

ORIGINAL RESEARCH ARTICLE

Effect of the ethanol extract of *Syzygium aromaticum* (clove) leaves on the lipid profile and body weight in testosterone-induced benign prostatic hyperplasia rats

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Abstract

The ethanol extract of *Syzygium aromaticum* (clove) has attracted attention for its potential effects on lipid metabolism and body weight. The current study investigated the effects of the ethanol extract of *Syzygium aromaticum* (clove) leaves on the lipid profile and body weight changes in testosterone-induced benign prostatic hyperplasia (BPH) rats. Thirty-six rats were divided into six groups ($n = 6$ /group): normal control, clove extract only (600 mg/kg body weight), testosterone-induced BPH control, finasteride-treated testosterone-induced BPH (3 mg/kg body weight), clove extract-treated testosterone-induced BPH (300 mg/kg body weight), and clove extract-treated testosterone-induced BPH (600 mg/kg body weight). The animals' body weight was recorded weekly. Treatment lasted for 28 days, after which blood samples were collected for biochemical analysis. Lipid profile analysis showed significant decreases in triacylglycerol, total cholesterol, low-density lipoprotein, and very low-density lipoprotein concentrations in the treatment groups compared with the testosterone-induced BPH control. A significant increase in high-density lipoprotein cholesterol concentration was observed in the treatment groups compared with the testosterone-induced BPH control. Additionally, body weight increased significantly in the treatment groups compared with the testosterone-induced BPH control. These findings suggest that the ethanol extract of clove leaves has anti-hyperlipidemic effects in BPH and may modulate body weight by promoting metabolic activity.

Keywords: *Syzygium aromaticum*; Lipid profile; Body weight; Testosterone; Benign prostatic hyperplasia; Finasteride

1. Introduction

Benign prostatic hyperplasia (BPH) is a prevalent, non-malignant enlargement of the prostate gland that primarily affects aging males and is a major cause of lower urinary tract symptoms. The condition is characterized by excessive proliferation of stromal and epithelial cells within the prostate, leading to urethral compression and bladder outlet obstruction.¹ Although BPH is traditionally associated with aging and androgenic stimulation, growing evidence indicates that metabolic disturbances—particularly dyslipidemia, obesity, and systemic inflammation—play critical roles in its onset and progression.²

Testosterone and its more potent metabolite, dihydrotestosterone, are central to the pathophysiology of BPH. In experimental settings, testosterone-induced BPH in rats is a well-established model that closely mimics human disease, reproducing prostate enlargement, hormonal imbalance, inflammatory changes, and metabolic alterations.³ Testosterone administration has also been shown to disrupt lipid metabolism, resulting in elevated serum cholesterol, triglycerides, and low-density lipoprotein (LDL) levels, as well as increased body weight and adiposity. These metabolic abnormalities may exacerbate prostatic growth by promoting oxidative stress, chronic inflammation, and insulin resistance.⁴

Alterations in lipid profile are increasingly recognized as both a risk factor and a consequence of BPH. Hypercholesterolemia and increased body weight contribute to prostatic inflammation and stromal proliferation by enhancing cytokine production and activating growth-promoting signaling pathways.⁵ Consequently, therapeutic interventions that improve lipid metabolism and regulate body weight may offer dual benefits in the management of BPH and its associated metabolic complications.

Patients with BPH are mostly treated with $\alpha 1$ -adrenergic receptor antagonists, which lower smooth muscle tone in the prostate and bladder neck, and 5 α -reductase inhibitors, which shrink the prostate.⁶ In the past, finasteride and tamsulosin were the most often recommended medications for treating BPH.⁷ According to McConnell *et al.*,⁸ only 64% of males receiving both drugs demonstrated a lower risk of clinical advancement, which is defined as worsening symptoms, acute urine retention, incontinence, and urinary tract infection. Unpleasant side effects of these drugs included asthenia, postural hypotension, erectile dysfunction, poor libido, and sporadic syncope.⁹ For the treatment of urinary outlet obstruction in BPH, it is highly desirable to develop an $\alpha 1$ -adrenergic antagonist or another medication that selectively suppresses the smooth muscle tone in the lower urinary tract without vascular

effects and reduces prostate volume without causing sexual dysfunction.¹⁰

Natural substances derived from plants have traditionally been the main source of innovative drugs used to treat a range of illnesses.¹¹ Recent research has focused on plant-based interventions for managing BPH and its associated symptoms. One such plant is *Syzygium aromaticum* (clove), which has long been used for its lipid-lowering, antioxidant, and anti-inflammatory properties.¹² Eugenol, one of clove's active ingredients, has shown promising pharmacological properties, making it a potential therapy for BPH.¹³ The medicinal potential of *Syzygium aromaticum* is attributed to its secondary metabolites, including polyphenols, flavonoids, alkaloids, and saponins. According to Nandeesh *et al.*,¹⁴ several of these substances have shown antioxidant activity, enabling them to scavenge free radicals generated by oxidation-reduction processes.

The growing incidence of BPH and related metabolic disorders, including obesity and dyslipidemia, has a substantial negative influence on older men's quality of life.¹⁵ This forms the basis for this study. Although medications and surgical procedures are common traditional therapies for BPH, they can sometimes be ineffective due to their frequent adverse effects, which deter patients from taking their prescribed medications. Furthermore, a comprehensive strategy that accounts for the systemic impact of these conditions and the metabolic abnormalities associated with BPH is required.¹⁶ *Syzygium aromaticum*, known for its anti-inflammatory, antioxidant, and lipid-lowering properties, presents a promising natural alternative for managing BPH and its metabolic consequences. The ethanol extract of clove leaf, rich in bioactive compounds such as eugenol, may offer therapeutic benefits by improving lipid profiles, regulating body weight, and potentially reducing the risk of BPH progression and improving overall metabolic health.¹⁷

The lipid profile is a vital indicator of metabolic health, and individuals with BPH often exhibit dysregulated lipid metabolism, resulting in dyslipidemia.¹⁸ Furthermore, maintaining a healthy weight is crucial, as obesity is a documented risk factor for the advancement of BPH.¹⁹ Therefore, the objective of this study is to evaluate the effects of the ethanol extract of clove leaf on the lipid profile and body weight in testosterone-induced BPH rats, given the extract's ability to modulate lipid metabolism and its anti-obesity properties. By doing so, this research aims to contribute to the growing body of evidence supporting the use of natural substances in the treatment of BPH and its associated metabolic problems.

2. Materials and methods

2.1. Plant materials

Fresh leaves of *Syzygium aromaticum* were collected from the Umudike community in the Ikwuano Local Government Area of Abia State, Nigeria. The fresh leaves were identified and authenticated by Dr. Ibe Ndukwe, a taxonomist in the Department of Forestry, at the College of Natural Resources and Environmental Management, Michael Okpara University of Agriculture, Umudike. The fresh leaves were washed, dried in the shade at room temperature, milled to a fine powder using an electric blender (QLink, Model QBL, Taiwan), and stored in airtight containers.

2.2. Extraction

The powdered leaves of *Syzygium aromaticum* (200 g) were soaked in two liters of ethanol for 48 h. The extract was then filtered using Whatman no. 1 filter paper, and the filtrate was dried in a hot-air oven at 40 °C. The dried extract was stored in the refrigerator for further use as the ethanol leaf extract of *Syzygium aromaticum*. For the experiment, the crude extract was diluted with distilled water: 20 g of the ethanol leaf extract of *Syzygium aromaticum* was dissolved in 200 mL of water to obtain a stock concentration of 0.1 g/mL (100 mg/mL) just before administration to the animals.

2.3. Chemicals and reagents

The chemicals and reagents used in this study were of analytical grade and were sourced from Sigma-Aldrich (United States of America [USA]) and AMEKO Inc. (China). Testosterone propionate had a catalog number of T1875, finasteride had a catalog number of F1293, ethanol had a catalog number of E7023, and olive oil (vehicle) had a catalog number of O1514. The total cholesterol assay kit had a catalog number of CH200, the triacylglycerol assay kit had a catalog number of TR210, the HDL-cholesterol assay kit had a catalog number of CH203, and the LDL-cholesterol assay kit had a catalog number of CH204.

2.4. Experimental animals

The experimental protocol was approved by the Ethical Review Committee of Michael Okpara University of Agriculture, Umudike, Abia State, Nigeria. Fifty-four male Wistar albino rats with a mean weight of 140 g were obtained from the Animal House, Department of Zoology and Environmental Sciences, Faculty of Biological Sciences, University of Nigeria, Nigeria. The rats were acclimatized to the environmental conditions for 14 days, with free access to a standard laboratory diet (vital feed) and drinking water ad libitum, and under a 12-h light/dark cycle.

2.5. Experimental design

Benign prostatic hyperplasia was induced in rats by subcutaneous injection of testosterone propionate in olive oil (5 mg/kg body weight) for 28 consecutive days. The rats were randomly assigned to six groups, each containing six rats. Group 1 served as the normal control, which was not testosterone-induced BPH; group 2 received clove extract only (600 mg/kg body weight); and group 3 served as the BPH control and was testosterone-induced BPH without treatment. Group 4 was the standard control, consisting of testosterone-induced BPH rats treated with 3 mg/kg body weight of finasteride, while groups 5 and 6 were testosterone-induced BPH rats treated with 300 and 600 mg/kg body weight of the ethanol extract of *Syzygium aromaticum* leaves, respectively. Treatments were administered to the rats 1 h after testosterone administration every day for 28 days consecutively. After the last administration of testosterone propionate and treatments on day 28, the rats were fasted overnight. Subsequently, the rats were anesthetized, and terminal blood collection was performed by cardiac puncture. Serum was immediately separated by centrifugation (3-16KL, Sigma Laborzentrifugen, Germany) at 3,000 × g for 15 min. The supernatant (serum) was collected and used for biochemical analyses. All rats used in this study were handled humanely in accordance with the National Institute of Health's guidelines for the care and use of animals for research.²⁰

2.6. Biochemical analyses

The lethal dose of the extract was determined by Lorke's method.²¹ Nine rats were divided into three groups of three rats each. The first group received the extract intraperitoneally (i.p.) at 10 mg/kg body weight; the second group received 100 mg/kg body weight (i.p.); and the third group received 1,000 mg/kg body weight (i.p.). The animals were observed for general signs and symptoms of toxicity, including mortality, over a period of 24 h. In the second phase, another 9 rats were divided into 3 groups of 3 each and administered the extract at doses of 1,600, 2,900, and 5,000 mg/kg body weight (i.p.). The animals were similarly observed for general signs and symptoms of toxicity, including mortality, over a 24-h period. Serum total cholesterol concentration was determined using the enzymatic colorimetric endpoint method as described by Zlatkis *et al.*²² The indicator, quinoneimine, is formed from hydrogen peroxide and 4-aminoantipyrine in the presence of phenol and peroxidase.

The underlying principle is as follows: free and esterified cholesterol in the sample are determined through coupled reactions. Cholesterol esters react with water in a reaction catalyzed by cholesterol esterase to produce free cholesterol

and fatty acid. The cholesterol produced reacts with oxygen to form cholestene-3-one and hydrogen peroxide in the presence of cholesterol oxidase. The hydrogen peroxide generated reacts with 4-aminoantipyrine and phenol, catalyzed by peroxidase, to form quinoneimine and four water molecules. The colored complex formed is measured spectrophotometrically at 500 nm (UV-1,800, Shimadzu Corporation, Japan).

Serum triacylglycerol (TAG) was determined by the method described by Foster and Dunn.²³ Quinoneimine, formed from hydrogen peroxide, 4-aminophenazone, and 4-chlorophenol under the catalytic influence of peroxidase, serves as the indicator.

The principle is as follows: Triglycerides in the sample are determined by coupled reactions that produce a colored complex, which is measured by spectrophotometry. Triglycerides react with water in a reaction catalyzed by lipase to produce glycerol and fatty acids. The glycerol formed is phosphorylated by adenosine triphosphate to produce glycerol-3-phosphate and adenosine diphosphate in a reaction catalyzed by glycerol kinase. Glycerol-3-phosphate reacts with oxygen to produce dihydroxyacetone phosphate and hydrogen peroxide. The hydrogen peroxide formed reacts with 4-aminophenazone and 4-chlorophenol in a peroxidase-catalyzed reaction to yield a colored complex.

Serum high-density lipoprotein (HDL) was determined according to the method described by Burstein *et al.*²⁴ The principle is as follows: LDL and very low-density lipoprotein (VLDL) and chylomicron fractions are quantitatively precipitated by the addition of phosphotungstic acid in the presence of magnesium ions. Following centrifugation, the cholesterol concentration in the HDL fraction remaining in the supernatant is determined. The precipitant was diluted at a 4:1 ratio (4 mL precipitant to 1 mL distilled water). Serum LDL and VLDL were determined using the method described by Friedewald *et al.*²⁵ LDL-cholesterol (LDL-C) was estimated from the values of total cholesterol, triglyceride, and HDL-cholesterol (HDL-C) using the following formula:²⁵

$$\text{LDL-C} = \text{Total cholesterol} - \text{Triglyceride}/5 - \text{HDL-C} \quad (1)$$

The animals' body weight was measured weekly using an electronic weighing scale (BC-533, Tanita, Japan).

2.7. Statistical analysis

The results obtained were analyzed statistically using one-way analysis of variance to determine the significant differences among group means. Duncan's multiple-range test and post hoc analysis were used to compare

means across the various treatment groups. Statistical analysis was performed at a 95% confidence level using Statistical Products and Service Solutions (SPSS Statistics version 22.0, IBM, USA). A p -value < 0.05 was considered statistically significant.

3. Results

3.1. Determination of the lethal dose (LD₅₀) of clove extract

The results in Tables 1 and 2 indicate that the ethanol extract of clove has a high safety margin with a median lethal dose (LD₅₀) value above 5,000 mg/kg.

3.2. Effects of the ethanol extract of *Syzygium aromaticum* (clove) leaves on total cholesterol levels of testosterone-induced benign prostatic hyperplasia rats

Figure 1 illustrates the total cholesterol concentration in testosterone-induced BPH rats treated with the ethanol extract of clove leaf. There was a statistically significant decrease in total cholesterol concentrations in the treatment groups (300 and 600 mg/kg body weight) compared with the untreated testosterone-induced BPH group ($p < 0.05$).

3.3. Effects of the ethanol extract of *Syzygium aromaticum* (clove) leaves on the triacylglycerol levels of testosterone-induced benign prostatic hyperplasia rats

As shown in Figure 2, there was a statistically significant decrease in TAG concentrations in the treatment groups (300 and 600 mg/kg body weight) compared with the untreated testosterone-induced BPH group ($p < 0.05$).

3.4. Effects of the ethanol extract of *Syzygium aromaticum* (clove) leaves on high-density lipoprotein cholesterol levels of testosterone-induced benign prostatic hyperplasia rats

As shown in Figure 3, there was a statistically significant increase in HDL-C concentrations in the treated testosterone-induced BPH groups (300 and 600 mg/kg body weight) compared with the untreated testosterone-induced BPH group ($p < 0.05$).

3.5. Effects of the ethanol extract of *Syzygium aromaticum* (clove) leaves on low-density lipoprotein cholesterol levels of testosterone-induced benign prostatic hyperplasia rats

As shown in Figure 4, there was a statistically significant decrease in LDL-C concentrations in the treated testosterone-induced BPH groups (300 and 600 mg/kg body weight) compared with the untreated testosterone-induced BPH group ($p < 0.05$).

Table 1. Phase one median lethal dose results

Group	Dose (mg/kg)	No of death	Observation
1	10	0/3	Animals were active and physically stable. Signs of toxicity, like agitation, roughness of hair, depression, writhing reflexes, and death, were absent.
2	100	0/3	Animals were active and physically stable. Signs of toxicity, like agitation, roughness of hair, depression, writhing reflexes, and death, were absent.
3	1,000	0/3	Animals were active and physically stable. Signs of toxicity, like agitation, roughness of hair, depression, writhing reflexes, and death, were absent.

Table 2. Phase two median lethal dose (LD₅₀) results

Group	Dose (mg/kg)	No of death	Observation
1	1,600	0/3	Animals were active and physically stable. Signs of toxicity, like agitation, roughness of hair, depression, writhing reflexes, and death, were absent.
2	2,900	0/3	Animals were calm and physically inactive for about 25 minutes, then resumed physical activity. Signs of toxicity, like agitation, roughness of hair, depression, writhing reflexes, and death, were absent.
3	5,000	0/3	Animals were calm and physically inactive for about 3 hours, then resumed physical activity. Signs of toxicity, like agitation, roughness of hair, depression, writhing reflexes, and death, were absent.

Note: LD₅₀ > 5,000 mg/kg body weight.

3.6. Effects of the ethanol extract of *Syzygium aromaticum* (clove) leaves on very low-density lipoprotein cholesterol levels of testosterone-induced benign prostatic hyperplasia rats

As shown in Figure 5, there was a significant decrease in VLDL-C concentrations in the treated testosterone-induced BPH groups (300 and 600 mg/kg body weight) compared with the untreated testosterone-induced BPH group ($p < 0.05$).

3.7. Effects of the ethanol extract of *Syzygium aromaticum* (clove) leaves on the body weight of testosterone-induced benign prostatic hyperplasia rats

Changes in body weight in testosterone-induced BPH rats treated with the ethanol extract of clove leaf are presented in Table 3. There was a significant ($p < 0.05$) increase in weight gain in the treated testosterone-induced BPH groups (300 and 600 mg/kg body weight) compared with

the untreated testosterone-induced BPH group.

4. Discussion

The study evaluated LD₅₀, body weight changes, and lipid profile alterations following treatment with the ethanol extract of *Syzygium aromaticum* leaves in testosterone-induced BPH rats. The findings suggest that *Syzygium aromaticum* is safe at high doses, supports healthy weight gain, and positively modulates lipid profiles in this model.

The LD₅₀ test indicated that the ethanol extract of clove caused no mortality at doses up to 5,000 mg/kg, demonstrating a high safety margin. This aligns with Chiong *et al.*,²⁶ who reported that plant extracts with LD₅₀ values above 5,000 mg/kg are generally considered safe for therapeutic use. The absence of toxicological signs, such as agitation, rough hair, depression, and writhing reflex, further confirms the low toxicity of the clove extract. These results demonstrate the extract's potential for further pharmacological investigations.

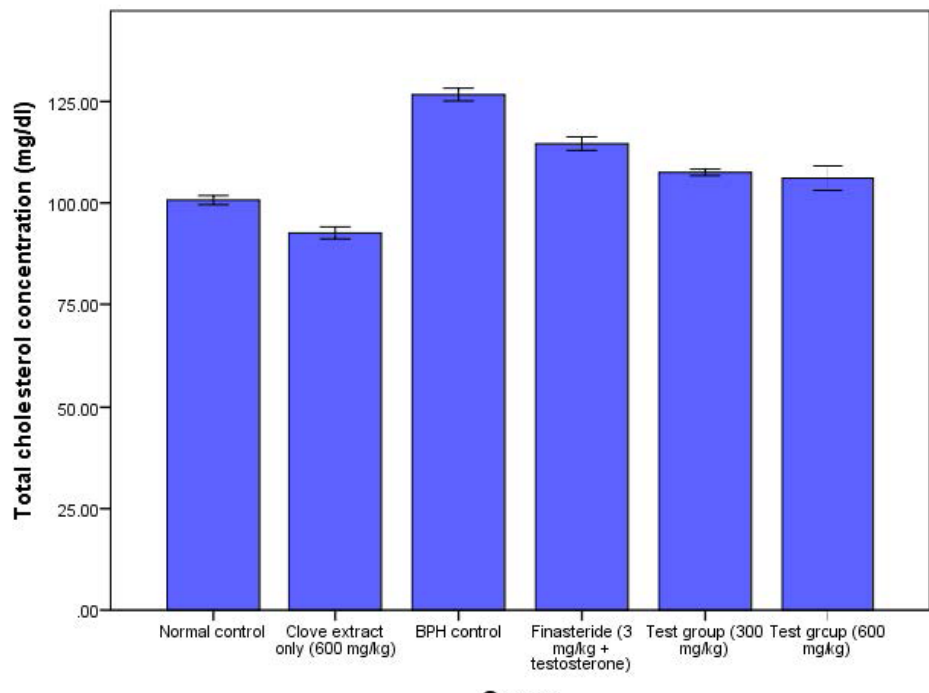


Figure 1. Total cholesterol concentration in testosterone-induced BPH rats treated with the ethanol extract of clove leaf. Values are presented as mean \pm standard deviation ($n = 6$).
Abbreviation: BPH: Benign prostatic hyperplasia.

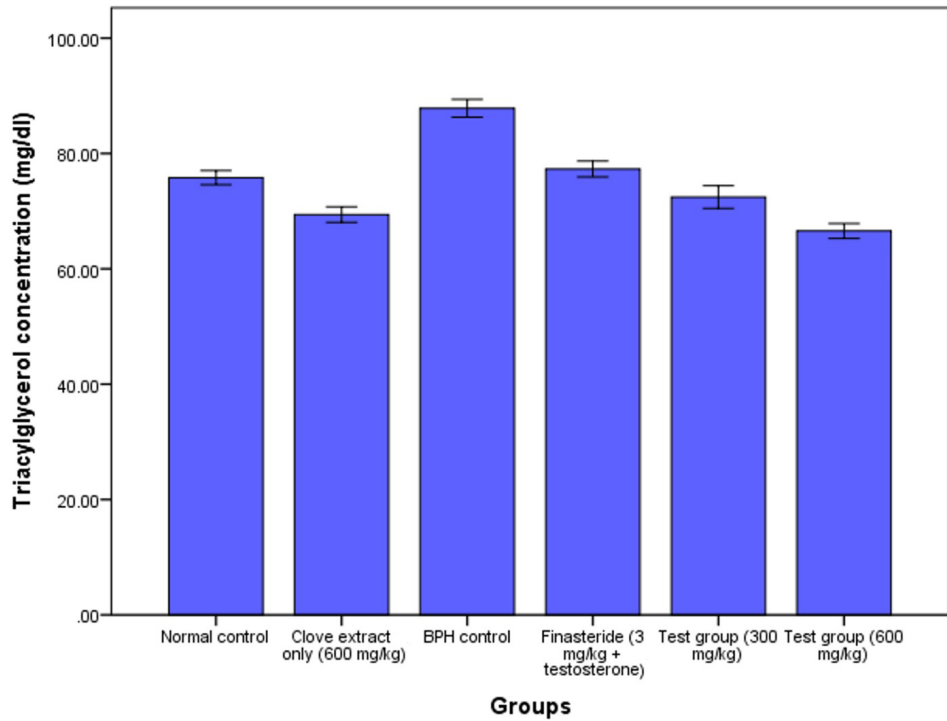


Figure 2. Triacylglycerol concentrations in testosterone-induced BPH rats treated with the ethanol extract of clove leaf. Values are presented as mean \pm standard deviation ($n = 6$).
Abbreviation: BPH: Benign prostatic hyperplasia.

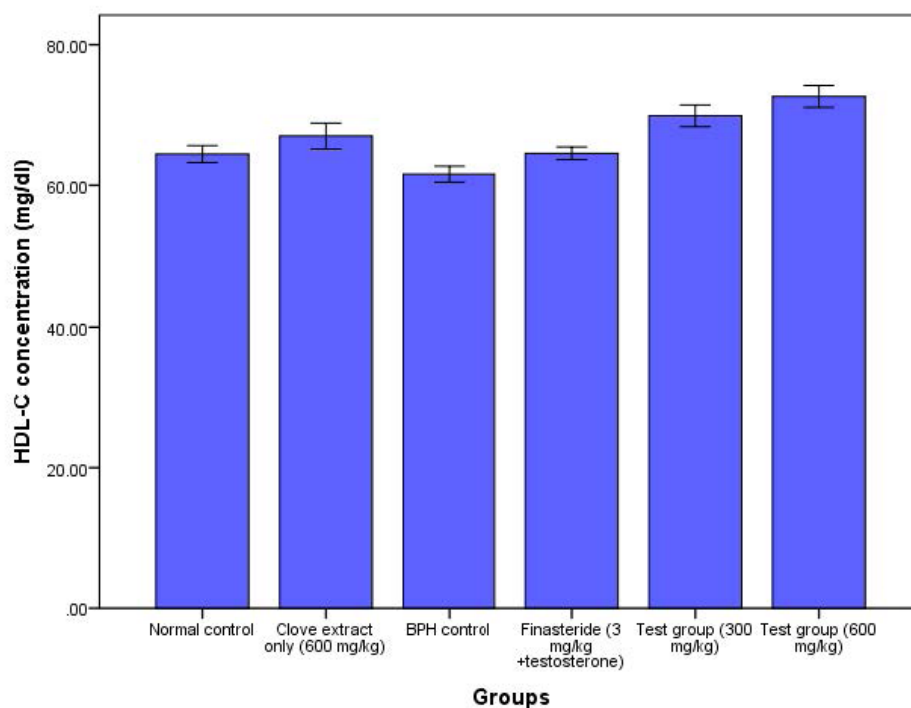


Figure 3. High-density lipoprotein cholesterol (HDL-C) concentration in testosterone-induced BPH rats treated with the ethanol extract of Clove leaf. Values are presented as mean \pm standard deviation ($n = 6$).

Abbreviation: BPH: Benign prostatic hyperplasia.

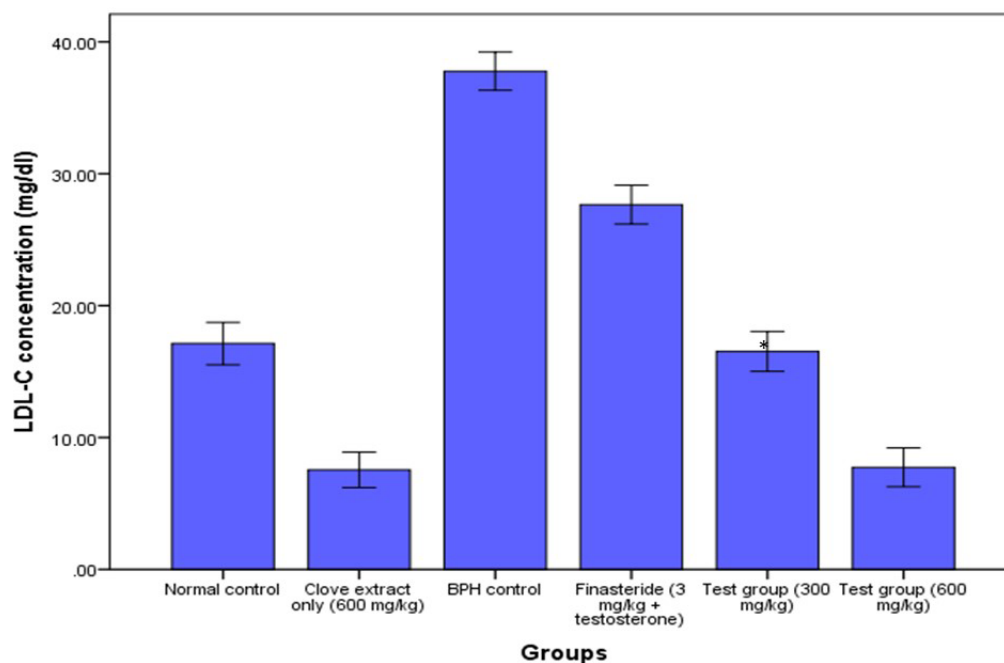


Figure 4. Low-density lipoprotein cholesterol (LDL-C) concentrations in testosterone-induced BPH rats treated with the ethanol extract of clove leaf. Values are presented as mean \pm standard deviation ($n = 6$).

Abbreviation: BPH: Benign prostatic hyperplasia.

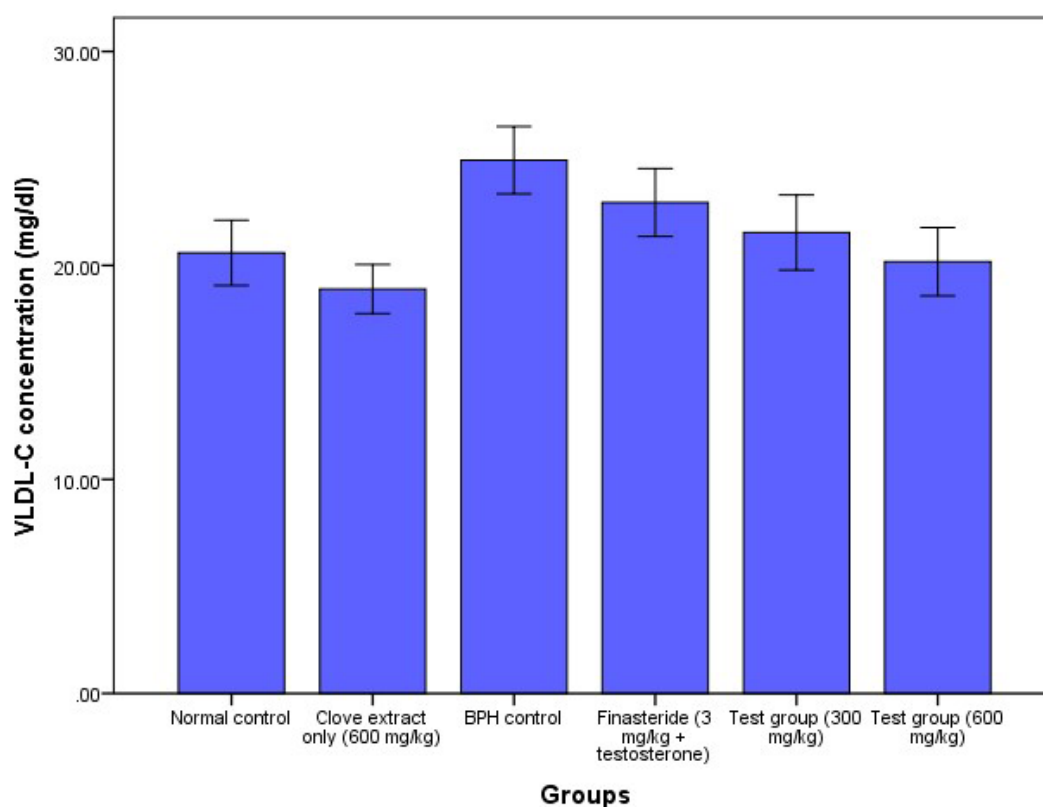


Figure 5. Very low-density lipoprotein cholesterol (VLDL-C) concentration in testosterone-induced BPH rats treated with the ethanol extract of clove leaf. Values are presented as mean \pm standard deviation ($n = 6$). Abbreviation: BPH: Benign prostatic hyperplasia.

Table 3. Body weight changes in testosterone-induced benign prostatic hyperplasia (BPH) rats treated with the ethanol extract of clove leaf

Treatment	Initial body weight (g)	Final body weight (g)	Weight gain (g)	Percentage weight gain (%)
Normal control	120.13 \pm 5.60 ^a	157.30 \pm 11.82 ^a	37.17 \pm 5.17 ^{a,b}	31.60 \pm 7.88 ^a
Clove extract only (600 mg/kg)	122.33 \pm 8.60 ^a	163.97 \pm 10.67 ^{a,b}	41.63 \pm 2.38 ^{a,b}	34.07 \pm 1.29 ^{a,b}
BPH control (Testosterone only)	126.27 \pm 5.08 ^a	157.73 \pm 4.20 ^a	31.47 \pm 1.80 ^a	24.97 \pm 2.18 ^a
Finasteride (3 mg/kg) + testosterone	127.60 \pm 5.90 ^a	161.83 \pm 3.85 ^{a,b}	34.23 \pm 3.36 ^a	26.93 \pm 3.65 ^a
Clove extract (300 mg/kg) + testosterone	129.63 \pm 9.95 ^a	175.90 \pm 4.10 ^{b,c}	46.27 \pm 8.08 ^{b,c}	36.12 \pm 8.65 ^{a,b}
Clove extract (600 mg/kg) + testosterone	125.47 \pm 4.75 ^a	181.57 \pm 13.20 ^c	56.10 \pm 10.64 ^c	44.68 \pm 8.12 ^b

Note: Values are presented as mean \pm standard deviation ($n = 6$), and values with different superscript letters^{a,b,c} within the same column are significantly different ($p < 0.05$).

The bar graphs (Figures 1–5) demonstrated significant effects of clove extract on lipid profile parameters, including total cholesterol, TAG, HDL-C, LDL-C, and VLDL-C, in testosterone-induced BPH rats. Clove extract significantly reduced total cholesterol levels in testosterone-induced BPH rats, similar to the effects of finasteride. This hypolipidemic effect is consistent with previous studies showing that clove contains bioactive compounds, such as eugenol and flavonoids, that reduce cholesterol levels.²⁷ The cholesterol-lowering effect may be attributed to clove's antioxidant activity, which prevents lipid peroxidation and thereby reduces overall cholesterol levels.²⁸

Triacylglycerols, the main components of body fat in humans, were also significantly reduced in clove-treated groups compared to the testosterone-induced BPH control. The reduction was dose-dependent, indicating greater efficacy at higher concentrations. Csikós *et al.*²⁹ suggested that clove extracts modulate lipid metabolism by inhibiting lipogenic enzymes, thereby decreasing circulating TAG levels.

High-density lipoprotein cholesterol, the “protective” cholesterol responsible for reverse cholesterol transport from peripheral tissues to the liver and other tissues,³⁰ increased significantly in clove extract-treated testosterone-induced BPH groups. This finding is consistent with Parsons *et al.*,³¹ who reported that phenolic compounds in clove enhance HDL-C levels by promoting reverse cholesterol transport. The increase in HDL-C further supports clove's protective role against cardiovascular complications.

Low-density lipoprotein cholesterol, a key marker for cardiovascular risk,³² was markedly reduced in the treated groups, particularly at the higher clove dose. This reduction is clinically relevant because elevated LDL-C is a risk factor for atherosclerosis. Akbari *et al.*³³ reported similar LDL-C-lowering effects, attributing them to clove extracts' antioxidant properties.

Very low-density lipoprotein cholesterol decreased in the clove extract-treated testosterone-induced BPH groups, and is in parallel with TAG, as VLDL-C is directly derived from TAG. The significant reduction in VLDL-C levels may result from clove extract's regulatory effects on hepatic lipid metabolism. Mandal *et al.*³⁴ demonstrated that bioactive compounds in clove extract effectively reduce VLDL-C levels by suppressing hepatic lipogenesis and promoting the clearance of circulating lipoproteins.

Body weight analysis revealed a significant increase in weight gain among clove extract-treated groups compared to the testosterone-induced BPH control. The highest

percentage weight gain was observed in rats receiving 600 mg/kg clove extract. This indicates that clove has restorative effects against testosterone-induced BPH, which is often associated with reduced physical activity and metabolic changes. These results are in agreement with Wu *et al.*,³⁵ who reported that plant extracts with anti-inflammatory and antioxidant properties promote general health and weight gain in experimental models. The observed weight gain may also reflect improved nutrient absorption and metabolic activity induced by the extract.

5. Conclusion

The findings of this study indicate that the ethanol extract of *Syzygium aromaticum* exerts a significant therapeutic effect on body weight and lipid profile in a rat model of BPH. Its safety at high doses, along with the observed increases in HDL-C levels, and reductions in total cholesterol, TAG, LDL-C, and VLDL-C, reinforce clove's potential as a beneficial natural treatment for metabolic dysregulation associated with BPH. These findings are consistent with prior studies on clove's hypolipidemic and antioxidant properties and provide a foundation for future research into its mechanisms and broader therapeutic applications.

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Conflict of interest

The authors declare that they have no conflict of interest.

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Ethics approval and consent to participate

The authors hereby declare that the “Principles of Laboratory Animal Care” (NIH publication no. 85–23, revised 1985) were strictly followed in this study, along with applicable national regulations. All experimental procedures were reviewed and approved by the appropriate institutional ethical committee. No animal ethics approval number was given.

Consent for publication

Not applicable.

Availability of data

Data are available from the corresponding author on reasonable request.

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