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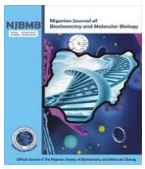

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Research Article

Saponins Extracted from *Tetrapleura tetraptera* Modulates Fasting Blood Sugar and Insulinotropic Genes in Streptozotocin Diabetic Wistar Rats

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ABSTRACT

In Africa, medicinal plants such as *Tetrapleura tetraptera* are widely used for the management of diabetes due to their affordability and perceived safety. This study investigated the *in vivo* antidiabetic activities of total saponin fractions from the root bark of *T. tetraptera* in streptozotocin-induced diabetic male Wistar rats. Rats received oral doses of *T. tetraptera* saponins (TTS) (10, 20, 40 mg/kg), and metformin (100 mg/kg) for 12 weeks. Fasting blood sugar (FBS), insulin levels, and insulin sensitivity (using HOMA-index) were investigated. Also, the expression of insulinotropic genes (GLUT-2, GLUT-4, GLP-1, GIP, DPP-4) were quantified using reverse-transcriptase polymerase chain reaction (RT-PCR). A significant ($p < 0.05$) reduction in FBS was noted in diabetic rats treated with TTS at 10 mg/kg. Insulin concentrations significantly ($p < 0.05$) increased in all treated groups, notably in the group administered TTS at 40 mg/kg. In addition, insulin sensitivity significantly ($p < 0.05$) improved in the groups administered TTS at 10 and 40 mg/kg. A significant upregulation in the expression of insulin, GLUT-2, GLUT-4, GLP-1, and GIP genes were observed in the treated diabetic groups as well as the downregulation of DPP-4 gene. These results demonstrate that *T. tetraptera* saponins exert antidiabetic effects through multiple mechanisms, supporting their potential as a natural therapeutic agent, especially at lower doses of 10 mg/kg body weight.

Keywords: *Tetrapleura tetraptera, Saponins, Antidiabetic, Insulinotropic Genes*

INTRODUCTION

For decades, extensive research has been conducted to find effective therapies and potential cures for metabolic diseases. Despite rapid advances in technologies to improve the conventional treatment of these groups of diseases, there seems to be no end in sight for a permanent cure for them (Yedjou *et al.,* 2023). Diabetes mellitus (DM) is one of the most prevalent metabolic diseases, and it has emerged as one of the leading global causes of morbidity and mortality (Shidlovskaya and Navalkivska, 2020). With each passing decade, the global record of people living with diabetes shows a geometric progression (Shidlovskaya and Navalkivska, 2020). Diabetes is characterized either by insufficient insulin production from the pancreatic β-cells or by impaired cellular responsiveness to insulin (Pawan and Mathews, 2021).

Orthodox antidiabetic drugs, though effective, are often associated with serious side effects such as hypoglycemic coma, as well as liver and kidney disorders (Yedjou *et al.,* 2023). These adverse effects have led many patients to seek alternative remedies, with medicinal plants becoming a popular option due to their affordability and perceived safety (Frimpong *et al.,* 2024). Medicinal plants such as *Tetrapleura tetraptera* have long been recognized for their role in the management of diabetes (Yakubu *et al.,* 2015). They are rich in bioactive compounds, including saponins, flavonoids, alkaloids, phenolics, and tannins, that act as antihyperglycemic agents. These compounds have the potential to regulate fasting blood sugar levels, enhance insulin sensitivity, and modulate incretins and glucose transporters (Govindappa, 2015; Jacob and Narendhirakannan, 2019). Furthermore, triterpenoidal saponins in particular have also been found to improve

glucose uptake by tissues and promote pancreatic β-cell regeneration (Ogunlakin and Sonibare, 2024).

Previous studies have also documented the antidiabetic, antihyperlipidaemic, and antioxidant properties of the aqueous extract of *T. tetraptera* (Omonkhua *et al.,* 2014). The aqueous root bark extract of *T. tetraptera* has also been reported to contain saponins, as suggested by its ability to produce froth in water (Omonkhua *et al.,* 2014; Uyoh *et al.,* 2013). Although the precise antidiabetic mechanism(s) of *T. tetraptera* remain unclear, its phytochemical constituents especially saponins may contribute significantly to this effect. In the light of these observations, this study was designed to investigate the *in vivo* antidiabetic and insulinotropic effects of saponins extracted from the root bark of *T. tetraptera* in streptozotocin-induced diabetic Wistar rats using gene expression techniques.

MATERIALS AND METHODS

Plant collection and identification

Tetrapleura tetraptera was collected from Akungba-Akoko, Ondo State, South-Western Nigeria and was verified in the Department of Microbiology and Botany, University of Ibadan, Nigeria. Herbarium specimens was stored at the Herbarium of the University of Ibadan, Nigeria with herbarium number UIH22320. The plant material was washed thoroughly under running water, shade dried and then pulverized.

Extraction of saponins

Saponins were fractionated from *T. tetraptera* root bark by a method adapted from Hostettmann *et al.* (1991).

Animals and experimental protocol

Forty-two (42) adult male rats of the Wistar strain, with average weight of 120g, were purchased from the Faculty of Life Sciences, University of Benin, Edo State, Nigeria. The animals were kept in a well aerated room at the Animal House, Department of Anatomy, University of Benin, with 12h light and 12h dark cycles. They were fed twice a day (standard pelleted feed) and given clean water *ad libitum*.

Induction of diabetes and experimental grouping

Rats in groups 2 to 6 were injected (intraperitoneally) with streptozotocin (STZ) dissolved in citrate buffer (pH 4.5) at a dose of 65 mg/kg body weight after a 12-hour fast. Seven (7) days later, diabetes was confirmed by measuring fasting blood sugar (FBS). After stable diabetes was established (FBS > 180 mg/dl), treatments of experimental rats commenced and lasted for 12 weeks. Following the induction, animals-normal and streptozotocin-diabetic rats were divided into the following groups of seven (7) rats each: (1) normal control (untreated normal rats), (2) diabetic control (untreated diabetic rats), (3) positive control (diabetic rats treated with metformin), (4) diabetic rats treated with 10 mg/kg, (5) 20 mg/kg, and (6) 40 mg/kg body weight of TTS.

Preparation and administration of plant saponins

The freeze-dried *T. tetraptera* total saponins (TTS) fraction was reconstituted appropriately in distilled water. Different doses of TTS, and metformin at 100 mg/kg body weight, were administered orally (by *gavage*) daily for 12 weeks (3 months) of the study.

Biochemical investigations

The biochemical investigations carried out included fasting blood sugar (FBS), measured using the glucose oxidase method described by Barham and Trinder (1972); plasma insulin analysis, determined by enzyme-linked immunosorbent assay (ELISA) as described by Burgi *et al.* (1988); insulin resistance, assessed using the HOMA method described by Matthews *et al*. (1985); and gene expression analysis as described by Elekofehinti *et al.* (2018).

Isolation and purification of total RNA

The Trizol-preserved liver, kidney, ileum, muscle, and pancreatic tissues were homogenized in an Eppendorf tube using a plastic pestle to permit thorough exposure of the cell's nucleus. The homogenized tissues were partitioned using chloroform as a gradient separation medium. Isoamyl alcohol was added as a precipitating solution, after which the sample was treated with DNase (NEB) for 10 min before the RNA pellet was washed with ethanol to remove any DNA and phenol contamination, respectively. The DNase-free RNA was suspended in nuclease-free water. The purity was determined by measuring the absorbance at 260 and 280 nm, respectively (Oluyede *et al.,* 2021).

cDNA synthesis: polymerase chain reaction (PCR) and amplification of gene of interest

The total RNA was converted to complementary DNA (cDNA) using reverse transcriptase. After the synthesis of the cDNA, the genes of interest were amplified using a designed and optimized set of primers (**see Table 1**), which comprised forward and reverse primers. The PCR Master Mix catalyzes the amplification using a thermocycler (Eppendorf Mastercycler AG 22,331) Hamburg for 30 cycles. The GAPDH gene was used to normalize the relative level of expression of each gene (housekeeping gene) (forward primer AGACAGCCGCATCTTCTTGT, reverse primer CTTGCCGTGGGTAGAGTCAT).

Table 1. List of designed, optimized, and synthesized primers specific to each gene

Genes	Forward primer sequence	Reverse primer sequence
INSULIN	GTCCTCTGGGAGCCAAG	ACAGAGCCTCCACCAGG
GLUT-2	TAGTCAGATTGCTGGCCTCAGCTT	TTGCCCTGACTTCCTCTTCCAACT
GLUT-4	TTGCCCTTCTGTCCTGAGAG	CGCTCTCTTTCCAACTTCCG
GLP-1	TCCCAAAGGAGCTCCACCTG	TTCTCCTCCGTGTCTTGAGGG
GIP	GCTGGAACCGCATCATAGTG	GTTGGCAAATCTCAGCACC
DPP-4	GCAAGACGTGGGTAATGATG	AGCCTGGTTGGGTTTGTATG

Statistical analysis

The data were expressed as means of 4 to 7 determinations ± S.E.M. The differences among groups were analyzed by the one-way analysis of variance (ANOVA). Inter-group comparisons were done by Duncan's post hoc test. The value of $P < 0.05$ was accepted as significant. IBM SPSS Statistics, version 26 (IBM Corp., Armonk, N.Y., USA) was used for the analysis. Gene expression analysis was done using the ImageJ software. This software helped to estimate densitometrically the thickness of the bands from agarose gel electrophoresis, while Graphpad Prism 8.0.1 (San Diego California, USA) was used to plot the graph.

RESULTS

In Figure 1, all fasting blood sugar concentrations were within normal range at baseline (week 0). After injection of streptozotocin (STZ), the fasting blood sugar (FBS) of all groups (except normal control) rose above 200 mg/dl. At week 6, group 1 (normal control) remained within the normal range, while the fasting blood sugar concentration of *Tetrapleura tetraptera* Saponins (TTS) and metformin treated groups were generally lower than group 2 (diabetic control). Finally at week 12, the fasting blood sugar concentration of diabetic control group, metformin and TTS 20 mg/kg remained above 200 mg/dl, however, the fasting blood sugar concentration of 10 and 40 mg/kg TTS treated groups were reduced with 10 mg/kg body weight TTS treated group recording the lowest reduction at 168.33 mg/dl.

Figure 2A shows no statistical difference in insulin concentration in all the groups when compared to normal control. However, the result for HOMA index (Figure 2B) shows that normal control group had significantly reduced insulin resistance relative to diabetic control group. While there was no significant difference in the metformin and 20 mg/kg TTS treated groups, there were significant reductions in insulin resistance in the groups administered TTS at 10 and 40 mg/kg body weight, especially at 10 mg/kg body weight.

The effect of TTS on the gene expression of insulin is shown in Figure 3. The insulin expression was significantly up-regulated in diabetic control relative to normal control. While it was demonstrated that oral administration of all treated groups (metformin, TTS 10 mg/kg, TTS 20 mg/kg, and TTS 40 mg/kg) down-regulated the expression of insulin in comparison with diabetic control.

As shown in Figure 4A, there was significant up-regulation of glucagon-like peptide-1 expression in the diabetic control group relative to the normal control group. A significant up-regulation of the expression of glucagon-like peptide-1 was observed after oral administration of TTS (10 mg/kg, 20 mg/kg, and 40 mg/kg) and metformin-treated groups compared with diabetic control. TTS 10 mg/kg was observed to have up-regulated the expression of pancreatic glucagon-like peptide-1 the most. In Figure 4B, there was a significant up-regulation of gastric inhibitory polypeptide expression in diabetic control compared to normal control. Oral administration of metformin and TTS (10 mg/kg, 20 mg/kg and 40 mg/kg), significantly up-regulated the expression of gastric inhibitory polypeptide in a dose-dependent manner relative to diabetic control.

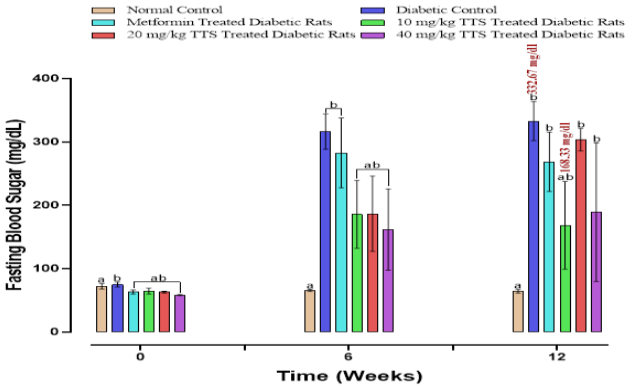

Figure 1. Effect of *Tetrapleura tetraptera* Saponins (TTS) on Fasting Blood Sugar (FBS) of STZ-Induced Diabetic Rats

Data are Means of 4-7 Determinations ± SEM. Error bars, which were less than 15% of the Mean Values, were omitted for clarity. Values Carrying Different Letters are Statistically Different at $p < 0.05$.

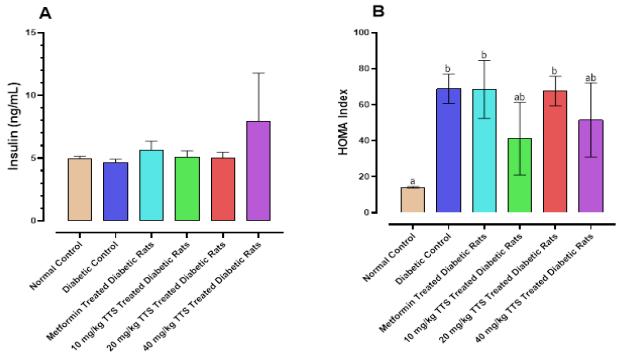

Figure 2. Effect of *Tetrapleura tetraptera* Saponins (TTS) on Insulin Concentration (A) and Homeostasis Model Assessment (HOMA) (B) of STZ-Induced Diabetic Rats

Data are Means of 4-7 Determinations ± SEM. Error Bars were less than 15% of Mean Values and are omitted for Lucidity. Values Carrying Different Letters are Statistically Different at $p < 0.05$.

As shown in Figure 5A, there was a significant up-regulation of ileum glucagon-like peptide-1 expression in diabetic control group compared to normal control group. A significant up-regulation of the expression of glucagon-like peptide-1 was observed after oral administration of metformin when compared with diabetic control. While TTS (20 mg/kg and 40 mg/kg) after oral administration significantly downregulated this gene when compared with diabetic control. However, there was no significant difference in the relative expression of glucagon-like peptide-1 from the group administered 10 mg/kg TTS compared to diabetic control. In Figure 5B, the gene expression of ileum gastric inhibitory polypeptide was significantly down-regulated in diabetic control compared to normal control. It was shown that there was significant up-regulation upon oral administration of metformin and TTS (10 mg/kg, and 20 mg/kg) treated groups when compared to diabetic control. The 40 mg/kg body weight treated group had gastric

inhibitory polypeptide levels that were similar to diabetic control treated group.

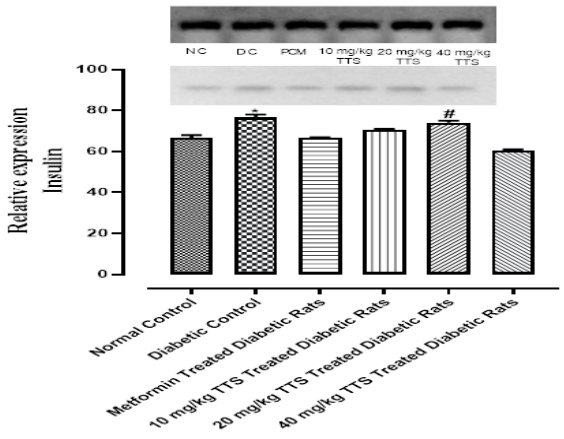

Figure 3. Effect of *Tetrapleura tetraptera* Saponins on Insulin Expression in the Pancreas of Streptozotocin (STZ) Induced Diabetic Wistar Rats

*Represent p < 0.05 to Normal Control and # Represent p < 0.05 to Diabetic Control. NC= Normal Control, DC= Diabetic Control, PCM= Positive Control (Metformin), TTS= *Tetrapleura tetraptera* Saponins

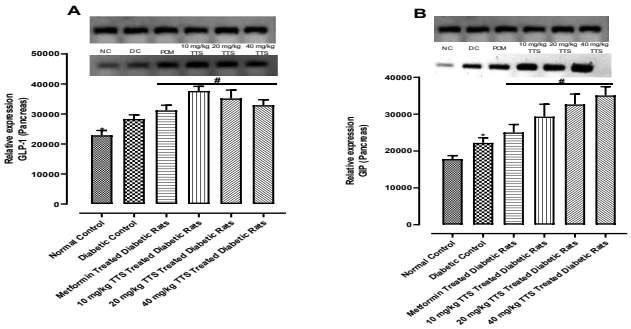

Figure 4. Effect of *Tetrapleura tetraptera* Saponins on Glucagon-like Peptide-1 (GLP-1) and Gastric Inhibitory Polypeptide (GIP) Expression in the Pancreas of Streptozotocin (STZ) Induced Diabetic Wistar Rats

* Represent p < 0.05 to Normal Control and # Represent p < 0.05 to Diabetic Control. NC= Normal Control, DC= Diabetic Control, PCM= Positive Control (Metformin), TTS= *Tetrapleura tetraptera* Saponins

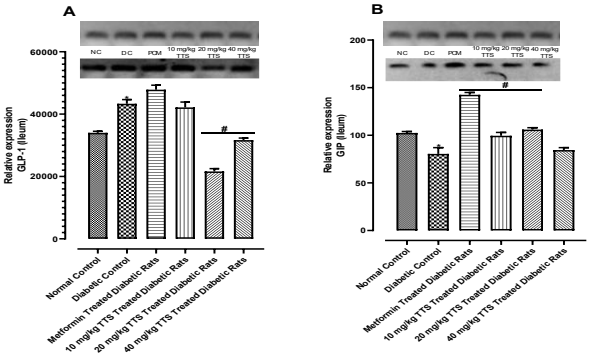

Figure 5. Effect of *Tetrapleura tetraptera* Saponins on Glucagon-like Peptide-1 (GLP-1) and Gastric Inhibitory Polypeptide (GIP) Expression in the Ileum of Streptozotocin (STZ) Induced Diabetic Wistar rats

* Represent p < 0.05 to Normal Control and # Represent p < 0.05 to Diabetic Control. NC= Normal Control, DC= Diabetic Control, PCM= Positive Control (Metformin), TTS= *Tetrapleura tetraptera* Saponins

Compared to the control group, there was significant (p < 0.05) down-regulation of DPP-4 gene expression in diabetic control group. It was demonstrated that there was a significant up-regulation of DPP-4 gene expression after oral administration of TTS (10 mg/kg) relative to diabetic control (Figure 6). However, oral administration of TTS at doses of 20 mg/kg and 40 mg/kg significantly down-regulated the gene expression of DPP-4 when compared with diabetic control, especially TTS at 40 mg/kg.

In the pancreas, GLUT-2 expression was statistically similar in diabetic control when compared with normal control. There was also no significant difference in the relative expression of GLUT-2 in the 40mg/kg of TTS treated group when compared to diabetic control group. However, the groups administered metformin, 10 mg/kg and 20mg/kg of TTS significantly up-regulated the expression of GLUT-2 in comparison with diabetic control, especially the 10 mg/kg and 20mg/kg of TTS treated groups (Figure 7A). In the kidney, GLUT-2 expression was significantly up-regulated in diabetic control relative to normal control. While it was demonstrated that oral administration of metformin significantly up-regulated the expression of GLUT-2 in comparison with diabetic control, oral administration of TTS (10 mg/kg, 20 mg/kg and 40 mg/kg), significantly down-regulated the expression of GLUT-2 in comparison with diabetic control (Figure 7B).

There was significant down-regulation of GLUT-4 expression in diabetic control relative to normal control (Figure 8). Relative to diabetic control, oral administration of metformin and TTS at 20mg/kg and 40mg/kg significantly down-regulated GLUT-4 expression, however, TTS at 10 mg/kg body weight had a significantly up-regulation expression of GLUT-4 when compared with diabetic control.

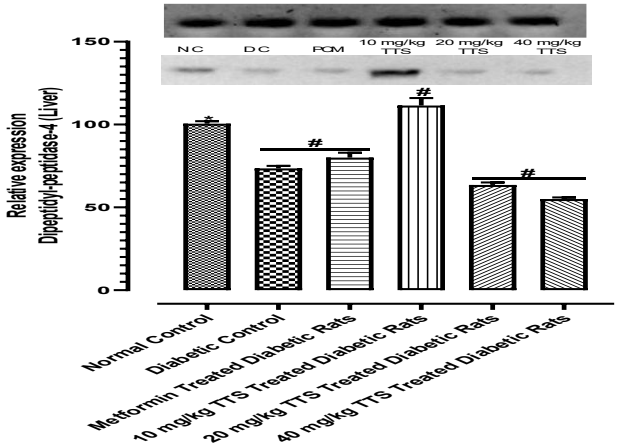

Figure 6. Effect of *Tetrapleura tetraptera* Saponins on Dipeptidyl-peptidase-4 (DPP-4) Expression in the Liver of Streptozotocin (STZ) Induced Diabetic Wistar rats

* Represent p < 0.05 to Normal Control and # Represent p < 0.05 to Diabetic Control. NC= Normal Control, DC= Diabetic Control, PCM= Positive Control (Metformin), TTS= *Tetrapleura tetraptera* Saponins

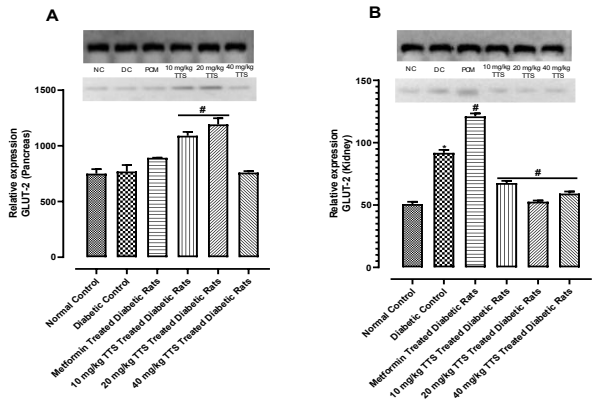

Figure 7. Effect of *Tetrapleura tetraptera* Saponins on Glucose Transporter 2 (GLUT-2) Expression in the Pancreas and Kidney of Streptozotocin (STZ) Induced Diabetic Wistar rats

* Represent $p < 0.05$ to Normal Control and # Represent $p < 0.05$ to Diabetic Control. NC= Normal Control, DC= Diabetic Control, PCM= Positive Control (Metformin), TTS= *Tetrapleura tetraptera* Saponins

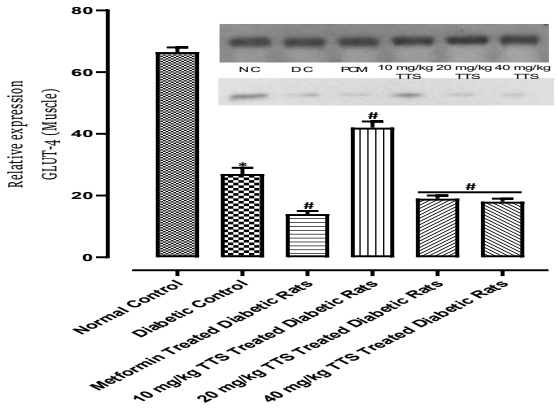

Figure 8. Effect of *Tetrapleura tetraptera* Saponins on Glucose Transporter 4 (GLUT-4) Expression in the Muscle of Streptozotocin (STZ) Induced Diabetic Wistar rats

* Represent $p < 0.05$ to Normal Control and # Represent $p < 0.05$ to Diabetic Control. NC= Normal Control, DC= Diabetic Control, PCM= Positive Control (Metformin), TTS= *Tetrapleura tetraptera* Saponins

DISCUSSION

Diabetes mellitus is a chronic endocrine disorder characterized by persistent hyperglycemia resulting from either absolute or relative insulin deficiency (Pawan and Mathews, 2021). Although treatment strategies have advanced significantly, conventional antidiabetic drugs are often associated with severe side effects such as hypoglycemic coma, hepatic impairment, and renal toxicity, which limit their long-term effectiveness and patient compliance (Yedjou *et al.,* 2023). Consequently, there has been increasing interest in medicinal plants and their bioactive constituents as safer and more affordable alternatives (Frimpong *et al.,* 2024). Among these bioactive compounds are saponins. Saponins are naturally occurring bioactive agents that have been reported to possess antidiabetic activity due to their rich antioxidant potential (Elekofehinti, 2015).

The present study evaluated the antidiabetic potential of *Tetrapleura tetraptera* saponins (TTS) and demonstrated multiple mechanisms through which TTS exerts medicinal effects. At a dosage of 10 mg/kg, TTS significantly reduced fasting blood sugar to 168.33 mg/dl compared to 332.67 mg/dl in the untreated diabetic control, thereby confirming its hypoglycemic activity (Atawodi *et al.,* 2014). In addition, while serum insulin concentration did not differ significantly among groups, the metformin-treated group and the 40 mg/kg TTS treatment enhanced insulin secretion, suggesting possible insulinomimetic or insulin secretagogue properties (Kibiti and Afolayan, 2015). Importantly, the assessment of insulin sensitivity using the HOMA-IR index revealed improved insulin utilization in the 10 and 40 mg/kg TTS-treated groups compared with metformin and untreated diabetic controls. This suggests that TTS not only promotes insulin production but also enhances insulin sensitivity. These observations align with earlier findings that certain herbal medicines can restore β-cell function (Wickramasinghe *et al.,* 2021). Kuate *et al.,* (2015) also reported the effect of *T. tetraptera* spice on insulin resistance using the HOMA index.

Incretins play a central role in glucose regulation by stimulating insulin release and suppressing glucagon activity (Campbell and Drucker, 2013; Grunberger, 2013). In this study, TTS treatments (10, 20, and 40 mg/kg) significantly upregulated glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP) expressions in the pancreas in a dose-dependent manner, thereby enhancing their insulinotropic effect. Comparable effects have been reported for several medicinal plants, including *Berberis vulgaris, Magnifera indica, Glycine max, Cinnamomum zeylanicum, Pinus koraiensis,* and *Prunus Africana*, which similarly augment incretin activity (Singh *et al.,* 2015). The upregulation of GLP-1 and GIP in the ileum, particularly at 10 and 20 mg/kg TTS and metformin, further demonstrates the ability of these agents to stimulate the gut-pancreas axis and promote glucose clearance. Singh *et al.,* (2015) reported that medicinal plants such as *Mangifera indica* enhanced incretin activity (GLP-1 and GIP), while Cho and Kieffer, (2011) demonstrated that metformin also exerts insulinotropic effects by increasing the expression of these incretins. Another key mechanism observed was the downregulation of dipeptidyl-peptidase-4 (DPP-4), an enzyme responsible for incretin degradation (Deacon, 2020). DPP-4 inhibitors help control blood sugar by boosting incretin levels, which promote insulin release and lower glucagon, improving glucose balance without added risk of hypoglycemia or weight gain (Ahrén, 2019). TTS at 20 and 40 mg/kg significantly reduced DPP-4 expression, thereby prolonging incretin activity and enhancing glycemic control. Similar effects have been reported with other medicinal plants such as *Anogeissus latifolia*, which inhibits DPP-4 activity to improve glucose homeostasis (Ansari *et al.,* 2021).

Glucose transporters (GLUTs) were also modulated by TTS treatment in this study. In the pancreas, upregulation of GLUT-2 in the 10 and 20 mg/kg TTS-treated groups suggests enhanced glucose sensing by β-cells, thereby stimulating

insulin secretion. Interestingly, in the kidney, TTS treatment downregulated GLUT-2 expression compared with diabetic control, indicating a potential nephroprotective effect by limiting glucose influx into renal cells, a key factor in diabetic nephropathy (Xu *et al.,* 2005). Nasri and Rafieian, (2014) reported that medicinal plants such as *Sclerocarya birrea*, *Persea americana*, *Ficus thonningii*, and *Helichrysium ceres* exhibit nephroprotective effects by suppressing hyperglycemia. In skeletal muscle, TTS at 10 mg/kg upregulated GLUT-4 expression, facilitating glucose uptake and storage, which further supports its antidiabetic action. Similar findings have been reported for other saponin-containing plants, where GLUT-4 modulation improved glycemic control (Elekofehinti *et al.,* 2014).

Overall, these findings suggest that *T. tetraptera* saponins (TTS) exert antidiabetic effects through multiple complementary mechanisms: (i) reducing hyperglycemia, (ii) enhancing insulin secretion and sensitivity, (iii) promoting β-cell regeneration, (iv) stimulating incretin activity, (v) inhibiting DPP-4 degradation, and (vi) regulating glucose transporter expression across tissues. These multi-targeted actions provide a strong pharmacological rationale for the use of TTS as a natural therapeutic option in diabetes management, particularly type 2 diabetes.

CONCLUSION

This study shows the pharmacological anti-diabetic potential of *T. tetraptera* saponins via various mechanisms of action, such as the ability of *T. tetraptera* saponins to reduce fasting blood sugar levels, as insulin secretagogues, as well as increasing insulin sensitivity. Its medicinal effects were also observed from gene expression via the significant increases in the expression of insulin, incretins (GLP-1 and GIP), and glucose transporters (GLUT-2 and GLUT-4), and the relative decrease in DDP-4 (incretin inhibitor) expression. The observable antidiabetic effects of *T. tetraptera* saponins through various mechanisms of action strongly suggest that this plant should be explored for its pharmacological health benefits, especially at a lower dose of 10 mg/kg body weight.

AUTHORS' CONTRIBUTIONS

Conceptualization, AAO; methodology, AAO; validation, AAO and AEE; formal analysis, AEE; investigation, AAO and AEE; resources, AAO and AEE; data curation, AEE; writing—original draft preparation, AEE; writing—review and editing, AAO; supervision, AAO; project administration, AAO; funding acquisition, AAO. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper.

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