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Lycopene, a Natural Hypolipidemic Adjuvant: Evidence from Cholesterol-Induced Wistar Rats

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ABSTRACT

Carotenoids are bioactive phytochemicals recognized for their health-promoting properties, with lycopene being a major representative. Several epidemiological studies have shown that Lycopene a red pigment in ripe tomatoes and their products reduces the risk of having cardiovascular disease (CVD). In this current study, the effect of lycopene on lipid profile in cholesterol-fed rats was investigated. The focus was on both dose- and time-dependent responses. Forty (40) Wistar rats (180–200 g) were assigned into five groups. The control group (n=5) received a basal diet only, while the cholesterol-induced group received 2% pure cholesterol without lycopene treatment. The treatment groups (n=10) were fed 2% cholesterol plus graded doses of lycopene (4, 8, and 12 mg/kg b.w.). Induction lasted 30 days, after which lycopene treatment was administered for 7 or 14 days. Blood samples collected from overnight-fasted rats were analyzed for lipid profile. Total cholesterol (TC), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C) were measured spectrophotometrically. In contrast, low-density lipoprotein cholesterol (LDL-C) and very-low-density lipoprotein cholesterol (VLDL-C) were calculated using the Friedewald–Friedrickson formula. The cholesterol-fed group showed significantly ($P<0.05$) elevated TC, TG, LDL-C, and VLDL-C with reduced HDL-C compared to controls. Lycopene supplementation significantly decreased ($P<0.05$) TC, TG, LDL-C, and VLDL-C in a concentration- and time-dependent manner. Moreover, HDL-C significantly increased ($P<0.05$) after 14 days of treatment, although changes at 7 days were not significant ($P>0.05$). These findings suggest that lycopene ameliorates dyslipidemia by enhancing HDL-C and reducing other lipids, indicating its potential role in preventing hyperlipidemia.

Keywords: Lycopene, Carotenoid, Lipid profile, Cholesterol-fed rats, Hyperlipidemia, Cardiovascular disease

1. INTRODUCTION

Cardiovascular disease (CVD) is known to be one of the leading causes of death globally (Victor et al., 2024). Studies have shown that people who regularly consume diet rich in fruits and vegetables are less likely to have heart diseases (Chen et al., 2023). Phytochemical compounds particularly carotenoids are considered to be responsible for the cardio-protective effects of vegetables and fruits (Sharma et al.,

2024). According to Giovannucci (2002), around 600 fat soluble pigments referred to as carotenoids attributes to the natural red, yellow and orange colours of fruits and vegetables. Lycopene is one of such carotenoids and is the pigment particularly responsible for the distinct red colour of ripe tomato (*Lycopersicon esculentum*) and tomato products (Shi, 2002). Wu *et al.* (2003) suggested that a high consumption of tomatoes and tomato products containing lycopene may protect against CVD. These findings have encouraged several animal model studies designed to test this hypothesis and to establish the beneficial effects of lycopene. The focus of this study is to determine the concentration and time-dependent effects of lycopene on lipid profile of cholesterol-fed Wistar rats.

2. MATERIALS AND METHODS

Forty (40) adult Wistar rats (180 - 200 g) were used for this study. The rats were placed in cages at the animal house in the Department of Anatomy, University of Benin, Benin City, Nigeria, and were acclimatized for a period of 14 days before the commencement of the study. The rats were kept in a temperature and humidity-controlled environment. The study done in agreement with the guidelines for care and use of laboratory animals of the National Institute of Health, and all efforts were made to minimize animal suffering.

The rats were divided into five groups at random: the first and second groups had 5 rats each while the third, fourth, and fifth groups had 10 rats each. The induction of hypercholesterolemia and treatment with different concentrations of lycopene was administered intragastrically once daily using a metal canula attached to a 1ml syringe.

The grouping is as follows:

Group 1: Control, received basal diet with no pure cholesterol or lycopene

Group 2: Cholesterol-fed group, received 2% cholesterol and no lycopene

Group 3: Received 2% pure cholesterol + 4 mg/kg b.w of lycopene

Group 4: Received 2% pure cholesterol + 8 mg/kg b.w of lycopene

Group 5: Received 2% pure cholesterol + 12 mg/kg b.w. of lycopene

Induction lasted for 30 days, after which lycopene treatment commenced for 7 days and 14. Following lycopene treatment, the rats were then fasted overnight and blood samples collected for analysis.

Drug

Lycopene was obtained from lycoset syrup. Each milliliter (1ml) of Lycoset contains 15 mg of lycopene. A high-fat diet constituted a mixture of 250 ml of groundnut oil and 25 g or 25,000 mg of pure cholesterol powder. Each milliliter (1ml) of high-fat diet contains 100 mg/kg b.w. of cholesterol. 2% of pure cholesterol powder is equivalent to 500 mg/kg b.w.

Collection and Preparation of Plasma Samples for Lipid Profile Analysis

Blood was collected from the overnight fasted animals via thoracic aorta into heparinised tubes (Lithium heparin). Samples were centrifuged at a speed of 3000 rpm for 10 minutes for the preparation of blood plasma. High Density Lipoprotein (HDL), Lipid profile (Total cholesterol (TC), and Triglyceride (TG) were estimated manually on a spectrophotometer, and LDL-C, calculated using the Friedewald-Fredrickson formula (Friedewald *et al*, 1972).

Assay for Plasma Total Cholesterol (TC)

Plasma total cholesterol level was estimated by CHOD-POD enzymatic colourimetric method, according to the method described by Stein (1987). Briefly, 1ml of the reagent was added to each of the tubes and then incubated for 10 minutes at 20 - 25°C after mixing, and the absorbance of the sample (Asample) and standard (Astandard) was estimated against the reagent blank within 10 minutes at 546nm.

Assay for Plasma Triglyceride (TG)

The plasma triglyceride level was estimated by GPO-POD enzymatic colourimetric reaction, according to the method of Tietz (1990). 1ml of the reagent was added to each of the samples and the standard. This was incubated for 10 minutes at 20 - 25°C after mixing, and the absorbance of the sample (Asample) and standard (Astandard) was determined against the reagent blank within 10 minutes at 546nm.

Assay for Plasma High-Density Lipoprotein Cholesterol

The plasma HDL-C level was estimated by precipitation and CHOD-POD enzymatic colourimetric reaction, according to the method described by Wacnic and Alber (1978). Low -density lipoprotein (LDL-C and VLDL-C) and chycomicrons fraction, in the sample were completely separated via precipitation by adding phosphotungstic acid in magnesium chloride. The mixture stood for 10 minutes at room temperature and centrifuged for 10 minutes at 4000 rpm. The supernatant represent HDL-C fraction. The concentration of cholesterol in the fraction, which remained in the value supernatant, was determined.

Low-Density Lipoprotein Cholesterol (LDL-C)

Low-density lipoprotein was estimated according to the Friedewald equation (Friedewald *et al*, 1972).

Very Low-Density Lipoprotein Cholesterol

VLDL-C was estimated according to Friedewald equation (Friedewald *et al*, 1972).

Statistical Analysis

SPSS was used to analyse data. Group data were presented as mean ± SEM and analyzed statistically using One-way ANOVA, and Duncan multiple range test was utilized to test the means. Student's t-test was also used to compare means. The level of significance was set at a P value of less than 0.05 (PO.05).

3. RESULTS

Plasma Total Cholesterol (Tc)

Figure 1 shows the effect of administering 2% pure cholesterol powder on the lipid profile of white Wistar rats after 30 days. The pure cholesterol powder induced hypercholesterolemia - the inducement resulted in a significant increase in TC ($p<0.01$) when a paired t-test was performed. After 7 days, and 14 days administration of lycopene concentrations of 4 mg/kg b.w, 8 mg/kg b.w, and 12 mg/kg b.w, TC was reduced significantly ($p<0.01$). This reduction of TC was in a concentration, and time-dependent manner (Figures 2 - 4).

Plasma Triglycerides (TG)

Figure 1 shows the effect of administering of 2% pure cholesterol powder on the lipid profile of white Wistar rats after 30 days. The inducement resulted in a significant increase in TG ($P<0.01$) when paired t-test was performed. On administration of lycopene at concentrations of 4 mg/kg b.w, 8 mg/kg b.w, and 12 mg/kg b.w, reduced TG significantly after day 7 ($P<0.01$) and day 14 ($P<0.05$) when a paired t-test, and one-way ANOVA were performed. This reduction of TG was in concentration-time dependent manner (Figures 2-3, 5).

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Plasma High Density Lipoprotein Cholesterol (HDL-C)

Figure 1 show the effect of 2% pure cholesterol powder on the lipid profile of white Wistar rats after 30 days of administration. The pure cholesterol powder upon inducement resulted in a significant decrease in HDL-C (PO.01). On administration of 4 mg/kg b.w, 8 mg/kg b.w. and 12 mg/kg b.w of lycopene, HDL-C increased significantly with concentration at day 7 ($P<0.01$) and day 14 (PO.05) when paired t-test was performed, but increased non significantly at day 7 ($P>0.05$) and significantly ($P<0.05$) at day 14 when one-way ANOVA was performed, thus lycopene increased HDL-C in concentration and time-dependent manner (Figures 2-3, 6).

Plasma Low Density Lipoprotein Cholesterol (LDL-C)

Figure 1 shows the effect of 2% pure cholesterol powder on the lipid profile of white Wistar rats after 30 days of administration. There was a significant increase in LDL-C ($P<0.05$) when a paired t-test was performed. Administration of 4 mg/kg b.w, 8 mg/kg b.w, and 12 mg/kg b.w of lycopene, LDL-C reduced significantly ($P<0.001$) with concentration at day 7 and day 14 when paired t-test, and one-way ANOVA were performed. Lycopene thus reduced LDL-C in a concentration and time-dependent manner (Tables 5-6 and Figures 2 - 3). There was a slight increase in the level of LDL-C despite the reduction at day 14 (Figure 7).

Plasma Very Low-Density Lipoprotein Cholesterol (VLDL-C)

Figure 1 shows the effect of administration of 2% pure cholesterol powder on the lipid profile of white Wistar rats after 30 days. There was a significant increase in VLDL-C (P<0.01) when a paired t-test was performed. Administration of 4 mg/kg b.w, 8 mg/kg b.w and 12 mg/kg b.w of lycopene reduced VLDL-C significantly in a concentration and time-dependent manner at day 7 (P<0.01), and day 14 (P<0.05) when a paired t-test and one-way ANOVA were performed (Figures 2-3, 8).

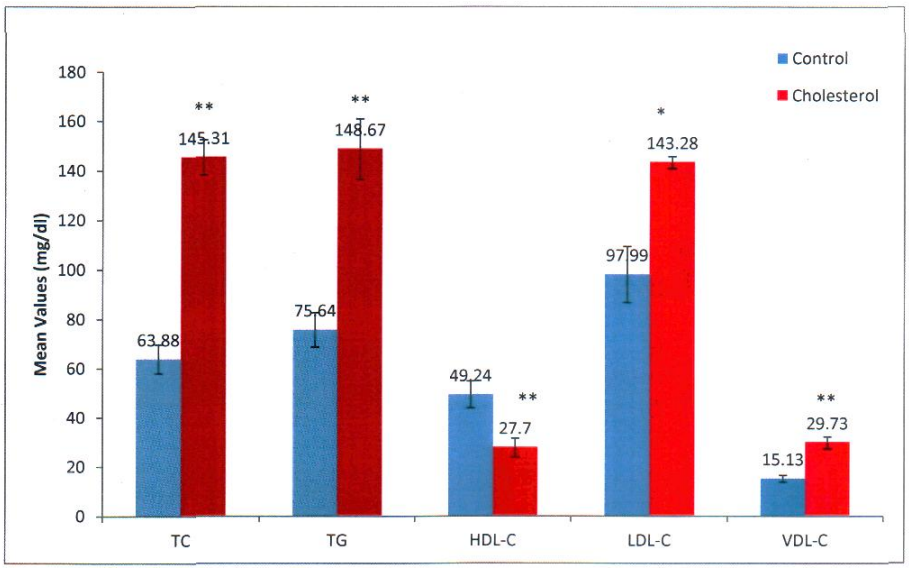

Figure 1: Bar chart shows effect of 2% pure cholesterol powder on lipid profile on Wistar rat. Figure showing significant increase in TC, TG, LDL-C and VLDL-C and a significant decrease in HDL-C after 30 days inducement with 2% cholesterol powder. Values are presented as Mean + SEM for n = 5.* P<0.01 – Highly Significant * P<0.05 – Significant.

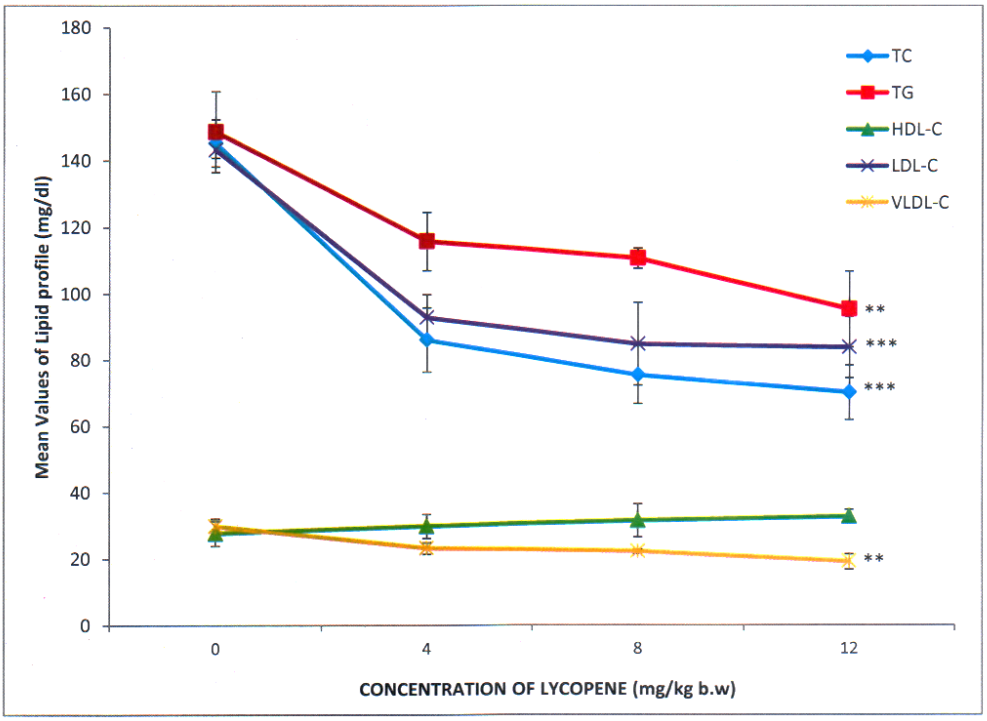

Figure 2: Concentration dependent effect of lycopene in cholesterol fed rats at day 7

Line graph showing significantly reduced TC, TG, LDL-C, and VLDL-C and increased HDL-C level, although not significant after 7 days supplementation with lycopene. Values are presented as Mean + SEM for n=5.***P<0.001, P<0.01 - Highly significant, NS – Not Significant

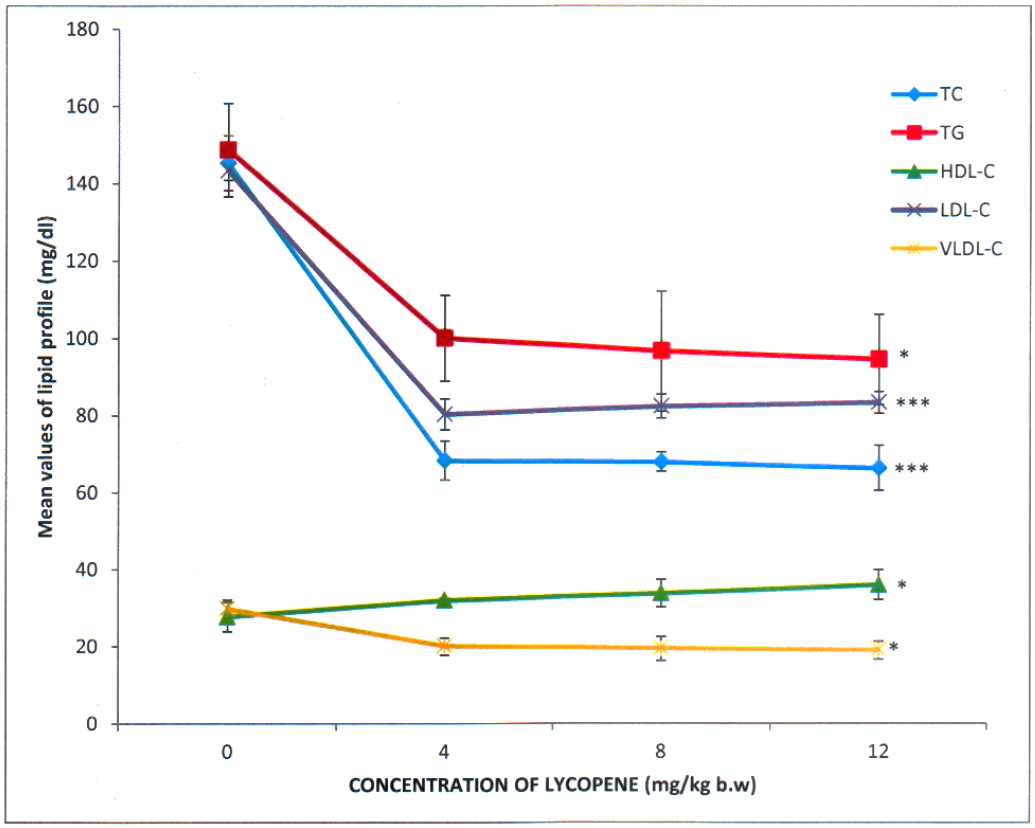

Figure 3: Concentration dependent effect of lycopene in cholesterol fed rats at day 14

Line graph showing significantly reduced TC, TG, VLDL-C and a significant increase in LDL-C. There was significant increase in HDL-C. Values are presented as Mean + SEM for n = 5. ***P<0.001- Highly significant; *P<0.05 – Significant

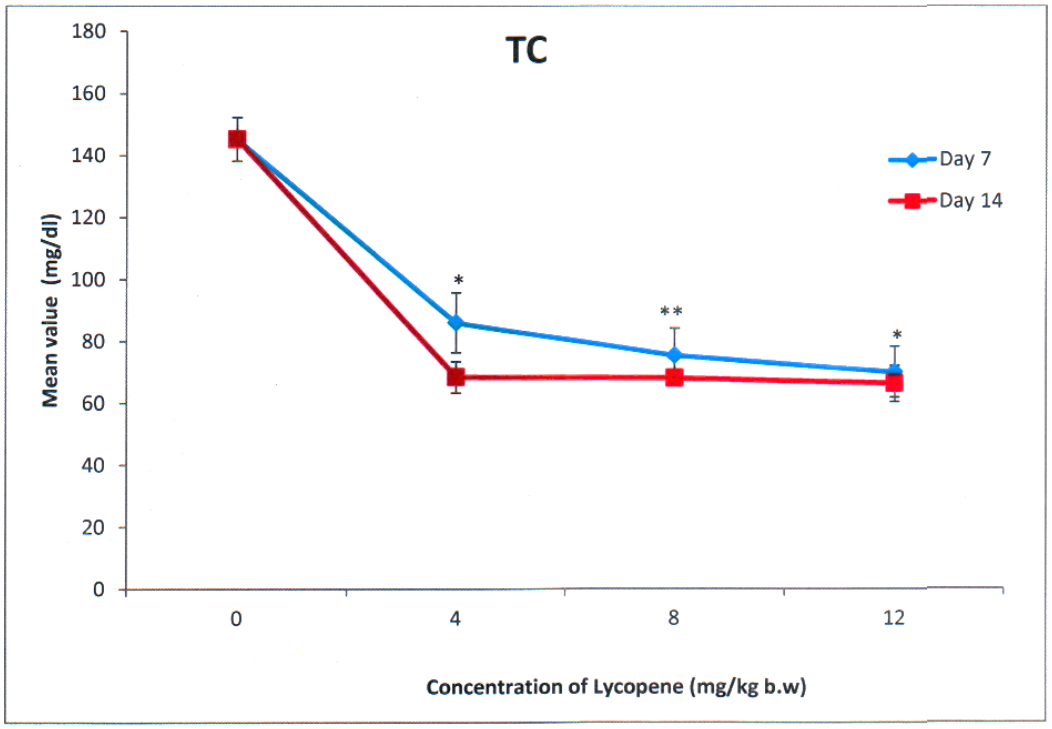

Figure 4: Time dependent and concentration effect of lycopene application on TC in cholesterol-fed rats at day 7 and day 14.

Line graph showing a significant reduction in TC at day 7, and day 14 in a concentration-dependent fashion. Values are presented as mean ± SEM for n = 5.**P<0.01- Highly significant *P<0.05 – Significant

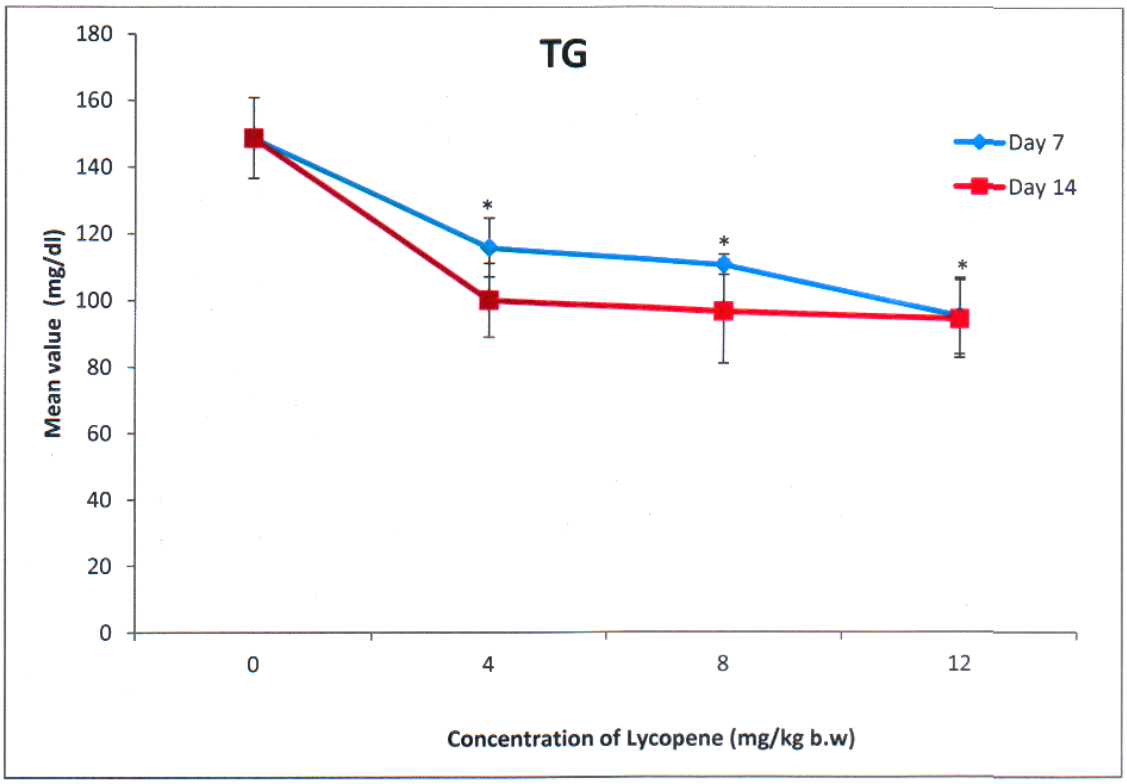

Figure 5: Time dependent and concentration effect of lycopene application on TG in cholesterol-fed rats at day 7 and day 14. Line graph showing a significant reduction in TG at day 7, and day 14 in a concentration-dependent fashion. Values are presented as mean ± SEM for n = 5.*P<0.05 – Significant

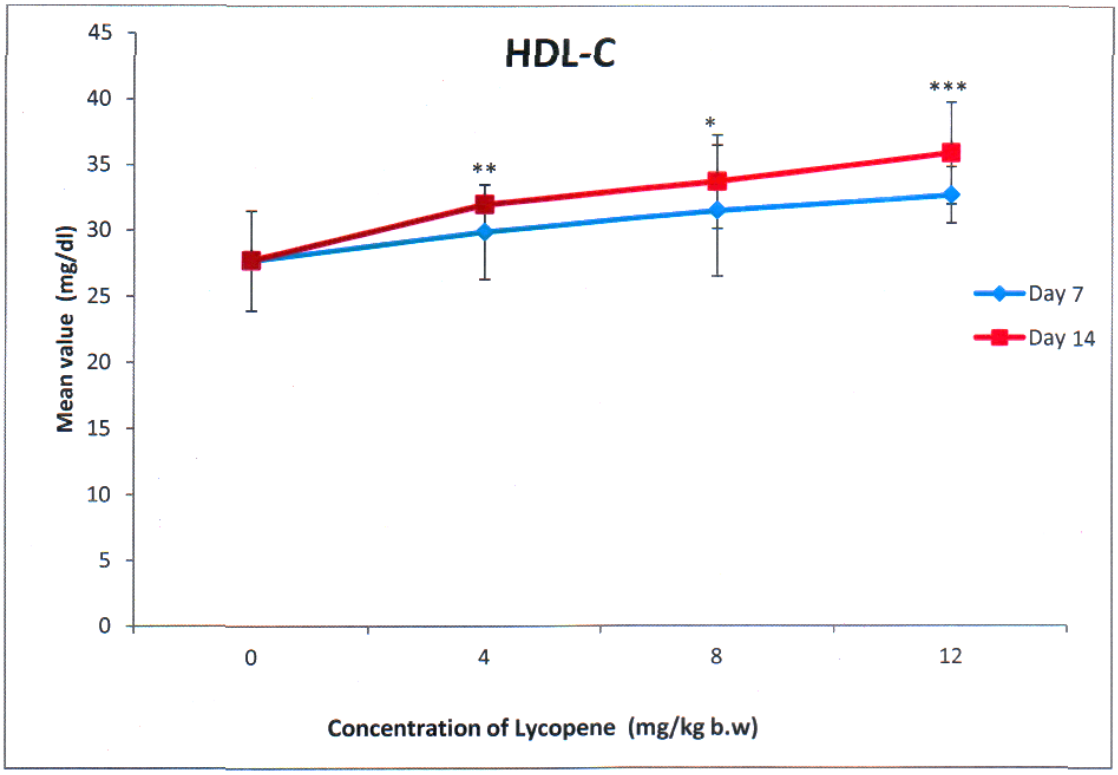

Figure 6: Time dependent and concentration effect of lycopene application on HDL-C in cholesterol fed rats at day 7 and day 14. Line graph showing a significant increase in HDL-C at day 7, and day 14 in a concentration-dependent fashion. Values are presented as mean ± SEM for n = 5. ***P<0.001,**P<0.01 -Highly significant *P<0.05 - Significant

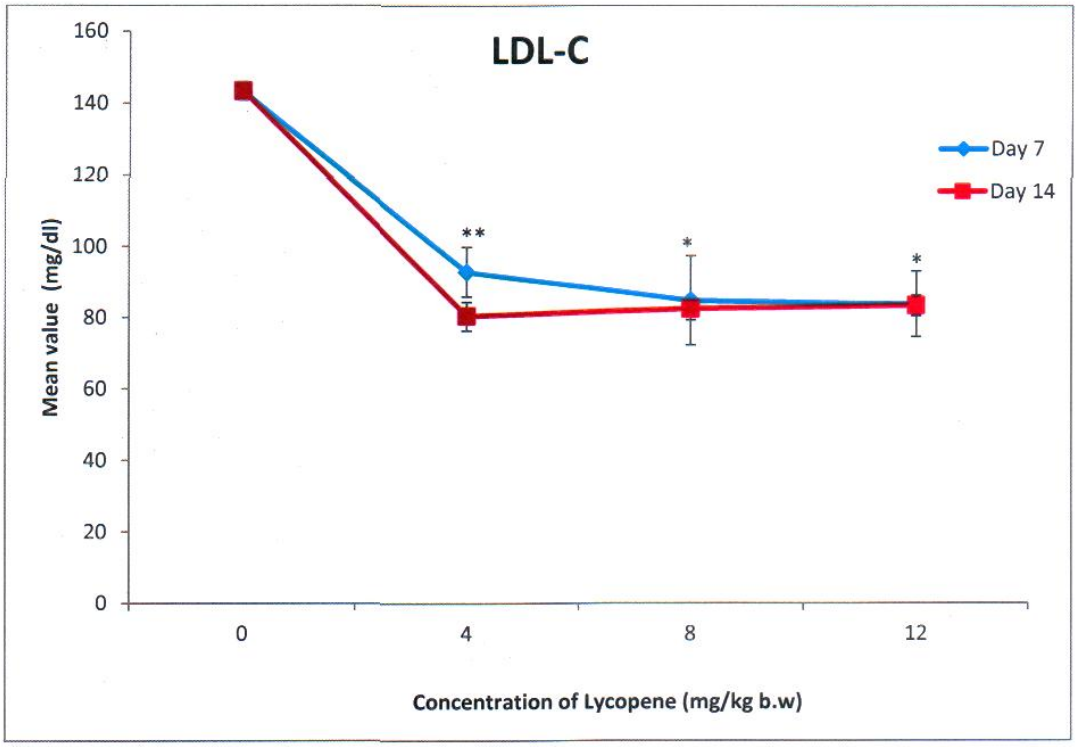

Figure 7: Time dependent and concentration effect of lycopene application on LDL-C in cholesterol fed rats at day 7 and day 14. Line graph showing a significant reduction in LDL-C at day 7, and day 14 in a concentration-dependent fashion. Values are presented as mean ± SEM for n = 5. **P<0.01- Highly significant; *P<0.05 – Significant

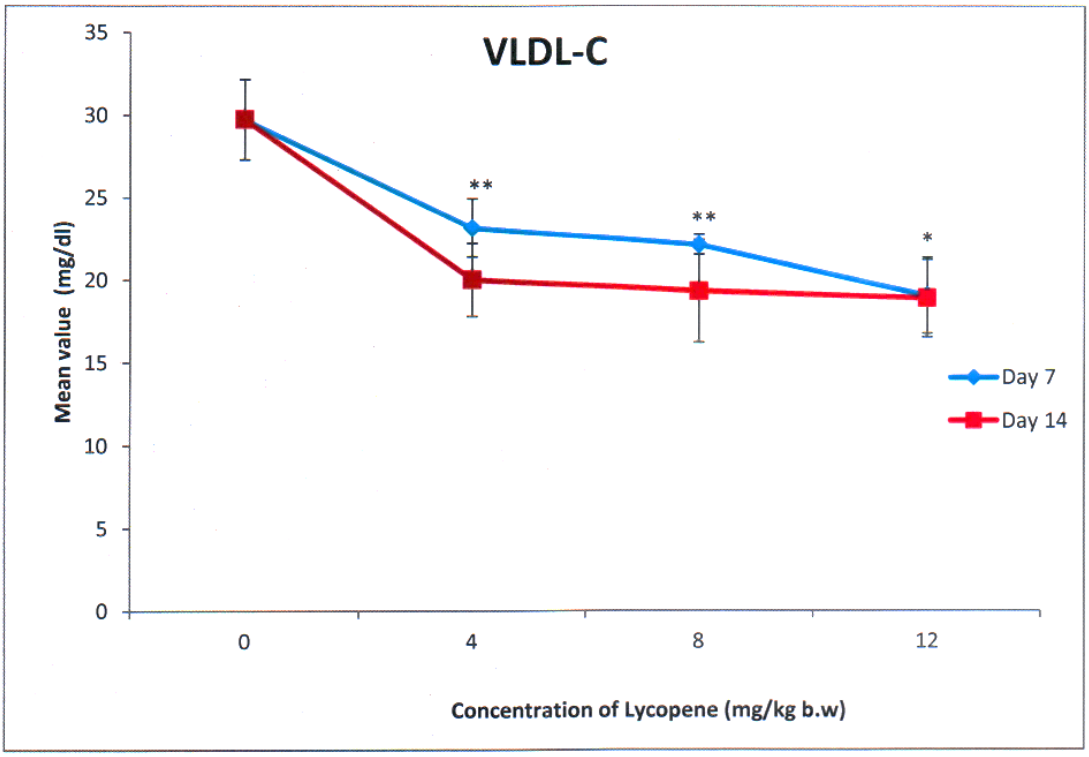

Figure 8: Time dependent and concentration effect of lycopene application on VLDL-C in cholesterol fed rats at day 7 and day 14. Line graph showing a significant reduction in VLDL-C at day 7, and day 14 in a concentration dependent fashion. Values are presented as mean ± SEM for n = 5. **P<0.01-Highly significant; *P<0.05 – Significant.

4. DISCUSSION

Hyperlipidemia is the elevation of lipids in the blood. It is characterized by high levels of plasma total cholesterol, triglycerides, low-density, high-density, and very low-density lipoprotein cholesterol. It plays a role in predisposing people to cardiovascular disease (CVD), which is a leading cause of death in the world. It has been established that an increase in low-density lipoprotein cholesterol (LDL-C) and serum cholesterol level, on the other hand are primary factor for predicting atherosclerosis and cardiovascular disease (Verschuren et al., 2011).

In this study, the increase in TC, TG, LDL-C, VLDL-C, and decrease in HDL-C following the administration of 2% pure cholesterol powder (Figure 3) might have been due to the increase in HMG-CoA reductase activity, expression or modulation of LDL-C receptor, ACAT activity, decrease in HDL-C receptor, increase in lecithin cholesterol acyl transferase (LCAT) and ABC protein that were reported to activate cholesterol biosynthesis in the liver (Roberts et al, 2004).

The concentration-dependent reduction in TC, TG, LDL-C, VLDL-C and increase in HDL-C following 7 days and 14 days supplementation of lycopene (figures 4-10) might have resulted from the action of lycopene that has been reported to inhibit cholesterol biosynthesis in the liver (Palozza et al., 2012). This is due to inhibition or reduction in the activity of hepatic 3-hydroxyl-3-methyl-glutharyl-CoA (HMG-CoA) reductase, which is the first committed enzymatic step of cholesterol biosynthesis (Palozza et al., 2012) and modulation of LDL-C receptor and ACAT activity (Fuhrman et al., 1997; Fujiwara et al., 2007; Hu *et al*, 2008; Verghese, 2008).

The increase in plasma HDL-C levels at all concentrations of lycopene administered in this study may be a result of a possible boost of HDL-C biosynthesis in the liver, as reported by Verghese (2008). In his study, the significantly lowered cholesterol may have contributed to the observed high plasma HDL-C in the animals. About 30% of cholesterol in the blood is in the form of HDL-C. It is hypothesized that HDL-C can remove cholesterol from antheroma within arteries and transport it back to the liver for excretion. This high level of HDL-C protects against cardiovascular disease (Wu et al., 2003).

The reduction in plasma LDL-C level at different concentrations may be due to the plasma cholesterol-lowering capability of lycopene, which possibly enhances reverse cholesterol transport and inhibition of production of apoB, needed for LDL-C production (Vasudevan et al., 2007).

The observed increase and decrease in plasma HDL-C and LDL-C levels, respectively, suggest a reduced risk of developing atherosclerosis following a repeated administration of lycopene.

The reduction in Triglycerides observed in this study could result from the action of lycopene on apoC-11, which is known to activate LpL (Vasudevan et al., 2007). The reduced plasma level of VLDL-C is consistent with the reported decrease in plasma triglyceride, meaning that a small amount of triglyceride was transported from the liver to extra-hepatic tissue.

5. CONCLUSION

In this study, an increase in plasma HDL-C with a concomitant decrease in other lipids (TC, TG, LDL-C, and VLDL-C) was observed. It can be concluded from the present data that lycopene produces significant improvement in all lipid parameters (TC, TG, LDL-C, VLDL-C, and HDL-C) in a concentration and time-dependent fashion. Therefore, lycopene can be utilized for the prevention of hyperlipidemia.

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Authors' Contributions

This research was carried out in collaboration of all the authors. Aigbuduokhai Charles Idonuan: Conceptualize and design the work, Uduak A. Inwang managed the literature searches, collected data, carried out data analysis and proof-read the work.

Ethical Approval

In this article, the animal regulations are followed as per the ethical committee guidelines of Department of Physiology, Faculty of Basic Medical Sciences, Alex Ekwueme Federal University, Ndufu Alike, Nigeria; the authors observed the Hypolipidemic Adjuvant effect of Lycopene from Cholesterol-Induced Wistar Rats. The Animal ethical guidelines are followed in the study for observation, identification & experimentation.

Informed Consent

Not applicable.

Conflicts of interests

The authors declare that they have no conflicts of interests, competing financial interests or personal relationships that could have influenced the work reported in this paper.

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Data and materials availability

All data associated with this study will be available based on the reasonable request to corresponding author.

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