



Research Article

Serum Biochemical Evidence of Hepatorenal Protective Effects of *n*-Hexane Extract of *Terminalia catappa* Nuts in Metabolic Syndrome-Induced Wistar Rats

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Abstract

Introduction: Metabolic syndrome is associated with hepatic and renal dysfunction driven by hyperglycaemia, hyperlipidaemia, oxidative stress, and electrolyte imbalance. *Terminalia catappa* nuts (TCN) are rich in lipophilic bioactive compounds with reported antioxidant and anti-inflammatory properties. This study investigated the effects of the *n*-hexane extract of TCN on serum biochemical markers of hepatic and renal function in Wistar rats with metabolic syndrome. **Methods:** Forty-eight male Wistar rats were divided into six groups ($n = 8$): negative control, metabolic syndrome control, standard drug (metformin + atorvastatin), and TCN-treated group (200, 400, and 800 mg/kg/day). Metabolic syndrome was induced using a high-fat and high-sugar diet. Serum liver enzymes, serum proteins, total bilirubin, creatinine, urea, and electrolytes were analysed. Data were evaluated using one-way ANOVA with Tukey's post-hoc test ($p < 0.05$). **Results:** The metabolic syndrome control group exhibited significant increases in ALP (148 ± 0.98 U/L), ALT (23.4 ± 0.25 U/L), AST (22.0 ± 0.01 U/L), urea (5.2 ± 0.49 mmol/L), creatinine (92.8 ± 1.22 μ mol/L), and bilirubin (10.4 ± 0.25 μ mol/L), alongside reduced total protein (65.0 ± 0.01 g/L) and albumin (31.0 ± 0.01 g/L). TCN treatment ameliorated these alterations. At 200 mg/kg, ALP, ALT, and AST levels decreased to 138 ± 1.22 U/L, 20.6 ± 0.98 U/L, and 17.8 ± 0.49 U/L, respectively, with urea and creatinine reducing to 4.8 ± 0.49 mmol/L and 86.2 ± 0.74 μ mol/L. The 400 mg/kg dose further improved these markers (ALP: 134 ± 1.71 U/L; ALT: 17.0 ± 0.01 U/L; urea: 4.2 ± 0.74 mmol/L; creatinine: 81.4 ± 0.74 μ mol/L). At 800 mg/kg, maximum efficacy was observed, with ALP (127 ± 1.22 U/L), ALT (12.6 ± 0.98 U/L), urea (3.6 ± 0.49 mmol/L), and creatinine (73.0 ± 1.22 μ mol/L) approaching baseline levels. TCN restored electrolyte balance across all doses, improved protein synthesis (TP: 68.2 ± 0.49 g/L, ALB: 37.8 ± 0.74 g/L), and reduced bilirubin to 6.8 ± 0.49 μ mol/L at the highest dose. **Conclusion:** The *n*-hexane extract of TCN demonstrates dose-dependent hepatoprotective and nephroprotective effects, as evidenced by improvements in serum biochemical and electrolyte markers in metabolic syndrome-induced Wistar rats.

Keywords

Terminalia Catappa Nuts, *n*-hexane Extract, Hyperglycaemia, Renoprotection, Hepatoprotection, Metabolic Syndrome Wistar Rats

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1. Introduction

Metabolic syndrome, characterised by a cluster of conditions including hyperlipidaemia, hyperglycaemia, hypertension, and obesity, has emerged as a global health challenge with significant implications for public health [1]. It is a major risk factor for the development of cardiovascular diseases, type 2 diabetes, and non-alcoholic fatty liver disease (NAFLD), as well as renal dysfunction [1, 2]. The increasing prevalence of metabolic syndrome, particularly in low- and middle-income countries (LMICs), has been attributed to rapid urbanisation, sedentary lifestyles, and dietary shifts towards high-calorie, processed foods [3, 4]. In Nigeria, for instance, the burden of metabolic syndrome is rising, with studies reporting a prevalence of up to 12% in 2010 to 24% in 2022 in some populations [5, 6]. This alarming trend underscores the urgent need for effective and accessible therapeutic interventions to manage and mitigate the complications associated with metabolic syndrome.

The liver and kidneys are particularly vulnerable to the deleterious effects of metabolic syndrome [7, 8]. Metabolic syndrome: two hallmark features of the syndrome induce oxidative stress, inflammation, and cellular damage in these organs, thereby impairing function [9, 10]. Elevated liver enzyme levels, such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP), are commonly observed in individuals with metabolic syndrome, reflecting hepatocellular injury [11]. Similarly, renal dysfunction, marked by increased serum creatinine and urea levels, is a frequent complication of metabolic syndrome, often progressing to chronic kidney disease (CKD) if left unmanaged [7]. Additionally, metabolic syndrome disrupts electrolyte homeostasis, further exacerbating organ dysfunction and increasing the risk of cardiovascular complications [12]. Given the central role of the liver and kidneys in maintaining metabolic homeostasis, interventions that protect these organs and restore their function are critical for managing metabolic syndrome.

Conventional pharmacological therapies for metabolic syndrome, such as statins, metformin, and angiotensin-converting enzyme (ACE) inhibitors, have demonstrated efficacy in managing individual components of the syndrome. However, these drugs are often associated with adverse effects, high costs, and limited accessibility, particularly in resource-constrained settings [13]. For example, statins, while effective in lowering cholesterol, can cause hepatotoxicity and myopathy, whereas metformin, a first-line therapy for type 2 diabetes, is contraindicated in patients with renal impairment [14, 15]. These limitations have spurred interest in alternative and complementary therapies, particularly plant-based interventions, which are often more affordable, accessible, and perceived as safer by patients.

Medicinal plants have been used for centuries in traditional medicine systems to treat a wide range of ailments, including

metabolic disorders. *Terminalia catappa*, commonly known as the tropical almond or Indian almond, is one such plant with a long history of medicinal use in Africa, Asia, and South America [16]. The nuts, leaves, and bark of *Terminalia catappa* have traditionally been used to treat conditions such as diabetes, hypertension, and liver diseases [17]. Modern pharmacological studies have corroborated some of these traditional uses, demonstrating that *Terminalia catappa* possesses antioxidant, anti-inflammatory, antihyperglycaemic, and antihyperlipidaemic properties [17]. These bioactivities are attributed to the plant's rich phytochemical composition, which includes flavonoids, tannins, phenolic acids, and triterpenoids.

The *n*-hexane extract of *Terminalia catappa* nuts (TCN) is of particular interest due to its high concentration of lipophilic bioactive compounds, which may enhance its therapeutic efficacy [17]. Previous studies have shown that *n*-hexane extracts of medicinal plants exhibit potent antioxidant and anti-inflammatory activities, making them suitable candidates for managing oxidative stress-related disorders such as metabolic syndrome [18]. However, limited research has examined the effects of the *n*-hexane extract of TCN on liver and renal function biomarkers in the context of metabolic syndrome. Addressing this gap is crucial for understanding the therapeutic potential of TCN and its possible role in the management of metabolic syndrome. Despite these promising findings, the potential of *Terminalia catappa* nuts in mitigating metabolic syndrome-induced liver and renal dysfunction remains underexplored.

This study aimed to investigate the effects of the *n*-hexane extract of *Terminalia catappa* nuts (TCN) on liver and renal function biomarkers in hyperlipidaemic and hyperglycaemic Wistar rats. Specifically, the study evaluated the effects of TCN on serum liver enzymes (ALT, AST, and ALP), serum proteins (total protein and albumin), bilirubin, renal function markers (creatinine and urea), and serum electrolyte levels (sodium, potassium, bicarbonate, and chloride). The study hypothesised that the *n*-hexane extract of *Terminalia catappa* nuts would dose-dependently improve liver and renal function biomarkers and restore electrolyte homeostasis in metabolic syndrome-induced Wistar rats.

2. Materials and Methods

2.1. Study Design

This study employed an experimental design to investigate the effects of the *n*-hexane extract of *Terminalia catappa* nuts (TCN) on liver and renal function biomarkers in hyperlipidaemic and hyperglycaemic Wistar rats. The study used a randomised, controlled design with six experimental groups, including a negative control group, a metabolic syndrome

control group (induced with metabolic syndrome), a standard drug group, and three TCN treatment groups (200, 400, and 800 mg/kg/day). The investigation was conducted in 2024 between August and November at the Department of Human Physiology, Faculty of Basic Medical Science, Animal House, University of Port Harcourt, Nigeria.

2.2. Ethical Considerations

All experimental procedures were approved by the Research Ethics Committee of the University of Port Harcourt (Approval No: UPH/CERMAD/REC/MM90/216). Animal handling and experimental protocols were conducted in accordance with the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals (8th edition) and complied with the ARRIVE 2.0 guidelines for reporting animal research. Efforts were made to minimise animal suffering, reduce the number of animals used, and refine experimental procedures in line with the 3Rs principle (Replacement, Reduction, and Refinement) [19].

2.3. *Terminalia Catappa* Extract Preparation

The previously used methods of Batubo et al. (2023) [17] were employed for collecting, identifying, and preparing *Terminalia catappa* nuts. Briefly, fresh fruits were gathered between August and September 2024 from the campuses of the University of Port Harcourt and Rivers State University in Port Harcourt, Nigeria. A botanist from the Department of Plant Science and Biotechnology at the University of Port Harcourt authenticated the species with a voucher number—UPH/PBS/2023/047. The fruits were immediately washed under running water, drained, and gently dried. The edible nuts were separated from the fibrous husk and hard shell and air-dried. The dried nuts were ground into a uniform paste and extracted using Soxhlet with 85% aqueous *n*-hexane at a solid-to-liquid ratio of 1:30 (w/v). This extraction process was repeated four times for thoroughness. The combined extracts were filtered and concentrated under vacuum with a rotary evaporator (Heidolph GmbH & Co. K. G., Germany) to produce a semi-solid residue. The extract was stored in a dark amber container at 4 °C until needed.

2.4. Experimental Animals and Groups

Overall, forty-eight male Wistar rats weighing between 140–160 grams were used in this study. They were sourced from the University of Port Harcourt Animal House in Nigeria and allowed to acclimate to laboratory conditions for two weeks prior to the start of the experiment. During this period, they were housed in groups of six within well-ventilated, compartmentalised cages, maintained at 25 ± 2 °C temperature, $50 \pm 10\%$ relative humidity, and a 12-hour light/dark cycle. The rats had free access to standard feed and clean drinking water *at all times*. They were randomly assigned to six groups (eight rats per group):

- 1) Negative Control Group: Normal rats fed with a standard diet and water without treatment.
- 2) Metabolic syndrome: Metabolic syndrome Wistar rats, but they received no treatment.
- 3) Standard Drug Control): Metabolic syndrome induced Wistar rats treated with a combination of metformin (150mg/kg) and atorvastatin (10 mg/kg/day).
- 4) TCN 200 mg/kg Group: Metabolic syndrome induced Wistar rats treated with 200 mg/kg/day TCN extract.
- 5) TCN 400 mg/kg Group: Metabolic syndrome induced Wistar rats treated with 400 mg/kg/day TCN extract.
- 6) TCN 800 mg/kg Group: Metabolic syndrome induced Wistar rats treated with 800 mg/kg/day TCN extract.

2.5. Preparation of High-Fat and Sugar Diet

A high-fat and sugar diet (HFSD) was prepared to induce metabolic syndrome in Wistar rats, following the methods of Munshi et al. (2014). The HFSD consisted of two main parts: a high-fat mixture and a high-sugar solution. The high-fat component was prepared by mixing melted butter and coconut oil in a ratio of 3:1 (v/v), resulting in a final mixture that provided about 617 kcal per 100 mL from fats, 7.72 kcal from carbohydrates, and 5.40 kcal from proteins [20]. The high-sugar component was made by dissolving fructose at 25% (w/v) in distilled water in a ratio of 1:3 (v/v) to produce a solution aimed at inducing hyperglycaemia and insulin resistance. The rats had free access to this fructose solution and the high-fat mixture during the induction period.

2.6. Induction of Metabolic Syndrome

The method of Batubo et al. (2023) was used to induce metabolic syndrome in the Wistar rats [21]. Briefly, Baseline blood samples were collected from the tail vein of each Wistar rat in groups 2–6 to assess biomarkers for control reference for evaluating TCN-induced metabolic changes, including: (i) fasting lipid profile (such as total cholesterol, triglycerides, LDL-cholesterol) using an automated biochemical analyser [random access multibatch chemistry analyser (USA)]; (ii) fasting blood glucose levels using a glucometer (AccuChek Active Performa, Roche, Germany); (iii) serum liver enzymes, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP), were measured using standard enzymatic colourimetric kits (Bio-Systems, Spain). Additionally, renal function biomarkers, including serum creatinine and urea, as well as serum electrolytes, were assessed using commercial assay kits (Randox Laboratories, UK). Subsequently, Groups 2–6 developed metabolic syndrome after rats were given a daily gastric lavage of 3 ml high-fat and 3 ml high-sugar diet solutions for 6 weeks (42 days) (42). Blood samples were additionally collected at two critical time points—three and six weeks—to track changes in lipid profiles and blood glucose levels throughout the induction period.

2.7. Administration of Treatments

Following the confirmation of metabolic syndrome (with elevated LDL, TC, FBG and weight gain in the rats), and abnormal liver and renal biomarkers at 42 days of induction, Wistar rats in the TCN 200 mg/kg, TCN 400 mg/kg, and TCN 800 mg/kg groups received daily oral treatments with TCN for an additional six weeks (42 days) as indicated by their respective groups. The Standard drug group received a combination of metformin (10 mg/kg/day) and atorvastatin (10 mg/kg/day). The negative and metabolic syndrome control groups received an equivalent volume of distilled water. All treatments were delivered orally through gavage for 42 days. All rats were provided with clean water and standard rat pellets *ad libitum* throughout the treatment period.

2.8. Sampling Collection

At the conclusion of the 42-day treatment, the rats fasted overnight. Six Wistar rats from each group were anaesthetised with chloroform. Blood samples were drawn via cardiac puncture into ethylenediaminetetraacetic acid (EDTA) and plain tubes for measuring liver function, renal biomarkers, and serum electrolytes. To minimise bias, the researchers remained blinded to group assignments throughout data collection and analysis.

2.9. Biochemical Assay

Serum liver function biomarkers, including ALT, AST, ALP, total protein, albumin, and bilirubin, were measured using an automated biochemical analyser with commercially available assay kits. In addition, renal function biomarkers, such as serum creatinine and urea levels, were assessed using colourimetric assays. Furthermore, serum sodium (Na), potassium (K), bicarbonate (HCO_3^-), and chloride (Cl^-) levels were measured using ion-selective electrodes. All biochemical assays were analysed in triplicate to guarantee accuracy and reproducibility.

2.10. Statistical Analysis

Data generated from this experiment were analysed with one-way analysis of variance (ANOVA) to identify signifi-

cant differences among groups, with Tukey's post hoc test for multiple comparisons. Results are shown as mean $\pm$ standard error of the mean (SEM). A p-value less than 0.05 was deemed statistically significant. All analyses were conducted using R software (version 4.3.1). [22]

3. Results

3.1. Effect on Liver Enzymes

The results of the study investigating the effects of *n*-hexane extract of *Terminalia catappa* nuts (TCN) on serum liver enzyme activities are presented in Table 1. The baseline levels of alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) in the negative control group were 108 ± 1.22 U/L, 6.2 ± 0.49 U/L, and 7.2 ± 0.49 U/L, respectively. Induction of metabolic syndrome in the metabolic syndrome control group resulted in significant elevations in serum ALP, ALT, and AST levels compared to the negative control group ($p < 0.05$). Specifically, ALP increased to 148 ± 0.98 U/L, ALT rose to 23.4 ± 0.25 U/L, and AST reached 22.0 ± 0.01 U/L.

However, administration of the standard drugs (metformin and atorvastatin) significantly reduced the elevated liver enzyme levels compared to the metabolic syndrome control group ($p < 0.05$). The ALP, ALT and AST were 136 ± 1.71 U/L, 17.2 ± 0.49 U/L, and 14.2 ± 0.49 U/L in the standard drug group, respectively, compared to the negative control. In contrast, treatment with the *n*-hexane TCN extract demonstrated dose-dependent improvements in liver enzyme profiles. At a dose of 200 mg/kg/day TCN, serum ALP, ALT, and AST were 138 ± 1.22 U/L, 20.6 ± 0.98 U/L, and 17.8 ± 0.49 U/L, respectively, indicating significant reductions compared to the metabolic syndrome control group ($p < 0.05$). In addition to the 200 mg/kg/day TCN dose, the 400 mg/kg/day TCN dose further improved liver enzyme levels, with ALP at 134 ± 1.71 U/L, ALT at 17.0 ± 0.01 U/L, and AST at 14.8 ± 0.49 U/L. Furthermore, the 800 mg/kg/day TCN group showed the most significant effect. Serum ALP, ALT, and AST levels in the 800 mg/kg/day TCN group were 127 ± 1.22 U/L, 12.6 ± 0.98 U/L, and 13.2 ± 0.49 U/L, respectively, all significantly lower than the metabolic syndrome control group ($p < 0.05$).

Table 1. Effect of *n*-hexane extract of *Terminalia catappa* nut (TCN) treatment on Serum Liver enzymes.

Parameters (n=6)	Negative control	Metabolic syndrome control	Standard drug	200 mg/kg/day TCN	400 mg/kg/day TCN	800 mg/kg/day TCN
ALP (U/L)	108 ± 1.22	$148 \pm 0.98^*$	$136 \pm 1.71^{*#}$	$138 \pm 1.22^{*#}$	$134 \pm 1.71^{*#}$	$127 \pm 1.22^{*#a}$
ALT (U/L)	6.2 ± 0.49	$23.4 \pm 0.25^*$	$17.2 \pm 0.49^{*#}$	$20.6 \pm 0.98^*$	$17.0 \pm 0.01^{*#}$	$12.6 \pm 0.98^{*#a}$

Parameters (n=6)	Negative control	Metabolic syndrome control	Standard drug	200 mg/kg/day TCN	400 mg/kg/day TCN	800 mg/kg/day TCN
AST (U/L)	7.2±0.49	22.0±0.01*	14.2±0.49* [#]	17.8±0.49* [#]	14.8±0.49* [#]	13.2±0.49* [#]

All values are expressed as mean ± standard error of the mean. * $p < 0.05$, [#] $p < 0.05$, and ^a $p < 0.05$, significant when compared with the negative control, metabolic syndrome control, and the standard drugs (metformin and atorvastatin), respectively. TCN: *Terminalia catappa* nuts.

3.2. Effects on Serum Proteins and Bilirubin

The effect of *n*-hexane extract of *Terminalia catappa* nuts (TCN) on serum total protein (TP), albumin (ALB), and bilirubin (BIL) in metabolic syndrome Wistar rats is presented in Table 2. The negative control group had baseline values of TP, ALB, and BIL of 69.6 ± 0.98 g/L, 38.2 ± 0.74 g/L, and 5.6 ± 0.25 µmol/L, respectively. Induction of metabolic syndrome in the metabolic syndrome control group resulted in a significant reduction in total protein and albumin levels and a marked increase in serum bilirubin compared with the negative control ($p < 0.05$). Total protein and albumin levels in the metabolic syndrome control group were 65.0 ± 0.01 g/L and 31.0 ± 0.01 g/L, respectively, while bilirubin increased to 10.4 ± 0.25 µmol/L, indicating protein depletion and potential liver dysfunction (Table 2).

However, treatment with the standard drug partially restored serum protein levels and reduced bilirubin levels compared with the metabolic syndrome control ($p < 0.05$).

The standard drug group had total protein of 67.8 ± 0.49 g/L, albumin of 36.8 ± 0.49 g/L, and bilirubin of 8.2 ± 0.49 µmol/L (Table 2). Administration of *n*-hexane TCN extract demonstrated dose-dependent improvements in serum protein and bilirubin levels. At a dose of 200 mg/kg/day TCN, total protein and albumin levels were 64.8 ± 0.74 g/L and 35.0 ± 1.22 g/L, respectively, while bilirubin decreased to 8.8 ± 0.74 µmol/L, showing significant differences from the metabolic syndrome control group ($p < 0.05$). Similarly, the 400 mg/kg/day TCN dose showed further improvements in total protein (66.2 ± 0.74 g/L), albumin (37.8 ± 0.74 g/L), and BIL (7.8 ± 0.74 µmol/L) (Table 2).

The 800 mg/kg/day TCN exhibited the most substantial effects, bringing serum protein and bilirubin levels closer to those of the negative control group. The 800 mg/kg/day TCN treatment resulted in total protein of 68.2 ± 0.49 g/L, albumin of 37.8 ± 0.74 g/L, and bilirubin of 6.8 ± 0.49 µmol/L, which were significantly improved compared with the untreated metabolic syndrome control group ($p < 0.05$).

Table 2. Effect of *n*-hexane extract of *Terminalia catappa* nut (TCN) treatment on serum proteins & bilirubin in Wistar rats induced with metabolic syndrome (n=6).

Parameters (n=6)	Negative control	Metabolic syndrome control	Standard drug	200 mg/Kg/day TCN	400 mg/Kg/day TCN	800 mg/Kg/day TCN
TP (g/L)	69.6±0.98	65.0±0.01*	67.8±0.49	64.8±0.74*	66.2±0.74*	68.2±0.49 [#]
ALB (g/L)	38.2±0.74	31.0±0.01*	36.8±0.49 [#]	35.0±1.22 [#]	37.8±0.74 [#]	37.8±0.74 [#]
BIL (µmol/L)	5.6±0.25	10.4±0.25*	8.2±0.49*	8.8±0.74*	7.8±0.74 [#]	6.8±0.49 [#]

All values are expressed as mean ± standard error of the mean. * $p < 0.05$, [#] $p < 0.05$, and ^a $p < 0.05$, significant when compared with the negative control, metabolic syndrome control, and the standard drugs (metformin and atorvastatin), respectively. TCN: *Terminalia catappa* nuts. TP: Total protein; ALB: Albumin; and BIL: Total Bilirubin.

3.3. Effects on Renal Function Biomarkers

The effects of *n*-hexane extract of *Terminalia catappa* nuts (TCN) on the renal function markers in Wistar rats induced with metabolic syndrome are presented in Table 3. The serum urea level was 2.38 ± 0.07 mmol/L, while creatinine was 66.0 ± 1.22 µmol/L in the negative control group. Metabolic syndrome in the metabolic syndrome control group significantly

increased serum urea and creatinine levels to 4.23 ± 0.07 mmol/L and 91.0 ± 2.45 µmol/L, respectively, compared with the negative control group ($p < 0.05$).

However, treatment with the standard drug significantly reduced serum urea (4.12 ± 0.07 mmol/L) and creatinine (78.0 ± 1.22 µmol/L) levels compared with the metabolic syndrome control group ($p < 0.05$). Similarly, administration of *n*-hexane TCN extract at doses of 200, 400, and 800 mg/Kg/day resulted in dose-dependent reductions in urea and

creatinine levels (Table 3). At 200 mg/Kg/day TCN, serum urea was reduced to 3.60 ± 0.12 mmol/L and creatinine to 78.0 ± 1.22 μ mol/L. At 400 mg/Kg/day TCN, urea decreased further to 3.38 ± 0.07 mmol/L and creatinine to 73.0 ± 1.22

μ mol/L; at 800 mg/Kg/day TCN, the reductions were more pronounced, with urea at 3.16 ± 0.09 mmol/L and creatinine at 71.0 ± 2.45 μ mol/L.

Table 3. Effect of *n*-hexane extract of *Terminalia catappa* nut (TCN) treatment on serum proteins & bilirubin in Wistar rats induced with metabolic syndrome.

Groups (n=6)	Na ⁺ (mmol/L)	K ⁺ (mmol/L)	HCO ₃ ⁻ (mmol/L)	Cl ⁻ (mmol/L)	Urea (mmol/L)	Creatinine (μ mol/L)
Negative Control	139 $\pm$ 0.74	3.82 $\pm$ 0.07	24.8 $\pm$ 0.49	99.2 $\pm$ 0.49	2.38 $\pm$ 0.07	66.0 $\pm$ 1.22
Metabolic Syndrome Control	143 $\pm$ 0.25*	3.52 $\pm$ 0.05*	28.4 $\pm$ 0.25*	104.0 $\pm$ 0.49*	4.23 $\pm$ 0.07*	91.0 $\pm$ 2.45*
Standard Drug	139 $\pm$ 0.74 [#]	3.48 $\pm$ 0.05*	26.0 $\pm$ 0.01 [#]	102.0 $\pm$ 0.49*	4.12 $\pm$ 0.07*	78.0 $\pm$ 1.22* [#]
200mg/Kg/day TCN	139 $\pm$ 0.74 [#]	3.62 $\pm$ 0.05	25.2 $\pm$ 0.74 [#]	99.8 $\pm$ 0.49 [#]	3.60 $\pm$ 0.12* ^{#a}	78.0 $\pm$ 1.22* [#]
400mg/Kg/day TCN	138 $\pm$ 0.74 [#]	3.76 $\pm$ 0.03	25.6 $\pm$ 0.25 [#]	101.0 $\pm$ 0.49 [#]	3.38 $\pm$ 0.07* ^{#a}	73.0 $\pm$ 1.22* [#]
800mg/Kg/day TCN	138 $\pm$ 0.49 [#]	3.72 $\pm$ 0.05	25.8 $\pm$ 0.74 [#]	101.0 $\pm$ 0.74 [#]	3.16 $\pm$ 0.09* ^{#a}	71.0 $\pm$ 2.45* [#]

All values are expressed as mean $\pm$ standard error of the mean. * p <0.05, [#] p <0.05, and ^a p <0.05, significant when compared with the negative control, metabolic syndrome control, and the standard drugs, respectively. TCN: *Terminalia catappa* nuts. Na⁺: Sodium; K⁺: Potassium; HCO₃⁻: Bicarbonate; Cl⁻: Chloride.

In addition to the serum urea and creatinine levels, the serum Sodium (Na), Potassium (K), Bicarbonate (HCO₃), and Chloride (Cl⁻) were at 139 ± 0.74 mmol/L, 3.82 ± 0.07 mmol/L, 24.8 ± 0.49 mmol/L, and 99.2 ± 0.49 mmol/L, respectively, in the negative control group. In the metabolic syndrome control group, serum sodium significantly increased to 143 ± 0.25 mmol/L ($p < 0.05$), while serum potassium decreased significantly to 3.52 ± 0.05 mmol/L ($p < 0.05$) compared to the negative control. Additionally, the metabolic syndrome control group exhibited a significant increase in bicarbonate (28.4 ± 0.25 mmol/L) and chloride (104.0 ± 0.49 mmol/L), indicating electrolyte imbalances characteristic of metabolic syndrome. The administration of the standard drug normalised serum sodium levels to 139 ± 0.74 mmol/L and significantly reduced bicarbonate (26.0 ± 0.01 mmol/L) and chloride (102.0 ± 0.49 mmol/L) levels compared with the metabolic syndrome control group ($p < 0.05$). However, serum potassium level remained slightly lower at 3.48 ± 0.05 mmol/L compared to the negative control ($p < 0.05$).

Furthermore, treatment with *n*-hexane TCN extract demonstrated dose-dependent normalisation of electrolyte levels (Table 3). At 200 mg/Kg/day TCN, serum sodium level was 139 ± 0.74 mmol/L, potassium level was 3.62 ± 0.05 mmol/L, bicarbonate level was 25.2 ± 0.74 mmol/L, and chloride level was 99.8 ± 0.49 mmol/L (Table 3). The 400 mg/Kg/day dose further improved electrolyte balance, with serum sodium at 138 ± 0.74 mmol/L, potassium at 3.76 ± 0.03 mmol/L, bicarbonate at 25.6 ± 0.25 mmol/L, and chloride at 101.0 ± 0.49 mmol/L. The highest dose of 800 mg/Kg/day TCN demonstrated the most significant decrease in serum

sodium level at 138 ± 0.49 mmol/L, potassium at 3.72 ± 0.05 mmol/L, bicarbonate at 25.8 ± 0.74 mmol/L, and chloride at 101.0 ± 0.74 mmol/L.

4. Discussion

The findings of this study demonstrate the potential therapeutic effects of the *n*-hexane extract of *Terminalia catappa* nuts (TCN) on hepatic and renal parameters, as well as electrolyte levels, in Wistar rats with metabolic syndrome. The results highlight the extract's dose-dependent efficacy in mitigating metabolic disturbances and restoring physiological homeostasis, offering insights into its potential clinical and nutritional applications.

4.1. Liver Enzymes

The significantly elevated levels of liver enzymes, including alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST), observed in the metabolic syndrome control group, are indicative of hepatic injury and consistent with previous studies linking metabolic disorders to liver dysfunction [23]. This finding aligns with the known effects of metabolic syndrome on the liver, including induction of oxidative stress and lipid peroxidation, which compromise hepatocyte integrity [23, 24].

The treatment with *n*-hexane extract of *Terminalia catappa* (TCN), particularly at the highest dose (800mg/kg/day), significantly reduced these enzyme levels, demonstrating a

dose-dependent hepatoprotective effect, comparable to the effects of the standard drug (metformin and atorvastatin). The hepatoprotective effects of TCN observed in this study are consistent with previous research reporting similar reductions in ALT and AST levels in acute liver injury with *Terminalia catappa* extracts [25, 26]. The improvement in liver function is attributed to the extract's antioxidant properties, which neutralise free radicals and reduce inflammation. Overall, our findings corroborate earlier reports, reinforcing the potential of TCN as a hepatoprotective agent. This suggests that TCN possesses potent hepatoprotective properties, likely due to its antioxidant and anti-inflammatory constituents, such as polyphenols, flavonoids and tannins, which are known to mitigate oxidative stress and inflammation in liver tissues [17, 27]. The dose-dependent reduction in liver enzymes underscores the potential of TCN as a natural therapeutic agent for managing metabolic syndrome-associated liver damage.

4.2. Serum Proteins and Bilirubin

The reduction in serum total protein (TP) and albumin (ALB) levels observed in the metabolic syndrome control group indicates impaired protein synthesis, a hallmark of liver dysfunction, often linked to systemic inflammation and oxidative stress associated with metabolic syndrome [28]. Elevated bilirubin levels in the metabolic syndrome control group further indicate impaired hepatic clearance, suggesting reduced hepatic conjugation and excretion [29]. Treatment with *n*-hexane extract of *Terminalia catappa* (TCN) significantly improved TP and ALB levels while reducing bilirubin concentrations in a dose-dependent manner. The 800 mg/kg dose demonstrated the most pronounced effect, suggesting enhanced protein synthesis and hepatic clearance mechanisms. These findings align with a study by Luka et al., which reported similar improvements in hepatic protein synthesis and bilirubin clearance with *Terminalia catappa* in animal models of liver dysfunction [30]. The hepatoprotective effect is likely mediated by bioactive compounds, such as flavonoids and phenolics, which have been shown to mitigate oxidative stress and inflammation and to support protein production [17]. These findings suggest the ability of TCN to restore serum proteins and bilirubin levels and highlight its potential in addressing metabolic syndrome-related hepatic dysfunction.

4.3. Serum Urea and Creatinine

The significant increase in serum urea and creatinine levels in the metabolic syndrome control group indicates renal impairment, a common consequence of metabolic syndrome-induced nephrotoxicity [31]. Similar findings were observed in our study, in which metabolic syndrome induced nephrotoxicity in rats, characterised by increased urea and creatinine levels. Treatment with *n*-hexane extract of *Terminalia catappa* (TCN) significantly reduced urea and creatinine levels in a dose-dependent manner, with the 800 mg/kg

dose showing the most excellent nephroprotective effect. This improvement may be attributed to the antioxidant and anti-inflammatory properties of bioactive compounds in TCN, such as flavonoids and tannins, which mitigate oxidative stress, reduce renal damage, improve renal blood flow and inhibit inflammatory pathways [17]. Comparable effects were observed by Iheagwam, Odiba [32], who noted that *Terminalia catappa* extracts reduced nephrotoxicity markers in animal models of renal injury, highlighting its ability to preserve glomerular and tubular integrity [33]. The findings suggest that TCN could serve as a complementary therapy for preventing or managing metabolic syndrome-induced nephropathy.

4.4. Serum Electrolytes

The observed serum electrolyte imbalances, including elevated sodium (Na) and chloride (Cl) levels and decreased potassium (K) levels, in the metabolic syndrome control group are consistent with metabolic acidosis and renal dysfunction associated with metabolic syndrome [34, 35]. These findings are indicative of renal tubular dysfunction and disrupted fluid-electrolyte balance, often associated with hyperglycaemia and hyperlipidaemia [36]. Treatment with TCN restored electrolyte levels closer to those in the control group, particularly at the higher dose (800 mg/kg/day). The ability of TCN to modulate electrolyte balance is attributable to its bioactive components, which stabilise renal tubular function and improve systemic homeostasis. Similar outcomes were reported in previous studies, in which polyphenolic compounds from *Terminalia catappa* demonstrated efficacy in reversing electrolyte disturbances in animal models [33]. These findings suggest that TCN not only protects against structural kidney damage but also enhances renal functional capacity, thereby preserving electrolyte homeostasis. Overall, the nephroprotective effects of TCN observed in this study are consistent with existing literature, underscoring its potential as a complementary therapeutic agent for managing renal dysfunction associated with metabolic syndrome [24].

4.5. Comparative Analysis with Standard Drug

The efficacy of TCN in enhancing renal and hepatic function, electrolyte balance, and serum protein levels was comparable to, or superior to, that of the standard drug used in this study for the treatment of metabolic syndrome. While the standard drug demonstrated notable effects, TCN, particularly at the highest dose, exhibited superior outcomes in several parameters, including bilirubin and liver enzymes. This suggests that TCN may offer a safer and more effective alternative to conventional therapies, with additional benefits derived from its natural origin and polyphenolic content [17]. The therapeutic effects of TCN are attributed to its bioactive compounds, including ellagic acid, gallic acid, and flavonoids, which possess potent antioxidant, anti-inflammatory, and

lipid-lowering properties [17]. These compounds are likely to modulate oxidative stress pathways, enhance membrane stabilisation, and facilitate cellular repair mechanisms, contributing to the observed improvements in renal and hepatic function [37, 38].

4.6. Clinical and Nutritional Significance

The findings of this study underscore the clinical and nutritional significance of *Terminalia catappa* nuts (TCN) as a potential functional food or nutraceutical for the management of metabolic syndrome and its associated complications. Administration of TCN extract significantly improved hepatic and renal function, restored electrolyte balance, and normalised serum protein and bilirubin levels, thereby demonstrating its relevance in mitigating multi-organ dysfunction commonly observed in metabolic disorders [39]. The nephroprotective and hepatoprotective properties of TCN are particularly important in conditions such as diabetic nephropathy and non-alcoholic fatty liver disease, where oxidative stress and inflammation play central roles in disease progression. Moreover, the dose-dependent nature of the observed effects suggests that TCN could be strategically tailored for therapeutic use according to disease severity. Incorporating TCN into dietary interventions or developing standardised supplements positions it as a promising functional food ingredient, offering a cost-effective and accessible approach to managing metabolic syndrome, particularly in resource-limited settings [17].

4.7. Limitations and Strengths

This study has some limitations that warrant consideration. First, the study demonstrates positive effects on biochemical markers; the underlying molecular mechanisms remain unexplored, and further research is needed to elucidate how TCN exerts its beneficial actions at the cellular and molecular levels. Lastly, the findings are based on an animal model, and extrapolation to humans requires further clinical trials, as interspecies differences in drug metabolism and physiological responses may influence outcomes.

Despite these limitations, this study offers several strengths that enhance its scientific merit and relevance to metabolic disorder research. One of the key strengths is its comprehensive evaluation of biochemical parameters, including renal function markers (urea and creatinine), serum electrolytes, liver enzymes, and serum proteins, thereby providing a broad understanding of the effects of *Terminalia catappa* nuts. The use of a dose-dependent approach adds depth to the study, helping determine the optimal TCN concentration required for therapeutic benefit, which is crucial for future clinical applications. Moreover, the study's focus on both hyperlipidaemia- and hyperglycaemia-induced conditions enhances its clinical relevance, as these conditions often coexist and exacerbate one another, making them a critical area of research [40].

5. Conclusion

The *n*-hexane extract of *Terminalia catappa* nuts exhibits significant dose-dependent hepatoprotective, renoprotective, and electrolyte-balancing effects in metabolic syndrome-induced Wistar rats. These findings provide a basis for further studies and potential clinical applications of TCN in metabolic disorders.

Abbreviations

ALB	Albumin
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANOVA	Analysis of Variance
APCs	Antigen-Presenting Cells
ARRIVE	Animal Research: Reporting of In Vivo Experiments
AST	Aspartate Aminotransferase
BIL	Total Bilirubin
CKD	Chronic kidney disease
Cl ⁻	Chloride
EDTA	Ethylenediaminetetraacetic Acid
FBG	Fasting Blood Glucose
HFSD	High-Fat and Sugar Diet
HCO ₃ ⁻	Bicarbonate
K ⁺	Potassium
LDL	Low-Density Lipoprotein
LMICs	Low- and Middle-Income Countries
Na ⁺	Sodium
NAFLD	Non-Alcoholic Fatty Liver Disease
NIH	National Institutes of Health
p	Probability Value
REC	Research Ethics Committee
SEM	Standard Error of the Mean
TC	Total Cholesterol
TCN	<i>Terminalia catappa</i> Nuts
TP	Total Protein
U/L	Units per Litre
w/v	Weight per Volume
v/v	Volume per Volume

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Data Availability Statement

The datasets used and analyses in this study are available from the corresponding author upon request.

Conflicts of Interest

The authors report there are no competing interests to declare.

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