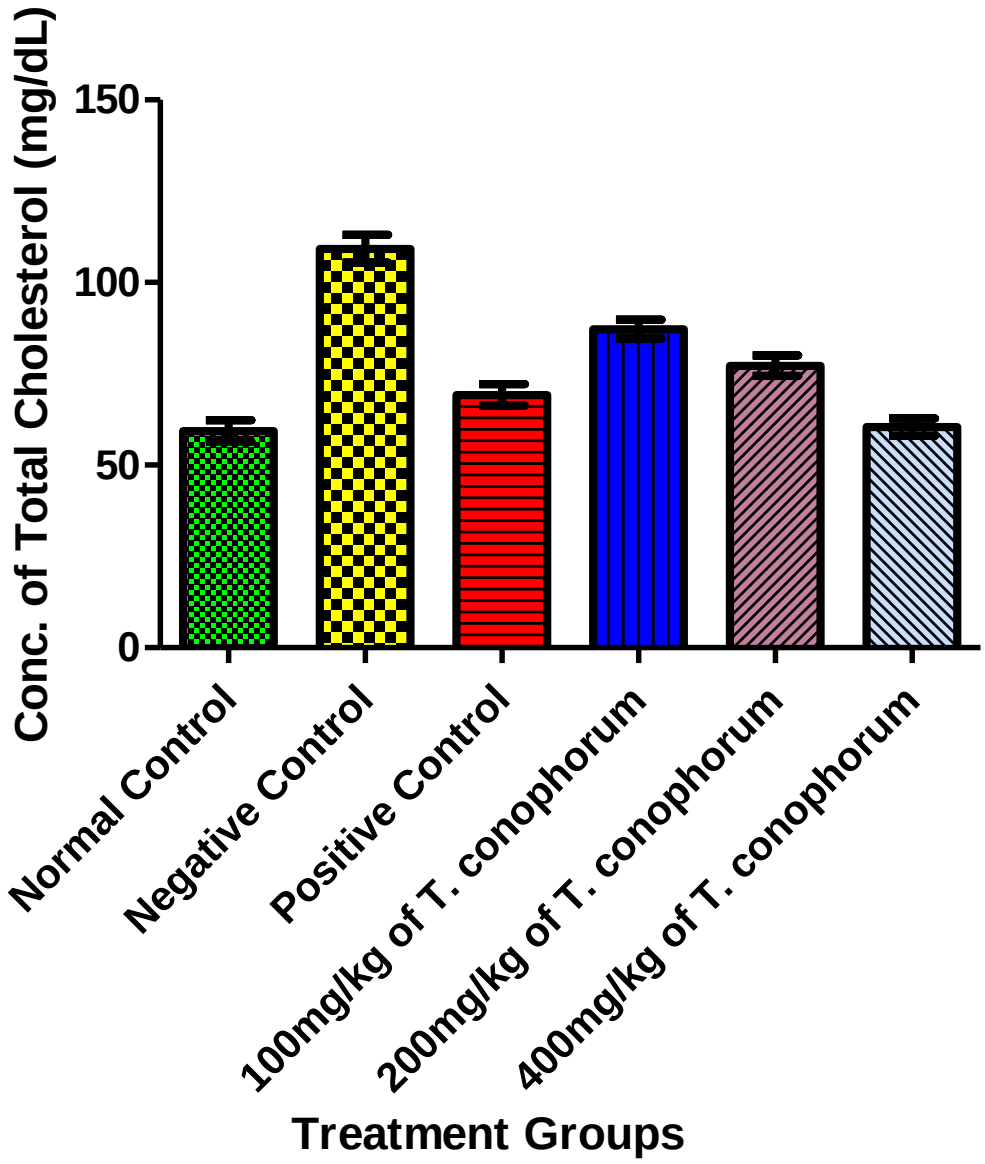

Fig. 6. Effect of different doses of *T. conophorum* seed administration on the concentration of total cholesterol of animals after 21 days of treatment

Results are presented as mean ± SEM with n = 6. Bars with different letters are significantly different at P≤0.05

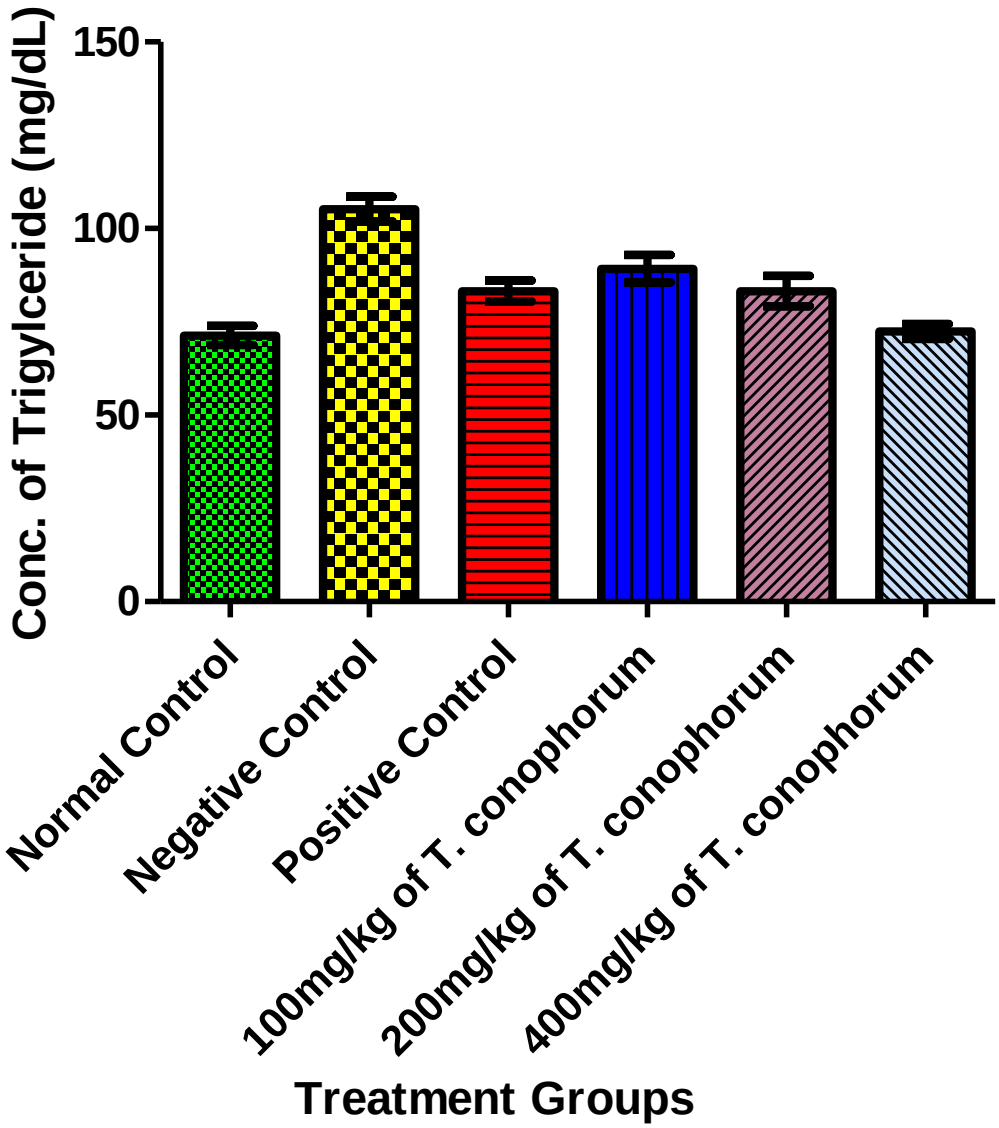

Fig. 7. Effect of different doses of *T. conophorum* seed administration on the concentration of triglyceride of animals after 21 days of treatment

Results are presented as mean ± SEM with n = 6. Bars with different letters are significantly different at P≤0.05

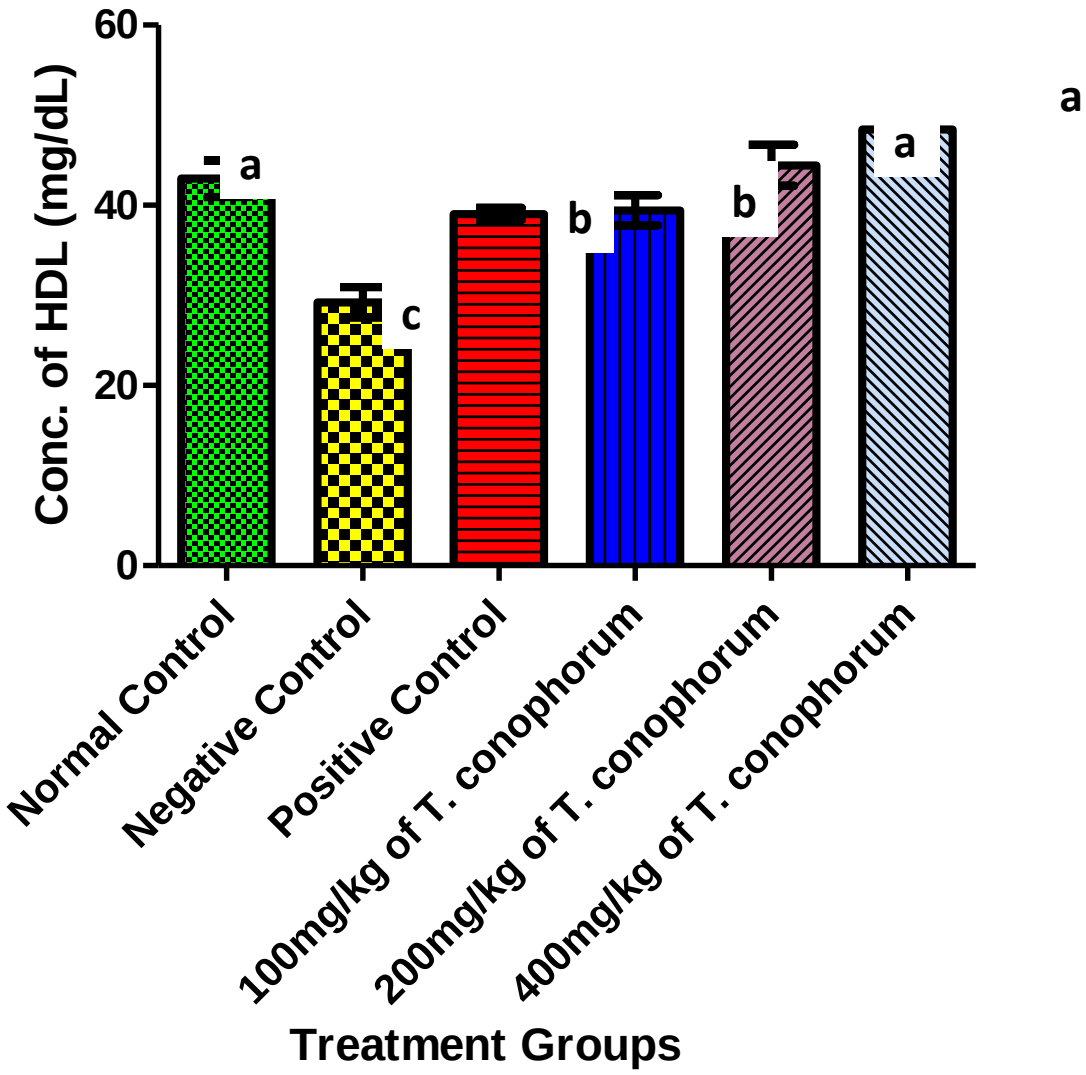

Fig. 8. Effect of different doses of *T. conophorum* seed administration on the concentration of high density lipoprotein (HDL) cholesterol of animals after 21 days of treatment

Results are presented as mean ± SEM with n = 6. Bars with different letters are significantly different at P≤0.05

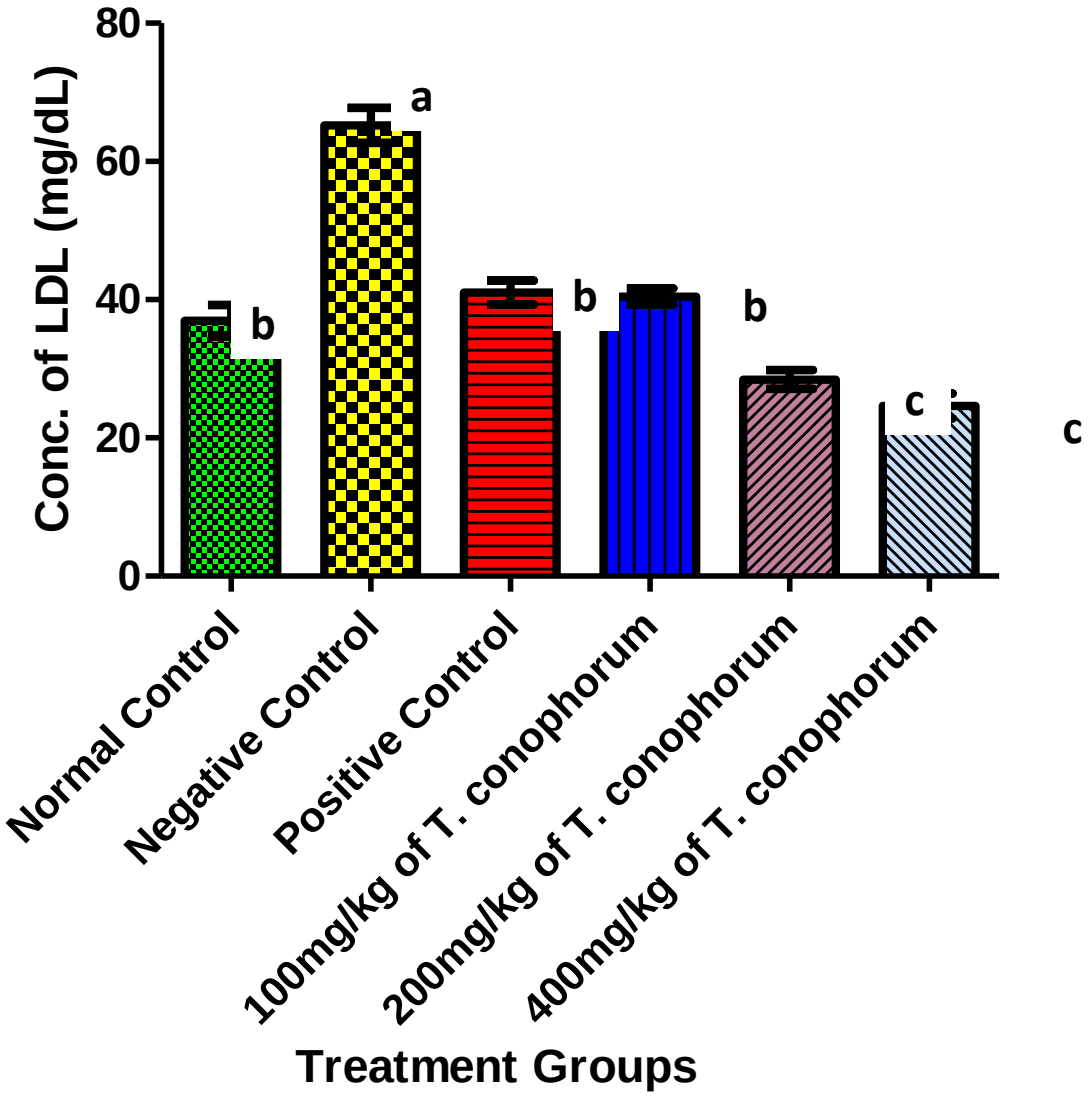

Fig. 9. Effect of different doses of *T. conophorum* seed administration on the concentration of low-density lipoprotein (LDL) cholesterol of animals after 21 days of treatment

Results are presented as mean ± SEM with n = 6. Bars with different letters are significantly different at P≤0.05

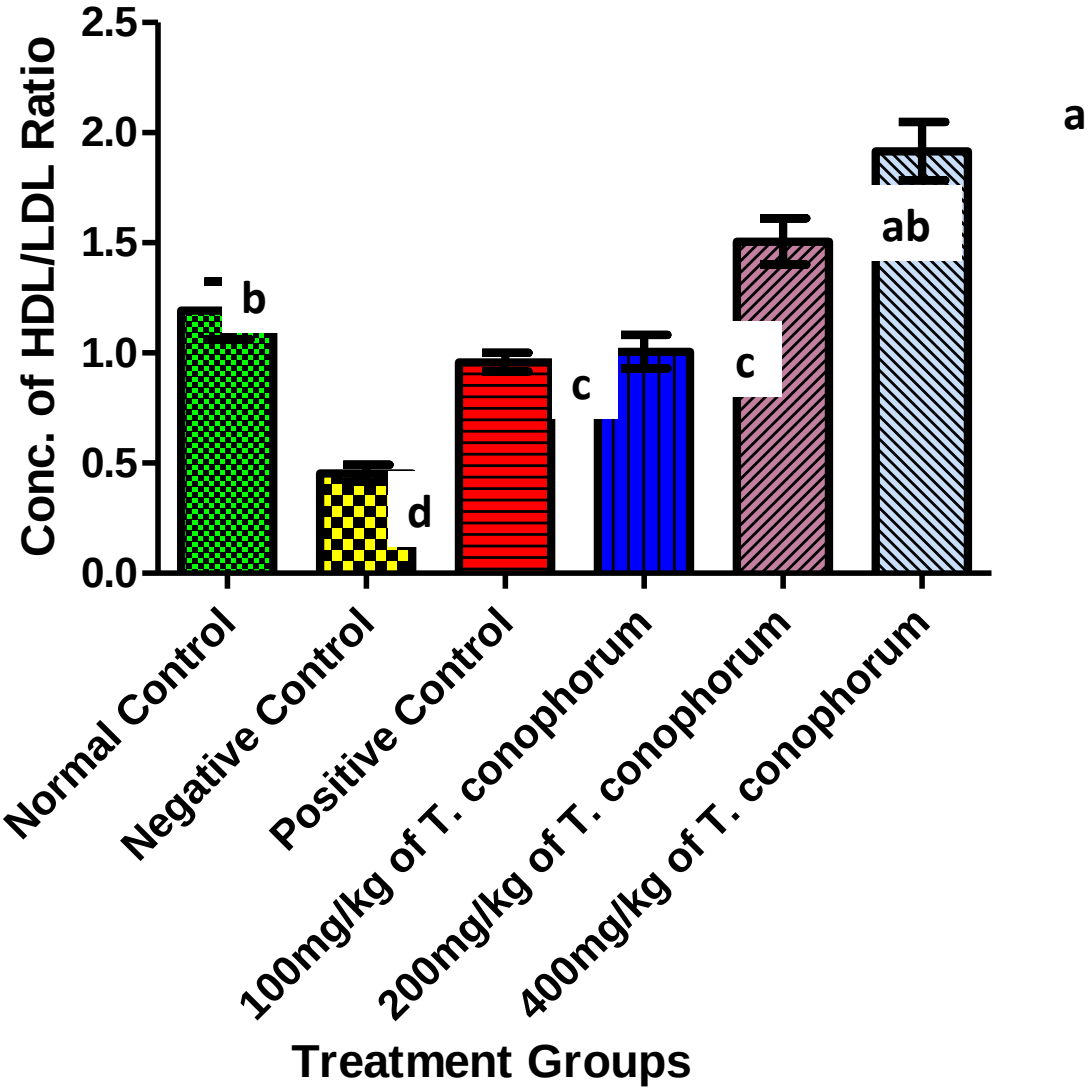

Fig. 10. Effect of different Doses of *T. conophorum* seed administration on the concentration of HDL/LDL ratio of animals after 21 days of treatment

Results are presented as mean ± SEM with n = 6. Bars with different letters are significantly different at P≤0.05

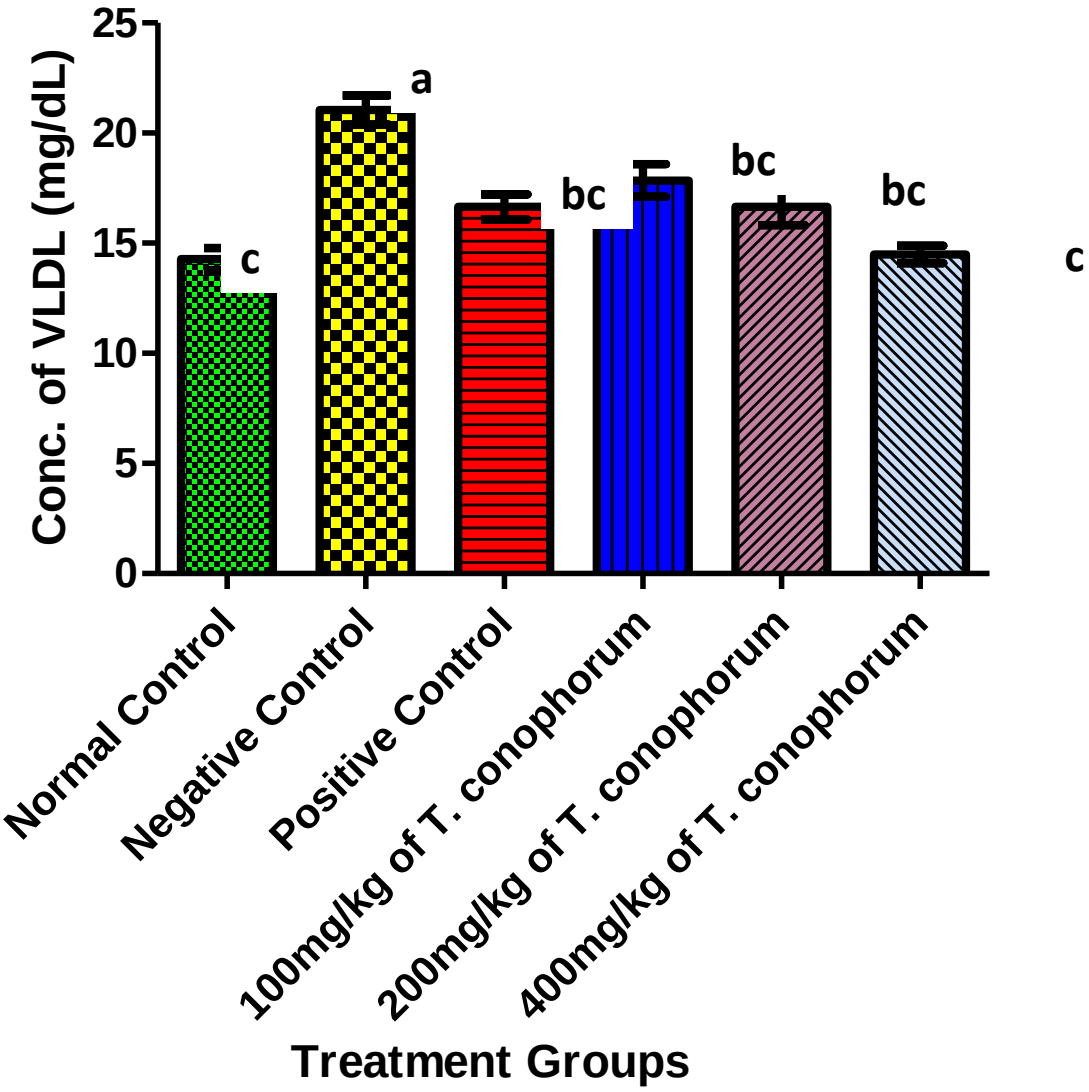

Fig. 11. Effect of different doses of *T. conophorum* seed administration on the concentration of very low-density lipoprotein (VLDL) cholesterol of animals after 21 days of treatment

Results are presented as mean ± SEM with n = 6. Bars with different letters are significantly different at P≤0.05

Diabetes mellitus (DM) is depicted by an upregulation in fasting blood glucose (FBG) concentration [29,30]. Rising in FBG levels in the diabetic group was noticed in this study. The results on diabetic rats sequel to daily oral administration of *Tetracarpidium conophorum* seed extract (100, 200, and 400 mg/kg) demonstrated a notable downregulation in FBG level after 21 days of treatment. *Tetracarpidium conophorum's* suppression of increased FBG levels in diabetic rats reflects a reversal of insulin resistance or an upsurge in insulin formation, perhaps *via* revitalization of pancreatic β-cells rendered incapacitated by alloxan cytotoxic effect in diabetic rats [31]. This result agrees with other studies by Sileshi et al. [32] and Toma et al. [33]. Thus, the present study unveiled that *Tetracarpidium conophorum* seed extract (100, 200, and 400 mg/kg) has a noticeable antihyperglycemic effect on Alloxan-induced diabetic rats in a dose and time-dependent manner.

Hyperlipidemia is depicted by enhanced levels of triglycerides, cholesterol, low-density lipoprotein cholesterol (LDL-c) [34,35]. The results of this *in vivo* study unveiled that ethanol extracts of the nut noticeably suppressed cholesterol, triglycerides, and LDL-c levels in normal and diabetic rats, with an equivalent rise in HDL-c when compared to their respective control groups. This improvement was facilitated by the administration of the *Tetracarpidium conophorum* at different doses. The diabetic control group portrayed a decline in the level of HDL-c compared with the intact control group. An evidence of DM is a fall in HDL-c levels, and *Tetracarpidium conophorum* extract treatment compensated for this decline in diabetic rats treated with the extract. The apparent increase in LDL cholesterol in diabetic rats may be due to an increase in hepatocytes' production of VLDL-c or a decrease in the removal of VLDL-c and LDL-c from circulation [36,37]. Hypercholesterolemia and hypertriglyceridemia are connected to DM on account of elevated hepatic lipolysis, fat mobilization from adipose tissue, and glucose underutilization due to insulin inadequacy or insensitivity [38]. Glibenclamide treated rats had a declined triglyceride and total cholesterol concentrations, while the seed extract (at 400 mg/kg body weight) had similar effect in LDL-c and HDL-c normalization. Since literature has reported a significant link between DM and hyperlipidemia [24,25], this extract can be utilized to maintain glucose homeostasis in DM and control dyslipidemia [39].

5. CONCLUSION

This study unveiled that consumption of *Tetracarpidium conophorum* nut exerts noticeable hypoglycemic and hypolipidemic effects on alloxan-induced diabetic rats. DM is a leading chronic disease caused by carbohydrate, lipid, and protein metabolism. Despite numerous advanced researches in medicine, there is no satisfactory drug in tackling DM. This study showed that *Tetracarpidium conophorum* seeds have valuable potentials for complementary therapy for the treatment of DM and its complications. Individuals who are predisposed to diabetes and those with a diabetic family history are encouraged to consume the nuts of *Tetracarpidium conophorum*.

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ETHICAL APPROVAL

Animal Ethic committee approval has been collected and preserved by the author(s)

AVAILABILITY OF DATA AND MATERIAL

On reasonable request, the corresponding author will make the datasets used and/or analysed during this study available.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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