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Original Research Article

Antihyperlipidemic and cardioprotective effects of n-hexane extract of *Terminalia catappa* nuts in hyperlipidaemic and hyperglycemic Wister rats

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ABSTRACT

Background: Dyslipidaemia and diabetes mellitus are significant risk factors for cardiometabolic disease. This study evaluates the lipid-lowering and cardioprotective effects of the n-hexane extract of *Terminalia catappa* nuts (TCN) in hyperlipidaemic and hyperglycaemic Wistar rats.
Methods: Wistar rats were divided into two groups: negative control and induced groups. The induced group was further subdivided into positive control, standard drug-treated, and TCN-treated groups with 200, 400, and 800 mg/kg/day for six weeks. Serum lipid profiles were assessed using standard biochemical methods after 42 days of treatment with TCN. Data were analysed using one-way ANOVA followed by Tukey's post-hoc test for multiple comparisons, with significance set at $p<0.05$.
Results: The untreated positive control group exhibited significant elevations in total cholesterol (TC), triglycerides (TG), and low-density lipoprotein (LDL) levels, alongside reductions in high-density lipoprotein (HDL) levels ($p<0.05$). Treatment with TCN at 400 mg/kg and 800 mg/kg significantly improved lipid profiles, with reductions in TC, TG, and LDL ($p<0.001$) and an increase in HDL ($p<0.001$) compared to the positive control group. At 800 mg/kg, the most substantial improvements were observed. Similarly, TCN treatment significantly reduced atherogenic indices, including the atherogenic index of plasma (AIP), atherogenic coefficient (AC), and Castelli risk indices I (CRI-I) and II (CRI-II). Improvements were dose-dependent, with the greatest reductions at 400 mg/kg and 800 mg/kg doses ($p<0.001$).
Conclusions: *Terminalia catappa* nuts demonstrates significant lipid-lowering and cardioprotective effects in hyperlipidaemic and hyperglycaemic conditions, supporting its potential as a natural therapeutic for managing cardiovascular risks and metabolic syndrome.

Keywords: Cardiometabolic disease, Cardioprotective, Dyslipidaemia, Hyperlipidaemia, Lipid profile, n-Hexane extract, *Terminalia catappa* nut, Wistar albino rats

INTRODUCTION

Metabolic syndrome is defined by the presence of hyperglycaemia or hyperinsulinemia, along with at least two additional criteria.[1] These criteria include: (1) waist circumference of at least 94 cm; (2) dyslipidaemia or hyperlipidaemia characterised by triglycerides of at least 1.7 mmol/l or HDL cholesterol levels below 1.03 mmol/l, and blood pressure of at least 140/90 mmHg or the use of blood pressure medication. Hyperglycaemia is identified by a fasting glucose level of at least ≥5.6 mmol/l, while hyperinsulinemia is defined as being in the upper fourth of fasting insulin levels among nondiabetic individuals.[2]

Hyperlipidaemia or dyslipidamia, is a medical condition characterised by abnormally elevated levels of lipids (fats) in the blood.[3] Dyslipidaemia of metabolic disorders of global concern due to the strong associations with chronic diseases, including cardiovascular disease, type 2 diabetes mellitus, and end-organ damage.[4,5] Hyperlipidaemia is a major modifiable risk factor for atherosclerosis and its clinical sequelae, including myocardial infarction and stroke, contributing significantly to increase morbidity and mortality, emphasising the urgent need for effective interventions.[6] Several risk factors has been link to dyslipidaemia, such as obesity, sedentary lifestyles, and unhealthy dietary patterns.[7] Together with diabetes, these metabolic disorders contribute significantly to the increasing global morbidity and mortality associated with non-communicable diseases.[8]

In Nigeria and other Sub-Saharan African countries, the prevalence of dyslipidaemia and diabetes is on the rise, propelled by urbanisation, economic transitions, and dietary shifts toward energy-dense and nutrient-poor foods.[9,10] The overall prevalence of low high-density lipoprotein cholesterol (l-HDL), elevated low-density lipoprotein cholesterol (e-LDL), hypertriglyceridemia (h-TG), and hypercholesterolaemia (h-CHL) were 72.5, 13.6, 21.4 and 7.5%, respectively.[11,12] This dual burden has heightened the urgency for effective therapeutic interventions without side effects that address both conditions simultaneously while being accessible and culturally acceptable to affected populations.

Natural products, particularly those derived from plants, have garnered considerable attention as alternative or complementary therapies for managing chronic diseases due to their bioactive compounds.[13,14] *Terminalia catappa*, commonly known as the Indian almond or tropical almond, is a tropical tree widely distributed across Asia, Africa, and the Americas, traditionally used in folk medicine for its anti-inflammatory, antioxidant, and cardioprotective properties.[15,16] Phytochemical analyses of *Terminalia catappa* have revealed the presence of flavonoids, tannins, and phenolic acids, which have been associated with lipid-lowering, glucose-modulating, and organ-protective effects.[17,18] While prior studies have demonstrated the efficacy of *Terminalia catappa* leaves in reducing cholesterol levels and improving antioxidant status in animal models. None of these studies explore the potential therapeutic benefits of *Terminalia catappa* nuts, particularly their antihyperlipidemic effects in animal model induced with hyperlipidemia.

Therefore, this study investigated the antihyperlipidemic of n-hexane extract of *Terminalia catappa* nuts in Wistar rats induced with hyperlipidaemia and hyperglycemia. By assessing lipid profiles and atherogenic indices, this study aims to provide insight into the adjuvant therapeutic potential of *Terminalia catappa* nuts for managing dyslipidemia, particularly in cardiovascular disease and metabolic syndrome.

METHODS

Study design

This study utilized an experimental, randomized, controlled design to evaluate the dose dependent effects of n-hexane extract of *Terminalia catappa* nuts (TCN) on lipid and glycemic profiles in Wistar rats induced with metabolic risk factors, including hyperlipidemia and hyperglycemia. Hyperlipidemia and hyperglycemia were induced by gastric gavage of daily meals of a high-fat and sugar diet (HFSD) for six weeks. The study was conducted from August 2023 to November 2023 at the animal house of the department of human physiology, University of Port Harcourt, Nigeria.

Ethical considerations

The animal experiments were conducted in accordance with the Institute of Laboratory Animal Resources guidelines, a guide for the care and use of laboratory animals.[19] The study protocol was reviewed and approved by the Research Ethics Committee of the University of Port Harcourt, Nigeria on 10 August 2023 with approval number UPH/CERMAD/REC/MM90/216.

Collection, identification, and preparation of plants

A similar method of Batubo, 2023 was used for the collection, identification, and preparation of *Terminalia catappa* nuts.[15] Briefly, the fresh fruits of *Terminalia catappa* were collected between August and November 2022 from the University of Port Harcourt and Rivers State University, Port Harcourt, Nigeria. The fruits were cleaned under running water immediately after collection, drained, and pat-dried. The edible nut was removed from the fibrous husk and the hard shell and air-dried under shade to retain bioactive compounds. Dried nuts were finely ground into a homogeneous powder and subjected to Soxhlet extraction using 85% aqueous n-hexane using a solid-to-liquid ratio of 1:30 (w/v). The extraction procedure was repeated four times to ensure that the extraction was adequately exhaustive. The collected extracts of *Terminalia catappa* nuts were pooled, filtered, and concentrated under a vacuum, using a rotary evaporator (Heidolph GmbH and Co. K.G., Germany) to

yield a semi-solid mass. The resultant extract was stored in a dark container at 4°C and reconstituted in a minimal amount of corn oil before administration.

Experimental animals

A total of sixty male Wistar rats weighing 180-200 grams were used in this study. The rats were obtained from the Rivers State University Animal House, Port Harcourt, Nigeria, and acclimatized to laboratory conditions for two weeks before the commencement of the experiment. During this period, the rats were housed in six groups in well-ventilated and compartmentalized cages, kept at a temperature of 25±2°C, and maintained under a 12-hour light and dark cycle.

Experimental design

The rats had unrestricted access to standard feed and clean drinking water ad libitum. The animals were randomly divided into five groups (n=10 per group) as follows:

Normal control: this group was fed with a standard diet without treatment with n-hexane extract of *Terminalia catappa* nuts (TCN).

Positive control: this group was induced with hyperlipidemia and hyperglycemia but received no treatment with TCN.

Standard drug control: this group was induced with hyperlipidemia and hyperglycemia and treated with atorvastatin and metformin (10 mg/kg/day) but without treatment with TCN.

200 mg/kg/day TCN group: this group was induced with hyperlipidemia and hyperglycemia and treated with 200 mg/kg/day of TCN.

400 mg/kg/day TCN group: this group was induced with hyperlipidemia and hyperglycemia and treated with 400 mg/kg/day of TCN.

800 mg/kg/day TCN group: this group was induced with hyperlipidemia and hyperglycemia and treated with a high dose (800 mg/kg/day) of TCN.

Study protocol

Preparation of high-fat and sugar diet

A high-fat and sugar diet (HFSD) was prepared to induce hyperlipidemia and hyperglycemia in the Wistar rats according to the methods highlighted by Munshi et al. Briefly, the HFSD included two components: a high-fat mixture and a high-sugar solution. First, the high-fat component was formulated by combining butter (president butter) and coconut oil in a 3:1 ratio (v/v). The final mixture provided approximately 617 kcal per 100 ml from fats, 7.72 kcal per 100 ml from carbohydrates, and 5.401 kcal per 100 ml from proteins. Secondly, the high-sugar component was prepared by dissolving fructose at a concentration of 25% (w/v) in distilled water in a 1:3 ratio (v/v), yielding a solution designed to induce hyperglycemia. The rats were provided ad libitum access to this fructose solution alongside the high-fat mixture throughout the induction phase.

Induction of hyperlipidemia and hyperglycemia

Hyperlipidemia and hyperglycemia were induced in Groups 2-6 by administering a high-fat and high-sugar diet (HFSD) over six weeks. Initially, baseline blood samples were collected from the tail vein of each Wistar rat to assess fasting lipid profile, including total cholesterol, fasting blood glucose, triglycerides, LDL-cholesterol, HDL-cholesterol, and blood glucose levels. These baseline measurements provided a control reference for evaluating diet-induced metabolic changes. After baseline collection, the HFSD regimen was initiated. Each rat received 3 ml of a high-fat diet daily through gastric gavage to ensure consistent intake. In addition, the rats were given ad libitum access to a high-sugar solution (25% fructose in distilled water) in bottles every 24 hours for six weeks. This solution was prepared daily to maintain palatability and consistency in sugar intake. Blood samples were subsequently collected at three key time points- baseline, three weeks, and six weeks- to monitor the progression of lipid profile changes and blood glucose levels during the induction period (findings as published).[15]

Treatment administration

Following the six-week induction of hyperlipidemia and hyperglycemia, rats in groups 3, 4, 5, and 6 received daily oral treatments for an additional six weeks as indicated by their respective groups. The standard drug control group received atorvastatin at a dose of 10 mg/kg body weight. All treatments were delivered orally through gavage to ensure precise dosing. All rats received distilled water and standard rat pellets ad libitum throughout the experimental period.

Sampling collection

At the end of the six-week treatment with TCN extract, the Wistar rats were fasted overnight and six (6) Wistar rats per group were anesthetized with chloroform. Blood samples were collected from the rats through the cardiac puncture into EDTA (ethylenediaminetetraacetic acid) for the determination of serum lipid levels.

Biochemical assay

Serum lipid levels, including total cholesterol (TC), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C), were measured using an automated biochemical analyser [random access multibatch chemistry analyzer (USA)] with commercially available assay kits with results expressed in mmol/l. The low-

density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula, provided TG levels are below 4.5 mmol/l: LDL=TC−(HDL+TG/2.2) (values in mmol/l).[20] The atherogenic index of plasma was calculated as log(TG/HDL-C) as described by Dobiasova.[21] The atherogenic Coefficient was calculated as (TC – HDL-C)/HDL-C.[22] The Castelli risk index I (CRI-I) was calculated as TC/HDL-C.[23]

Statistical analysis

Data analysis was conducted using one-way analysis of variance (ANOVA) to assess significant differences among the groups, followed by Tukey's post hoc test for pairwise comparisons. The results were expressed as mean±standard error of the mean (SEM). A p value <0.05 was considered statistically significant. Data analysis was performed using the R computing environment, version 4.4.2.[24]

RESULTS

Effect on lipid profile

The n-hexane extract of *Terminalia catappa* nuts (TCN) demonstrated significant improvements in fasting lipid profiles in hyperlipidemic and hyperglycemic Wistar rats (Table 1). The total cholesterol (TC), triglycerides (TG), and low-density lipoprotein (LDL) levels were significantly elevated in the untreated positive control group compared to the negative control group ($p<0.05$). Treatment with TCN at doses of 400 mg/kg and 800 mg/kg demonstrated a significant reduction in TC, TG, and LDL ($p<0.001$). Conversely, high-density lipoprotein (HDL) levels, which were reduced in the positive control group, exhibited a significant increase with TCN treatment, particularly at 800 mg/kg ($p<0.001$) (Table 1).

Table 1: Effect of n-hexane extract of *Terminalia catappa* nuts treatment on fasting lipid profile of hyperlipidemic and hyperglycemic Wistar rats (n=6).

Parameters	Negative control	Positive control	Standard control	200 mg/kg TCN	400 mg/kg TCN	800 mg/kg TCN
TC (mmol/l)	3.22±0.07	5.42±0.07*	4.70±0.01*#	4.76±0.10*#	4.18±0.07*#a	3.76±0.10*#a
TG (mmol/l)	0.98±0.05	2.08±0.05*	1.62±0.07*#	1.82±0.07*	1.64±0.10*#	1.50±0.12*#
LDL (mmol/l)	1.58±0.05	3.68±0.07*	2.92±0.05*#	2.74±0.03*#	2.12±0.05*#a	2.00±0.12*#a
HDL (mmol/l)	1.24±0.03	1.04±0.03*	0.98±0.05*	0.98±0.05*	1.14±0.03	1.36±0.03#

All values are expressed as mean±standard error of the mean. *, #, a indicates significance when compared with the negative control, positive control and standard drug control at p<0.001. TC: Total cholesterol; TG: Total triglyceride; LDL: Low-density lipoprotein-cholesterol; HDL: High-density lipoprotein-cholesterol; TCN: *Terminalia catappa* nuts

Table 2. Effects of n-hexane extract of *Terminalia catappa* nut (TCN) treatment on atherogenic lipid indices of hyperlipidemic and hyperglycemic Wistar rats (n=6).

Parameters	Negative control	Positive control	Standard control	200 mg/kg TCN	400 mg/kg TCN	800 mg/kg TCN
AIP	0.12±0.01	0.71±0.04*	0.43±0.03#	0.41±0.04#	0.21±0.03#a	0.22±0.02#a
AC	1.60±0.01	3.82±0.30*	3.84±0.23*	3.31±0.01*#a	6.76±0.01*#a	6.74±0.01*#a
CRI-I	2.60±0.01	5.22±0.05*	4.84±0.23*	4.77±0.21*	3.68±0.14*#a	2.77±0.13#a
CRI-II	1.80±0.34	3.55±0.15*	3.02±0.19*	2.82±0.11*	1.87±0.08#a	1.48±0.12#a

All values are expressed as mean ± standard error of the mean. *, #, a indicates significance when compared with the negative control, positive control and standard drug control at p< 0.001. AIP: Atherogenic index of plasma; AC: Atherogenic coefficient; CRI-I: Castelli Risk Index-I; CRI-II: Castelli Risk Index-II. *Terminalia catappa* nut (TCN)

These findings highlight the dose-dependent efficacy of TCN in ameliorating lipid profiles, suggesting its potential therapeutic application in the management of hyperlipidemia.

Effects on atherogenic indices

The effect of n-hexane extract of *Terminalia catappa* nut (TCN) on atherogenic lipid indices in hyperlipidemic and hyperglycemic Wistar rats demonstrated significant improvements across several markers, particularly at higher doses (Table 2). The atherogenic index of plasma (AIP) was markedly elevated in the untreated positive control group compared to the negative control ($p<0.05$). TCN treatment significantly reduced AIP at 400 mg/kg and 800 mg/kg doses ($p<0.001$). Similarly, the atherogenic coefficient (AC) and Castelli risk indices I (CRI-I) and II (CRI-II) were elevated in the untreated positive control but improved with TCN ($p<0.001$). CRI-I decreased in the 800 mg/kg group, while CRI-II was reduced in the 400 mg/kg and 800 mg/kg groups, respectively ($p<0.001$). These results highlight the dose-dependent efficacy of TCN in reducing atherogenic markers, suggesting its potential cardiovascular benefits for managing hyperlipidemia.

DISCUSSION

The findings from this study demonstrate the significant therapeutic potential of the *n*-hexane extract of *Terminalia catappa* nuts (TCN) in improving metabolic parameters associated with hyperlipidemia and hyperglycemia. These results highlight that the TCN extract possesses a dose-dependent efficacy in modulating lipid profiles, reducing atherogenic lipid indices, and enhancing glucose metabolism and insulin sensitivity in Wistar rats induced with hyperglycemia and hyperlipidemia.

Hypolipidemic activity of Terminalia catappa nut extract

This study investigated the antihyperlipidemic effect of *n*-hexane extract of *Terminalia catappa* nuts (TCN) in Wister rats induced with hyperlipidemia and hyperglycemia. The findings indicated significant reductions in total cholesterol (TC), triglycerides (TG), and low-density lipoprotein (LDL) levels, coupled with a marked increase in high-density lipoprotein (HDL), were observed in TCN-treated groups. These effects were most pronounced at the 800 mg/kg dose, highlighting the robust hypolipidemic activity of the TCN extract. The improvements in lipid profiles underscore the potential of TCN in modulating lipid metabolism and overall contribution to cardiovascular health. TCN is known to regulate lipid metabolism, enhance HDL levels, and reduce atherogenic lipids, thereby mitigating cardiovascular risk.[15] The observed lipid-lowering effects align with previous studies that attribute the efficacy of *Terminalia catappa* extracts to bioactive compounds such as flavonoids and polyphenols.[15] For example, a study conducted by Tabansi et al. in 2023 reported that *Terminalia catappa* fruits reduced the atherogenic lipid profile (e.g., TC, TG, LDL), suggesting an antihyperlipidemic effect.[25] In this current study, TCN exhibited dose-dependent improvements in lipid indices.

Overall, by increasing HDL levels and lowering atherogenic lipids, TCN demonstrates a strong cardioprotective potential, as HDL plays a critical role in protecting against atherosclerosis (references). The reductions in atherogenic indices such as the atherogenic index of plasma (AIP), atherogenic coefficient (AC), and Castelli risk indices I (CRI-I) and II (CRI-II) further emphasize the cardiovascular benefits of TCN. These findings suggest that TCN could significantly reduce the risk of cardiovascular events, offering a promising natural intervention for lipid abnormalities.

Clinical and nutritional significance

The findings of this study highlight the potential of the n-hexane extract of *Terminalia catappa* nuts (TCN) as a promising natural therapeutic agent for managing metabolic risk factors, including hyperlipidaemia and hyperglycaemia.[26] The significant improvement observed in lipid profiles and glycemic indices, particularly the reduction in atherogenic lipid indices and enhancement of insulin sensitivity, hold significant clinical relevance, especially in younger aged patients with type 2 diabetes mellitus, who are likely to have severe hyperglycemia, higher TG, and lower HDL-C.[27] These findings suggest that TCN may play a pivotal role in mitigating the burden of cardiovascular diseases and type 2 diabetes- two major contributors to global morbidity and mortality. In addition, the incorporation of bioactive-rich plant extracts like TCN into dietary interventions offers a complementary approach to conventional pharmacotherapy. This strategy provides a safer, cost-effective alternative with minimal side effects, aligning with the increasing interest in plant-based solutions for the prevention and management of chronic diseases.[28]

This study has some limitations that should be considered when interpreting the results. Firstly, the use of Wistar rats as an animal model, while informative, may not fully replicate human metabolic responses, necessitating further validation through human clinical trials.[29] Additionally, the study focused on short-term interventions, leaving the long-term efficacy and safety of the *Terminalia catappa* nuts (TCN) extract unexplored. The absence of oxidative stress markers evaluations limited the ability to comprehensively understand the mechanism of the therapeutic effects of TCN. Furthermore, while the study demonstrated significant hypolipidemic and antidiabetic effects, the underlying molecular mechanisms were not elucidated, warranting further investigation. Despite these limitations, the study possesses notable strengths. Firstly, it effectively explored the dose-dependent effects of the n-hexane extract of TCN, providing valuable insights into its optimal therapeutic range. Secondly, the comprehensive assessment of metabolic parameters, including lipid and glycaemic profiles, along with atherogenic indices, strengthens the reliability of the findings. Thirdly, this research contributes novel insights into the therapeutic potential of *Terminalia catappa* nuts, which is relatively understudied. Lastly, the methodological clarity of the study ensures its reproducibility, laying a solid foundation for future research in this area.

CONCLUSION

The n-hexane extract of *Terminalia catappa* nuts (TCN) demonstrated significant antihyperlipidemic and cardioprotective effects in a dose-dependent manner. These findings indicate that TCN may hold promise as a natural therapeutic agent for managing hyperlipidemia or dyslipidaemia in cardiometabolic conditions, with potential applications in reducing cardiovascular risk. Consequently, further clinical trials involving human subjects are warranted to substantiate its efficacy and safety.

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