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Original Research Article

Antidiabetic effects of n-hexane extract of terminalia catappa nuts in Wistar rats induced with hyperlipidaemia and hyperglycaemia

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ABSTRACT

Background: Hyperlipidaemia and hyperglycaemia significantly impair pancreatic function and glucose metabolism, necessitating therapeutic interventions. This study investigated the effects of n-hexane extract of *Terminalia catappa* nut (TCN) extract on glucose homeostasis and pancreatic histology in hyperlipidaemic and hyperglycaemic Wistar rats.
Methods: Wistar rats were divided into six groups: negative control, positive control, standard drug control (atorvastatin and metformin), and TCN-treated groups (200, 400, and 800 mg/kg). Fasting blood glucose (FBG), insulin levels, and HOMA indices were measured, and pancreatic tissue was histologically examined. 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: TCN treatment produced dose-dependent improvements in glucose metabolism. The 800 mg/kg TCN group exhibited significant reductions in FBG (4.56±0.03 mmol/l) and insulin resistance (HOMA2-IR: 1.30±0.10) and near-normal insulin levels (11.85±1.20 µU/ml), comparable to the negative control. Beta-cell function (HOMA2%B) improved progressively with TCN, with the 800 mg/kg dose achieving values similar to the negative control (118±4.00). Histologically, the negative control group displayed intact islets of Langerhans and organized acinar cells. Conversely, the positive control group showed severe necrosis, inflammation, and disrupted islets. TCN treatment demonstrated dose-dependent histological recovery, with the 800 mg/kg group achieving near-complete restoration of pancreatic architecture.
Conclusions: TCN extract improves glucose homeostasis, enhances beta-cell function, and restores pancreatic integrity in hyperlipidaemic and hyperglycaemic conditions. These findings highlight the therapeutic potential of TCN as an adjunct for managing metabolic disorders.

Keywords: Terminalia catappa nut, Wistar albino rats, Cardiometabolic disease, Diabetes, Hyplipidaemia, Hyperglycaemia, Glucose homeostasis, Pancreatic histology

INTRODUCTION

Cardiometabolic risk is the likelihood of developing cardiovascular diseases (CVD) and metabolic disorders, particularly type 2 diabetes. The primary cardiometabolic factors that increase the likelihood of CVD occurrence include hypertension, dyslipidemia, obesity, insulin resistance (IR), impaired glucose tolerance, and an unhealthy lifestyle.[1]

Hyperglycemia, a global metabolic disorder, is closely linked to chronic diseases such as cardiovascular disease,

type 2 diabetes mellitus, and end-organ damage.[2,3] Furthermore, hyperglycemia accelerates oxidative stress, inflammation, and glycation reactions, all of which contribute to tissue and organ dysfunction.[4] This metabolic risk factor significantly increases morbidity and mortality, underscoring the urgent need for effective interventions. Type 2 diabetes, characterized by insulin resistance and hyperglycemia, is associated with adverse alterations in lipid metabolism, commonly known as diabetic dyslipidaemia.[5-7] Together, these metabolic disorders contribute substantially to the rising global morbidity and mortality associated with non-communicable diseases.[8]

In Nigeria and other Sub-Saharan African countries, the prevalence of dyslipidemia and diabetes has been on the rise, primarily attributed to urbanization, economic transitions, and dietary shifts towards energy-dense and nutrient-poor foods.[9-11] For instance, a systematic review and meta-analysis among 91, 320 participants in Nigeria conducted by Adeloye et al reported that the age-adjusted prevalence rates of T2DM in Nigeria among persons aged 20-79 years increased from 2.0% in 1990 to 5.7%.[12] Similarly, another systematic review and meta-analysis among 14,650 participants in Nigeria conducted by Uloko et al reported that the overall pooled prevalence of diabetes Mellitus was 5.77%.[13] In poor adherence or compiance of antidiabetic medications due to side effects have been associated with cardiorenal outcomes.[14] This increasing burden and poor adherence has heightened the urgency for effective therapeutic interventions that address both conditions simultaneously while being accessible and culturally acceptable to affected populations.

Natural products, especially those derived from plants, have garnered significant attention as alternative or complementary therapies for managing chronic diseases due to their bioactive compounds.[15,16] TCN, 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, it has been attributed to its anti-inflammatory, antioxidant, and cardioprotective properties.[17] Phytochemical analyses of TCN have revealed the presence of flavonoids, tannins, and phenolic acids, which have been linked to lipid-lowering, glucose-modulating, and organ-protective effects.[18,19] While previous studies have demonstrated the efficacy of Terminalia catappa leaves in reducing cholesterol levels and enhancing antioxidant status in animal models, the potential therapeutic benefits of TCN nuts, particularly their antihyperlipidemic and antidiabetic effects, remain largely unexplored.

Consequently, this study investigated the antidiabetic effects of n-hexane extract of TCN nuts in Wistar rats induced with hyperlipidemia and hyperglycemia. Through assessment of serum glucose, insulin, and HOMA-IR, this study seeks to elucidate the potential adjuvant therapeutic role of TCN nuts in managing diabetes, particularly in cardiometabolic disorders.

METHODS

Study design

This study employed an experimental, randomized, and controlled design to assess the dose-dependent effects of n-hexane extract of TCN nuts 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 guidelines of the institute of laboratory animal resources (ILAR), a comprehensive resource for the care and utilisation of laboratory animals.[20] The study protocol underwent rigorous review and was duly approved by the research ethics committee of the university of Port Harcourt, Nigeria, on August 10, 2023, with approval number UPH/CERMAD/REC/MM90/216.

Collection, identification, and preparation of plants

A similar methodology employed by Batubo was utilized for the collection, identification, and preparation of TCN nuts.[17] In brief, the fresh fruits of TCN were harvested between August and November 2022 from the University of Port Harcourt and Rivers State University in Port Harcourt, Nigeria. The fruits were promptly cleaned under running water, drained, and pat-dried. The edible nut was extracted from the fibrous husk and the hard shell, and air-dried in the shade to preserve its bioactive compounds. The dried nuts were finely ground into a uniform powder and subjected to Soxhlet extraction using 85% aqueous n-hexane with a solid-to-liquid ratio of 1:30 (w/v). The extraction process was repeated four times to ensure complete extraction. The collected extracts of TCN nuts were pooled, filtered, and concentrated under vacuum conditions using a rotary evaporator (Heidolph GmbH and Co. K. G., Germany) to yield a semi-solid mass. The resulting extract was stored in a dark container at 4°C and subsequently reconstituted in a minimal amount of corn oil before administration.

Experimental animals

In this study, sixty male Wistar rats weighing between 180 and 200 grams were utilized. These rats were procured from the Rivers State university animal house in Port Harcourt, Nigeria, and underwent a two-week acclimatization period in laboratory conditions prior to the commencement of the experiment. During this acclimatization phase, the rats were housed in six distinct groups within well-ventilated and compartmentalized

cages. The cages were maintained at a temperature of 25±2°C, and a 12-hour light and dark cycle was implemented.

Experimental design

The rats were provided with unlimited access to standard feed and clean drinking water. They were randomly divided into five groups, each with ten Wistar rats, as fellow:

Normal control: These animals received a standard diet without any treatment.

Positive control: These animals were induced with hyperlipidaemia and hyperglycaemia but did not receive any treatment.

Standard drug control: These animals were induced with hyperlipidaemia and hyperglycaemia and received treatment with atorvastatin and metformin (10 mg/kg/day). However, they did not receive any treatment with TCN.

200 mg/kg/day TCN group: These animals were induced with hyperlipidaemia and hyperglycaemia and received treatment with 200 mg/kg/day of TCN.

400 mg/kg/day TCN group: These animals were induced with hyperlipidaemia and hyperglycaemia and received treatment with 400 mg/kg/day of TCN.

800 mg/kg/day TCN group: These animals were induced with hyperlipidaemia and hyperglycaemia and received treatment with a high dose (800 mg/kg/day) of TCN.

Study protocol

Preparation of high-fat and sugar diet

To induce hyperlipidaemia and hyperglycaemia in Wistar rats, a high-fat and sugar diet (HFSD) was prepared according to the methods outlined by Munshi et al. Briefly, the HFSD consisted of two components: a high-fat mixture and a high-sugar solution. 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. 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). This solution was designed to induce hyperglycaemia. The rats were provided ad libitum access to this fructose solution and the high-fat mixture throughout the induction phase.

Induction of hyperlipidaemia and hyperglycaemia

Hyperlipidemia and hyperglycemia were induced in groups 26 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, FBG, 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 via gastric gavage to ensure consistent intake. Additionally, the rats were provided 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 distinct time points-baseline, three weeks, and six weeks-to monitor the progression of lipid profile changes and blood glucose levels during the induction period.

Treatment administration

Following 6-week induction of hyperlipidemia and hyperglycemia, rats in groups 3-6 received daily oral treatments of TCN at 200, 400 and 800 mg/kg/day, respectively, for an additional six weeks, as specified in their respective groups. Standard drug control group was administered atorvastatin and metformin at a dose of 10 mg/kg body weight each. All treatments were administered orally through gavage to ensure precise dosing. Throughout the experimental period, all rats were provided with distilled water and standard rat pellets ad libitum.

Sampling collection

At the conclusion of six-week post-induction experimental period, the rats were fasted overnight. Six groups of Wistar rats were anesthetized with chloroform. Blood samples were collected from the rats through cardiac punctures into EDTA (ethylenediaminetetraacetic acid) and plain bottles for the determination of serum lipid levels, FBG levels, serum insulin levels, and the calculation of homeostatic model assessment (HOMA) of insulin resistance (HOMA-IR). Furthermore, the livers and pancreases harvested for histopathological examination.

Biochemical assay

The biochemical analysis of glycaemic and insulin sensitivity parameters was conducted using standardised procedures. The FBG levels were measured using a glucometer (AccuChek active Performa, Roche, Germany) at the blood collection point, with results expressed in mmol/l. Serum insulin levels were quantified using a rat-specific enzyme-linked immunosorbent assay (ELISA) kit from Elabscience. Blood samples were centrifuged at 3,000 rpm for 10 minutes to separate serum, and the ELISA assay was performed according to the manufacturer's instructions, with results expressed in μU/ml. The beta-cell function (HOMA2%B) and insulin resistance (HOMA2 IR) were calculated using the HOMA2 model, which integrates FBG and insulin levels. Both indices were computed using the HOMA2 calculator

based on inputted FBG and insulin values. All analyses were conducted in triplicate to ensure accuracy and reliability, with quality controls performed using known standards for glucose and insulin to validate the results.

Histopathological examination

The pancreas from each Wistar rats was excised, rinsed in ice-cold saline, and fixed in 10% neutral buffered formalin for histological analysis. Tissues were embedded in paraffin, sectioned at 5 µm thickness, and stained with hematoxylin and eosin (H and E). Histological sections examined under light microscope (Olympus CX43), and micrographs were captured to assess structural integrity.

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 mean (SEM). A $p<0.05$ was considered statistically significant. Data analysis were performed using R computing environment, version 4.4.2.[21]

RESULTS

Effects on glucose metabolism and insulin sensitivity

The *n*-hexane extract of TCN nuts demonstrated significant improvements in FBG, insulin levels, and HOMA indices in Wistar rats induced with hyperlipidaemia and hyperglycaemia (Table 1). Compared to the untreated positive control group, which exhibited markedly elevated FBG (9.34±0.03 mmol/l), treatment with TCN resulted in a dose-dependent reduction in FBG levels, with the 800 mg/kg dose achieving the most pronounced decrease (4.56±0.03 mmol/l, $p<0.001$). In addition, insulin levels, was significantly reduced in the positive control group (5.00±1.00 µU/ml). However, insuline were restored by TCN treatment. The highest dose of TCN (800 mg/kg) increased insulin levels to near-normal levels (11.85±1.20 µU/ml), comparable to the negative control group (12.00±2.00 µU/ml). Similarly, beta-cell function (HOMA2%B), which was impaired in the positive control group (68.0±3.00), showed dose-dependent improvement with TCN, with the 800 mg/kg group achieving the near-normal levels (118±4.00, $p<0.001$).

Furthermore, HOMA2-IR, an indicator of insulin resistance, was elevated in the positive control group (3.40±0.20). TCN treatment significantly reduced HOMA2-IR in a dose-dependent manner, with the 800 mg/kg dose achieving values (1.30±0.10) comparable to the negative control (1.20±0.10).

These findings indicate that TCN exerts antihyperglycaemic effects by improving glucose homeostasis, enhancing insulin secretion, and reducing insulin resistance, suggesting its potential as a therapeutic agent for managing hyperglycaemia and associated metabolic disorders.

Table 1: Effect of TCN nut extract treatment on glucose, insulin level, and HOMA indices of hyperlipidaemic and hyperglycaemic Wistar rats (*n*=6).

Parameters	Negative control	Positive control	Standard control	200 mg/kg TCN	400 mg/kg TCN	800 mg/kg TCN
FBG (mmol/L)	3.36±0.03	9.34±0.03*	3.44±0.03#	6.06±0.03*#	5.36±0.15*#	4.56±0.03*#
Insulin (µU/mL)	12.00±2.00	5.00±1.00*	9.01±1.24*#	8.00±1.00*#	11.50±1.20*#	11.85±1.20*#
HOMA2%B	120.0±5.00	68.0±3.00*	98.00±3.00*#	92.0±4.00*#	110±5.00*#	118±4.00*#
HOMA2 IR	1.20±0.10	3.40±0.20*	1.80±0.19*#	2.10±0.20*#	1.40±0.08#a	1.30±0.10*#

*All values are expressed as mean ± standard error of the mean. *, #,aindicates significance when compared with the negative control, positive control, and standard drug control at $p<0.001$. TCN nut.

Effect on pancreatic histopathology

The histopathological examination of pancreatic tissue demonstrates a protective and restorative effect of TCN on pancreatic architecture in hyperlipidaemic and hyperglycaemic Wistar rats (Figure 1). The pancreatic tissues in the negative control group exhibited normal histological features, with intact islets of Langerhans, well-organized acinar structures, and no evidence of inflammation or necrosis, indicative of a healthy pancreatic state (Figure 1A). In contrast, the positive control group showed severe pathological alterations, including disrupted islet architecture, necrosis, and significant infiltration of inflammatory cells, highlighting the damaging effects of hyperlipidaemia and hyperglycaemia (Figure 1B). The standard drug control group, treated with atorvastatin and metformin, demonstrated partial recovery of the pancreatic tissue. While there was some restoration of islet integrity and reduced inflammatory infiltration, the tissue still displayed mild structural abnormalities compared to the negative control group (Figure 1C). In the 200 mg/kg TCN-treated group, early signs of healing were observed, with reduced necrosis and partial restoration of islets. However, the recovery was incomplete, and some pathological changes remained (Figure 1D). The 400 mg/kg TCN-treated group showed significant therapeutic improvement, with substantial recovery of acinar structures and near-normalized islets of Langerhans (Figure 1E). The tissue architecture was notably more preserved, with minimal

inflammation and no apparent necrosis. Remarkably, the 800 mg/kg TCN-treated group displayed near-complete restoration of normal pancreatic histology. The islets of Langerhans appeared well-organized, acinar cells were intact, and only minimal pathological changes were evident, making this group most comparable to negative control in terms of structural integrity (Figure 1F).

These observations align with the biochemical findings, reinforcing the dose-dependent efficacy of TCN extract in protecting and restoring pancreatic tissue in hyperlipidaemic and hyperglycaemic conditions.

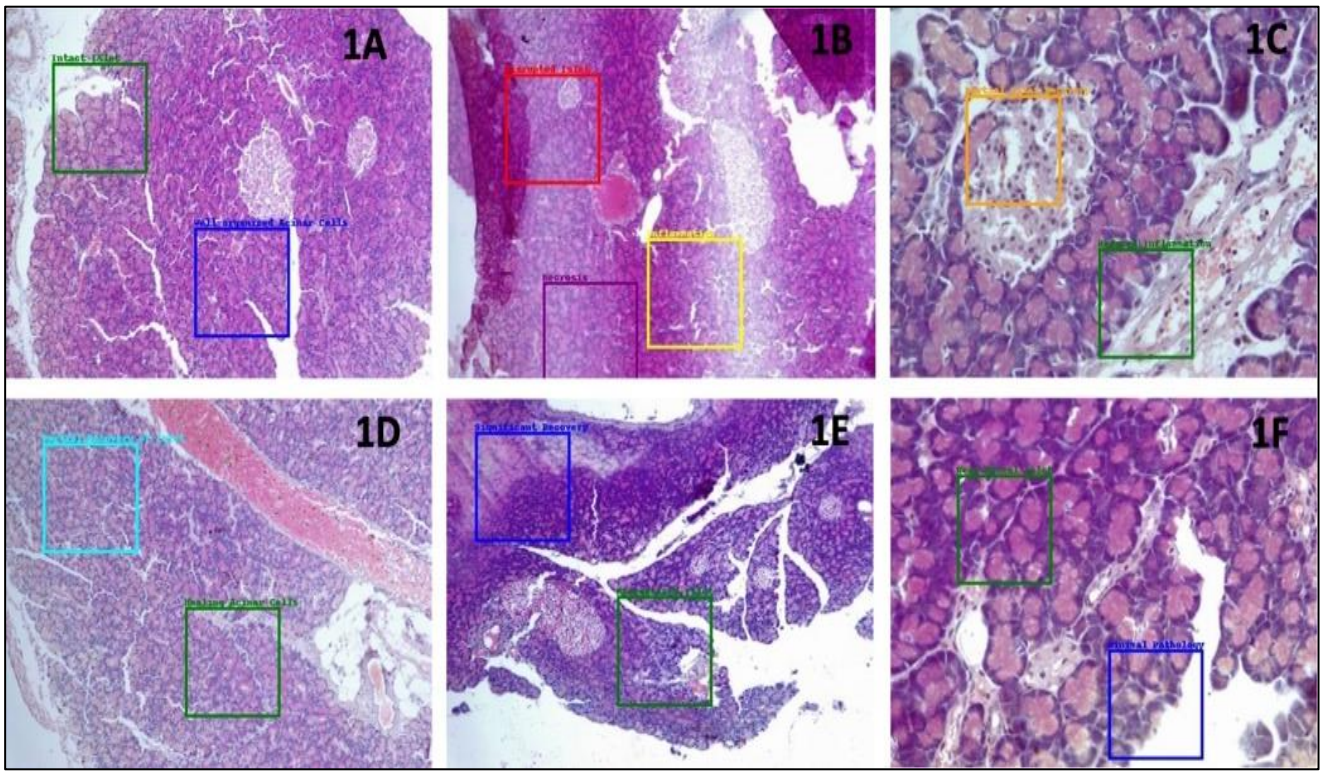

Figure 1: Pancreas section (H and E, x400) from hyperlipidaemic and hyperglycaemic Wistar rats treated with TCN nut extract. (A) negative control, (B) positive control, (C) standard control, (D) 200 mg/kg TCN, (1) 400 mg/kg TCN and (F) 800 mg/kg TCN.

DISCUSSION

The current stydy findings of this study elucidate the substantial therapeutic potential of the current study demonstrates the potential of TCN nut extract in addressing hyperglycemia, a condition closely linked to cardiometabolic disorders. The observed effects, both biochemical and histopathological, provide compelling evidence for its therapeutic value.

Antidiabetic activity

The FBG levels in the positive control group were elevated, which is consistent with findings from similar studies where hyperglycemic rats exhibited significant glucose dysregulation.[22] In our study, TCN treatment resulted in a dose-dependent reduction in FBG levels, similar to the effects observed in other natural products like *Cinnamomum verum* and *Momordica charantia*, which have been shown to improve glycemic control through insulin sensitisation and enhanced beta-cell function.[23-25] Notably, TCN treatment also improved insulin secretion and sensitivity, as evidenced by the HOMA2-B and HOMA2-IR indices, which is comparable to the beneficial effects of metformin in diabetic mice models.[26] This suggest that TCN facilitates glucose uptake and supports pancreatic function. These results underscore potential of TCN as an effective natural antidiabetic agent.

Moreover, previous research has supported the use of TCN in traditional medicine for managing hyperglycaemia and related metabolic conditions. For instance, Divya et al reported that the ethanol extract of TCN leaf (500 mg/kg) had significant anti-diabetic activity by reducing blood glucose, while increasing insulin levels.[27] A similar study by Anand et al and Batubo et al highlighted that the phytoconstituents, such as phenol, flavonoid, and carotenoid are responsible for the anti-inflammatory, antidiabetic, and antioxidant activity of TCN nuts.[17,28] The improvements in glucose metabolism and insulin sensitivity observed in this study highlight the therapeutic potential of TCN as a natural antidiabetic intervention. By reducing insulin resistance and protecting pancreatic beta cells, TCN could play a critical role in managing

hyperglycemia and preventing the progression of diabetes. These findings not only validate the traditional use of TCN nut but also suggest its utility as a complementary treatment for metabolic disorders.

The mechanisms underlying the beneficial effects of TCN may involve modulation of key cellular pathways involved in insulin signaling and oxidative stress. The observed improvements in insulin sensitivity and pancreatic histology suggest that TCN could influence the insulin signaling pathway, similar to other plant-derived compounds like Berberis vulgaris, which have shown effects on insulin receptor phosphorylation and glucose uptake.[29,30] Furthermore, the anti-inflammatory and antioxidant activities of TCN, as suggested by its effects on the pancreas, may contribute to the preservation of beta-cell function and reduced pancreatic damage.[17,31,32]

Pancreatic histopathology

The histopathological analysis revealed significant damage to the pancreatic tissue in untreated hyperglycemic and hyperlipidemic rats, including islet shrinkage, beta-cell degeneration, and inflammatory infiltration. These findings are consistent with earlier studies that have demonstrated pancreatic damage in rodent models of diabetes and dyslipidemia, driven by chronic hyperglycemia and lipotoxicity.[33,34] Treatment with TCN extract at higher doses (400 mg/kg and 800 mg/kg) preserved the pancreatic architecture, reduced inflammatory cell infiltration, and maintained beta-cell integrity, which mirrors the protective effects of other plant extracts such as *Allium sativum* and *Glycyrrhiza glabra*.[35,36] These improvements in histopathology suggest that TCN may reduce oxidative stress and inflammation in the pancreas, potentially through its antioxidant properties, as seen in similar studies where polyphenolic and Flavonoids compounds from plants demonstrated protective effects against pancreatic tissue damage.[37] The ability of TCN to mitigate glucotoxicity and lipotoxicity, thereby preserving pancreatic function, is a novel finding that could have significant implications for the management of diabetes and metabolic syndrome.

Clinical implications

The findings from this study position TCN as a promising natural therapeutic agent for managing metabolic risk factors, including hyperlipidaemia, hyperglycaemia, and pancreatic dysfunction.[28] The significant improvement observed in glycaemic indices, particularly the 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.[38] The dose-dependent effects of TCN in improving both glycemic control and pancreatic health align it with established therapeutic agents, such as metformin and statins, while offering the advantage of being a natural, potentially safer alternative. Its ability to target both lipid and glucose metabolism, while also protecting against pancreatic injury, provides a multifaceted approach to managing cardiometabolic disorders, which are major risk factors for CVD. 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.[39]

Limitations and strengths

This study has certain limitations that should be considered when interpreting the results. Firstly, while the results of this study are promising, the long-term efficacy and safety of TCN treatment in larger animal models and clinical trials are yet to be established.[40] Secondly, future studies should also explore the molecular pathways through which TCN exerts its effects, including its impact on inflammatory cytokines, oxidative stress markers, and adipokine secretion. Additionally, exploring the synergistic effects of TCN with other pharmacological agents could offer novel therapeutic strategies for treating metabolic disorders.

Despite these limitations, the study possesses several notable strengths, such as: (i) it effectively explored the dose-dependent effects of the n-hexane extract of TCN, providing valuable insights into its optimal therapeutic range; (ii) the comprehensive assessment of metabolic parameters, including lipid and glycaemic profiles, as well as atherogenic indices, enhances the reliability of the findings; (iii) this research contributes novel insights into the therapeutic potential of TCN nuts, which is relatively understudied; and (iv) 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 TCN nuts demonstrates significant antihyperglycemic, antihyperlipidemic, and cardioprotective effects in hyperlipidemic and hyperglycemic Wistar rats. Its ability to improve glycemic control and preserve pancreatic function underscores its potential as a therapeutic agent for the management of diabetes and related complications, warranting further investigation into its clinical application.

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