ISSN: 2573-9573

Research Article

Journal of Ophthalmology & Clinical Research

Molecular Modulation of Incretin System, Glucose Transport Pathway and Inflammatory Cytokine by *Sphenostylis stenocarpa–Ficus exasperata* Fortified Biscuits in Diabetic Rats

Sidiqat A. Shodehinde[1,2], Olamide V. Awelewa[1,2], Lateef Bello[1,2*], Victor O. Awojulu[1,2], Daniel O. Nwankwo[1], Basit K. Dauda[1], Peace O. Onikoro[1], Bamidele Ogunleye[1], Oluwafemi A. Orosun[1], Precious O. Ibitolu[1] and Simbiat O. Olatunde[1]

[1]*Department of Biochemistry, Faculty of Science, Adekunle Ajasin University, Akungba-Akoko, Ondo, Nigeria*

[2]*Phyto-Fakts Laboratory, Akungba-Akoko, Ondo, Nigeria*

***Corresponding Author**
Lateef Bello, Department of Biochemistry, Faculty of Science, Adekunle Ajasin University, Akungba-Akoko, Ondo, Nigeria.

Submitted: 2025, Oct 24; **Accepted:** 2025, Nov 14; **Published:** 2025, Nov 24

Citation: Shodehinde, S.A., Awelewa, O. V., Bello, L., Awojulu, O.V., Nwankwo, D. O., Dauda, B. K., Onikoro, P.O., Ogunleye, B., Orosun, O. A., Ibitolu, P. O and Olatunde, S.O. (2025). Molecular Modulation of Incretin System,Glucose Transport Pathway and Inflammatory Cytokine by Sphenostylis stenocarpa–Ficus exasperata FortifiedBiscuits in Diabetic Rats. *J ophthalmol Clin Res, 9*(2), 01-09.

Conflict of Interest: The authors confirm that there are no relevant conflicts of interest associated with this manuscript.

Abstract

Introduction/Background of the study: *Diabetes mellitus is characterized by chronic hyperglycemia and inflammation, involving disruptions in incretin hormones, glucose transport, and inflammatory cytokines. Functional foods fortified with bioactive plants offer potential complementary therapies. This study investigates the molecular modulation effects of biscuits fortified with varying proportions of Sphenostylis stenocarpa and Ficus exasperata on key diabetes-related biomarkers in streptozotocin-induced diabetic rats.*

Materials and Methods: *Biscuits were prepared with reciprocal ratios of Ficus exasperata leaf (fermented and unfermented) and Sphenostylis stenocarpa flour. Diabetic rats were administered fortified biscuits for 14 days. Pancreatic tissues were analyzed for gene expression of GLP-1, DPP-4, GLUT-4, and IL-6 via RT-PCR. Statistical analysis was performed using ANOVA with significance set at $p<0.05$.*

Results: *Fortification with 20g Ficus exasperata and 40g Sphenostylis stenocarpa significantly upregulated GLP-1 gene expression, enhancing incretin signaling. Higher Ficus exasperata doses (40g) downregulated DPP-4 and IL-6 genes expression. While fermented Ficus exasperata biscuits improved insulin-stimulated glucose transport via upregulation of GLUT-4 gene expression at both doses, the unfermented formulations showed superior upregulation of GLP-1 gene expression, anti-inflammatory and DPP-4 inhibitory effects.*

Conclusion: *S. stenocarpa–F. exasperata fortified biscuits positively modulate molecular pathways implicated in diabetes, improving glycemic control and attenuating inflammation. These functional biscuits hold promise as adjunct dietary interventions for diabetes management. Further studies are warranted to explore bioactive profiles and clinical efficacy.*

1. Introduction

Elevated blood glucose levels brought on by either insufficient or ineffective insulin are the hallmark of diabetes mellitus (DM), a metabolic disorder. The release of insulin and function are influenced by a variety of factors, such as genetics, lifestyle choices, and inheritance and epigenetic predisposition [1]. In this study, we investigated the modulatory effects of functional biscuits on key biomarker including the glucagon-like peptides (GLP-1), Dipeptidyl peptidase-4 (DPP-4), Glucose transporter type 4 (GLUT4) and interleukin-6 (IL-6) involved in diabetes progression.

The incretin hormone family includes the glucagon-like peptides GLP-1 and GLP-2, as well as the glucose-dependent insulinotropic polypeptide (GIP) [2]. These incretin hormones are secreted from the gut in response to nutrient intake and enhance insulin secretion in a glucose-dependent manner, helping to lower postprandial blood glucose levels. In addition, GLP-1 has cardioprotective properties, inhibits glucagon secretion, slows stomach emptying, and increases satiety. GIP is involved in lipid metabolism and mainly increases the release of insulin. These hormones are important targets in the treatment of type 2 diabetes because they collectively regulate energy balance and glucose homeostasis [3]. GLP-1 and GIP are inactivated by DPP-4, an enzyme prevalent in the bloodstream and on various cell types. DPP-4 inhibitors can increase active levels of GLP-1 and GIP by two to three times post-meal by preventing DPP-4 from functioning [4].

Glucose transporter type 4 (GLUT4) is essential for glucose uptake from the bloodstream, predominantly found in skeletal muscle and adipose tissue [5,6,7]. Its decreased expression is linked to elevated blood glucose levels, insulin resistance, and diabetes onset [8]. Additionally, interleukin-6 (IL-6), a pro-inflammatory cytokine, plays a significant role in diabetes mellitus (DM) [9]. Increased expression of IL-6 was previously linked to inflammation, glucose intolerance, insulin resistance, and the development of type 2 diabetes (T2DM), establishing it as a risk factor for insulin resistance and T2DM [10].

The rise in diabetes mellitus cases has prompted significant research into natural products as possible alternative therapies. *Ficus exasperata* commonly known as the "SANDPAPER LEAF," a species belonging to the Moraceae family that is widely distributed in tropical and subtropical regions, including Africa and Asia, where it has been traditionally utilized for various therapeutic purposes, have been reported to possesses significant antioxidant and antidiabetic activities, mediated through restoration of thiol defenses, reduction of oxidative stress, and modulation of insulin signaling genes [11-13]. *Ficus exasperata* leaf extract contains bioactive compounds including caffeic, ferulic, tannic acids, apigenin, naringenin attributed to its wide range of pharmacological activities including antiulcer, hypotensive, hypoglycemic, anti-inflammatory, antimicrobial, and insecticidal properties [14]. *Sphenostylis stenocarpa*, an underutilized legume, native to West and Central Africa have been reported to possess antioxidant, antihyperglycemic, hypolipidemic activities, nutrient-rich tubers and seeds with a low glycemic index [15-17]. Its high protein, dietary fiber, and slow-digesting carbohydrates make it suitable for functional foods aimed at managing blood glucose levels.

Wheat is a widely consumed staple grain known for its low cost and eases of access, primarily used in baked goods. However, its consumption has become problematic due to associated nutritional disorders, with approximately 0.35% to 1% of the population suffering from celiac disease and about 1–3% affected by other gluten disorders and other autoimmune disorders such as type 1 diabetes and inflammatory bowel [18-20]. African yam bean is gluten-free, making it suitable for those with gluten intolerance or celiac disease. While extensive studies have documented the individual hypoglycemic and vast array of pharmacological activities of *Sphenostylis stenocarpa* and Ficus exasperata, however, no previous research has examined the synergistic potential of combining these two botanicals into a functional food format on diabetes management. Replacing part of the wheat flour in biscuits with African yam bean flour and fortifying them with *Ficus exasperata* leaves could enhance nutritional quality and provides therapeutic benefits, offering a novel dietary approach for managing diabetes. This study evaluates the molecular effects of S. stenocarpa- and F. exasperata-fortified biscuits on GLP-1, DPP-4, GLUT-4 and IL-6 genes expression in STZ-induced diabetic rats. While focusing on evaluating the modulatory effect of fortified biscuits, the study also recognize the need for future investigations comparing the bioactive profiles of *Sphenostylis stenocarpa* enriched biscuits fortified with fermented or unfermented *Ficus exasperata* leaf.

2. Materials and Methods

2.1. Collection of Plant Samples

The leaves of *Ficus exasperata* was obtained from Akungba Akoko and the raw ingredients required for biscuit formulation and *Sphenostylis stenocarpa* bean seed were purchased at Osele market in Ikare Akoko, Ondo State, Nigeria [7.5248 ºN, 5.7669 ºE]. The plants were identified and authenticated in the herbarium of Plant Science and Biotechnology Department, Adekunle Ajasin University, Akungba Akoko and voucher specimens were deposited for further references.

2.2. Preparation of plant samples

Ficus exasperata Leaf Powder was prepared according to the method described by Shodehinde et al. (2025) as reported by Bello et al. (2025) [12,14]. Preparation of *Ficus exasperata* Leaf Powder involved washing fresh leaves with potable water, shading them to drain, and then fermenting some wrapped in plantain leaves while air-drying others for three weeks. Both fermented and unfermented samples were pulverized, sieved for uniformity, and stored in airtight containers for biscuit fortification. *Sphenostylis stenocarpa* (African Yam Bean) mature seeds were sorted, rinsed, dried, and milled into fine flour, which was also stored in airtight containers for biscuit formulation.

2.3. Preparation of Functional Biscuits

INREDIENTS	CONTROL	*Ficus*	*exasperata*		
		FERMENTED	FERMENTED	UNFERMENTED	UNFERMENTED
PLANT SAMPLE (g)	-	20	40	20	40
WHEAT FLOUR (g)	200	140	140	140	140
AYB (g)	-	40	20	40	20
SUGAR (g)	60	-	-	-	-
SUGAR CANE (g)	-	60	60	60	60
FAT (g)	40	40	40	40	40
SALT (g)	2	2	2	2	2
VANILA (g)	1	1	1	1	1
WATER (mL)	65	65	65	65	65
GMS					
(EULSIFIER)(mg)	-	0.5	0.5	0.5	0.5

Table 1: Composition of dough with varying proportions of ingredients for preparation of Stephnostylis stenocarpa- Ficus exasperate fortified biscuits

2.4. Animal Handling
Twenty eight rats (28) weighing 100-150g from the Department of Animal and Health Production, Federal University of Technology Akure were acclimatized for two weeks and place on ad libitum on a commercial diet. The handling of animals was carried out in accordance with the recommended international standard.

2.5. Experimental Design and Induction of Diabetes
The experiment was conducted with 4 rats per experimental group to assess the potential of biscuits fortified with *Ficus exasperata* and *Stephnostylis stenocarpa* flours on incretin system, glucose transport pathway and inflammatory cytokine in STZ-induced diabetic rats. The animals were subjected to the overnight fast before induction of diabetes. Freshly prepared streptozotocin (STZ) in citrate buffer (0.1 M, pH 4.5) was administered intraperitoneally at a single dose of 60 mg/kg body weight except the normal control group which receives citrate buffer. After 72 hours glucose test was conducted on animals to ascertain high glucose in the blood. Animals with blood glucose >250 mg/dL were considered diabetic.
Group 1: Received 1 citrate buffer (0.1 M, pH 4.5)
Group 2: DM + 500mg/kg Metformin
Group 3: DM + No Treatment
Group 4: DM + *Stephnostylis stenocarpa*-20g fermented *Ficus exasperata* biscuits (20g FFE BIS)
Group 5: DM + *Stephnostylis stenocarpa*-40g fermented *Ficus exasperata* biscuits (40g FFE BIS)
Group 6: DM + *Stephnostylis stenocarpa*-20g unfermented *Ficus exasperata* biscuits (20g UFFE BIS)
Group 7: DM + *Stephnostylis stenocarpa*-40g unfermented *Ficus exasperata* biscuits (40g UFFE BIS).

2.6. Gene expression study
2.6.1. Isolation of total RNA
At the end of 14 days, the rats were sacrificed by cervical dislocation. Total RNA was isolated from the pancreas tissues with Quick-RNA MiniPrep™ Kit (Zymo Research). The DNA contaminant was removed following DNAse I (NEB, Cat: M0303S) treatment. The RNA was quantified at 260 nm and the purity confirmed at 260 nm and 280 nm using A&E Spectrophotometer (A&E Lab. UK).

2.6.2. cDNA Conversion
One (1 μg) of DNA-free RNA was converted to cDNA by reverse transcriptase reaction with the aid of cDNA synthesis kit based on ProtoScript II first-strand technology (New England BioLabs) in a condition of 3-step reaction: 65 °C for 5 min, 42 °C for 1 h, and 80 °C for 5 min [21].

2.6.3. PCR amplification and agarose gel electrophoresis
Polymerase chain reaction (PCR) for the amplification of genes of interest, dipeptidyl peptidase 4 (DPP-4), glucagon-like peptide (GLP-1), Glucose transporter 4 (GLUT-4) and Interleukin 6 (IL-6) were carried out with OneTaqR2X Master Mix (NEB) using the following primers (Inqaba Biotec, Hatfield, South Africa). PCR amplification was performed in a total of 25 µl volume reaction mixture containing cDNA, primer (forward and reverse) and Ready Mix Taq PCR master mix. Under the following condition: Initial denaturation at 95°C for 5 min, followed by 30 cycles of amplification (denaturation at 95°C for 30 s, annealing for 30 s and extension at 72°C for 60 s) and ending with final extension at 72°C for 10 min. The amplicons were resolved on 1.0% agarose gel. The GAPDH gene was used to normalize the relative level of expression of each gene, and quantification of band intensity was done using "image J" software [22].

2.6.4. Statistical Analysis
GraphPad Prism was used for the statistical analysis, statistical significance was evaluated using one way analysis of variance (ANOVA), followed by Turkey's multiple range tests to compare

the means. Data points correspond to the mean of independent experiments and error bars (S.E.M); the level of significance was set at p<0.05.

3. Results

The gene expression analysis provided important insights into the antidiabetic and modulatory potential of the functional biscuits. Functional biscuits significantly upregulated and downregulated GLP-1 and DPP-4 genes expression respectively compared to diabetic controls (Figure 1 and Figure 2), suggesting enhanced incretin activity promoting insulin secretion, glucose regulation and improved glucose homeostasis. The substantially downregulation of DPP-4 gene expression indicates a decreased inactivation of incretin hormones (GLP-1). IL-6 is linked to insulin resistance and chronic inflammation in diabetes, its downregulation (Figure 3) reflects mitigation of disease progression. The observed upregulation in GLUT-4 gene expression indicates enhanced glucose uptake which is critical for lowering blood glucose levels and improving insulin sensitivity (Figure 4). The variation in gene expression correlated with biscuit formulations as shown in Table 1, where ratios of *Sphenostylis stenocarpa* and *Ficus exasperata* (20:40, 40:20) and fermentation of Ficus leaves affected the magnitude of molecular changes, suggesting dose-dependent and bioactive compound availability effects.

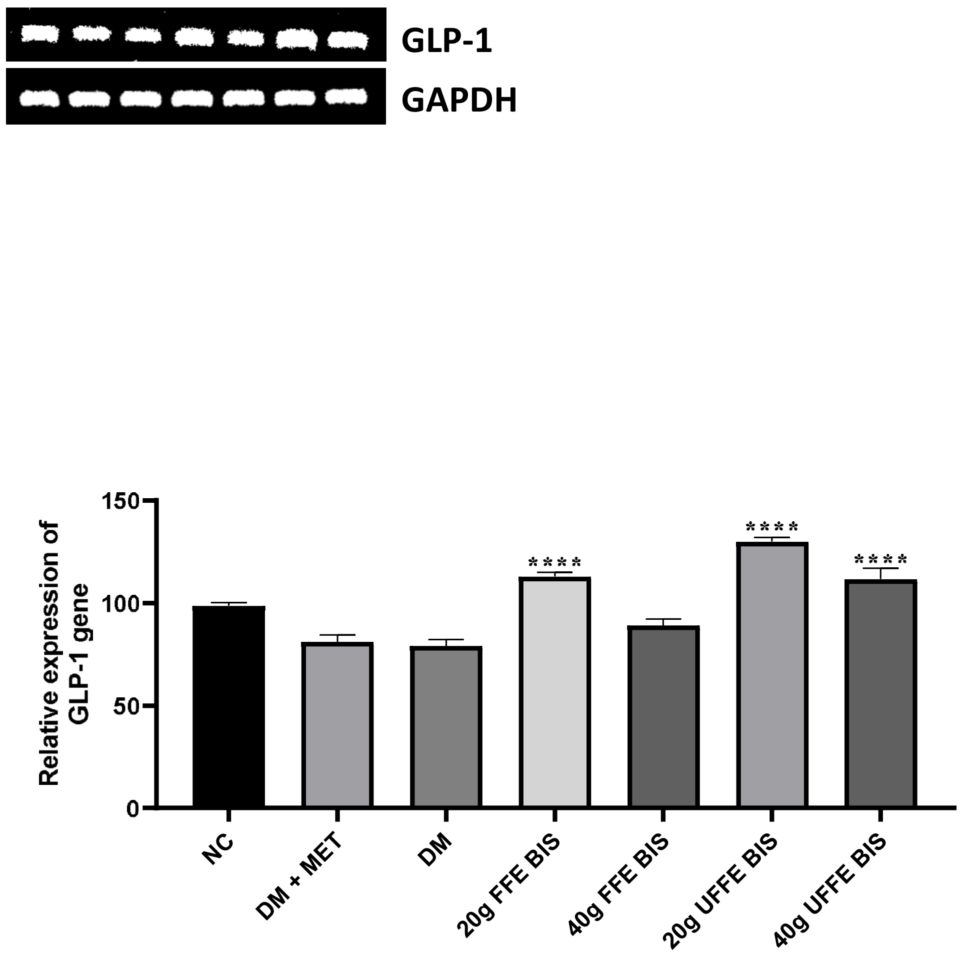

Figure 1: Effect of *Sphenostylis stenocarpa* Biscuit fortified with *Ficus exasperata* on Gene expression of Glucagon-Like Peptide-1 (GLP-1).

Bars are represented in mean ± SEM (n = 4). Values are significantly different ****p < 0.0001 compared to DM. FFE: *Fermented Ficus* exasperata, UFFE: Unfermented *Ficus exasperata*, BIS: Biscuit, NC: Normal Control, DM: Diabetes Mellitus, MET: Metformin.

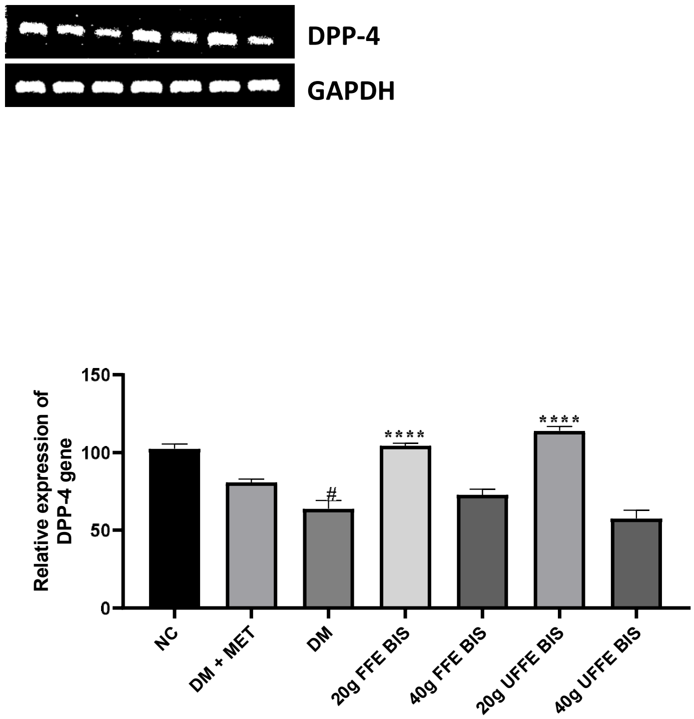

Figure 2: Effect of *Sphenostylis stenocarpa* Biscuit fortified with *Ficus exasperata* on Gene expression of Dipeptidyl peptidase-4 (DPP-4).

Bars are represented in mean ± SEM (n= 4). Values are significantly different ****p<0.0001 compared to DM, #p<0.05 compared to DM+MET. FFE: *Fermented Ficus* exasperata, UFFE: Unfermented *Ficus exasperata*, BIS: Biscuit, NC: Normal Control, DM: Diabetes Mellitus, MET: Metformin.

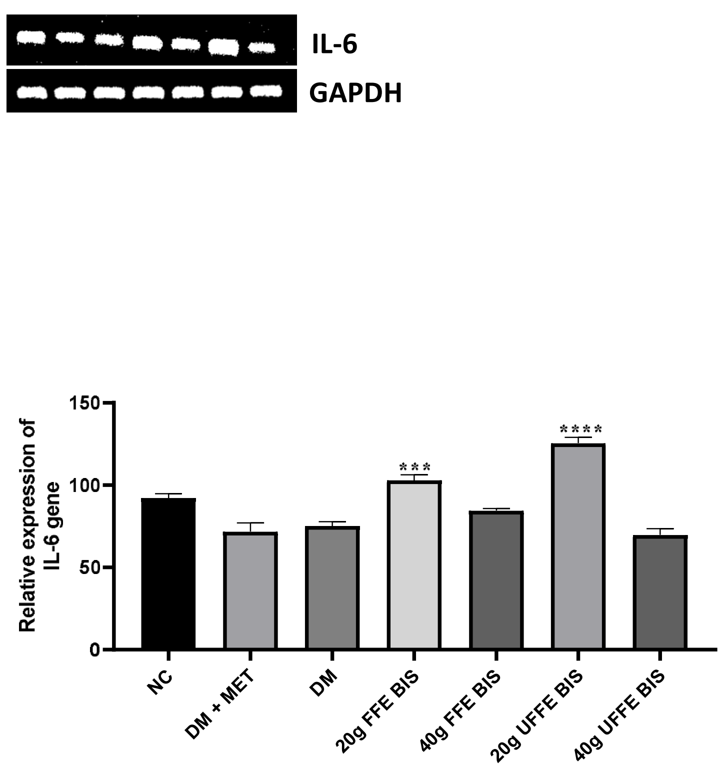

Figure 3: Effect of *Sphenostylis stenocarpa* Biscuit fortified with *Ficus exasperata* on Gene expression of Interleukin-6 (IL-6)

Bars are represented in mean ± SEM (n= 4). Values are significantly different ***p<0.05, ****p<0.0001 compared to DM. FFE: Fermented *Ficus exasperata*, UFFE: Unfermented *Ficus exasperata*, BIS: Biscuit, NC: Normal Control, DM: Diabetes Mellitus, MET: Metformin.

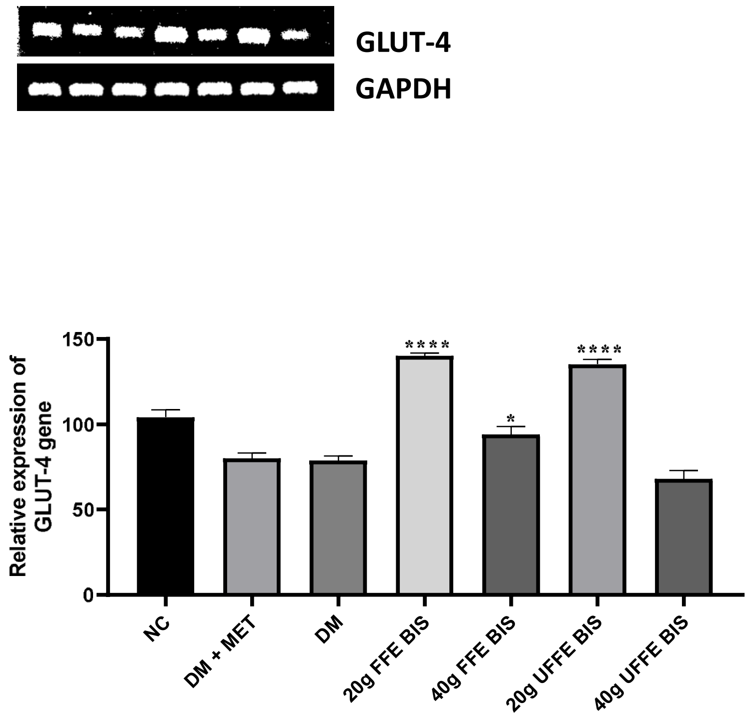

Figure 4: Effect of *Sphenostylis stenocarpa* Biscuit fortified with *Ficus exasperata* on Gene expression of Glucose Transporter 4 (GLUT-4).

Bars are represented in mean ± SEM (n= 4). Values are significantly different *p<0.05, ****p<0.0001 compared to DM. FFE: Fermented *Ficus exasperata*, UFFE: Unfermented *Ficus exasperata*, BIS: Biscuit, NC: Normal Control, DM: Diabetes Mellitus, MET: Metformin.

4. Discussion

This study investigated the molecular modulation effects of biscuits fortified with varying proportions of *Sphenostylis stenocarpa* and *Ficus exasperata* on key diabetes-related biomarkers in streptozotocin-induced diabetic rats. The biomarkers studied, including incretin hormones (GLP-1, DPP-4), glucose transporter (GLUT-4), and inflammatory cytokine (IL-6), are pivotal in the pathophysiology of diabetes mellitus and its complications. The results obtained from this study have provided valuable insights into the therapeutic efficacy of *Sphenostylis stenocarpa* and Ficus exasperata, as well as the role of functional foods in regulating glucose levels and ameliorating common diseases associated with metabolic dysregulation.

Through the PI3K/Akt pathway, GLP-1 not only increases the release of insulin but also improves the responsiveness of pancreatic β-cells to insulin, boosting insulin signal transduction and raising peripheral tissue sensitivity [23,24]. Thus, as observed in Figure 1, the rise and upregulation of GLP-1 gene expression is expected to improve glycemic control and β-cell health. Native GLP-1 is rapidly inactivated by DPP-4, giving it a plasma half-life of ~1–2 minutes; that's why either raising GLP-1 or inhibiting DPP-4 is mainstream strategies. DPP-4 is the key enzyme that inactivates GLP-1 and GIP, limiting their insulinotropic effects [25]. The result (Figure 2) from this study show lower DPP-4 gene expression in biscuit-treated groups which implies prolonged endogenous GLP-1 action and better post-prandial insulin responses. This is consistent with foundational and clinical literature on DPP-4 biology and incretin pharmacology [26].

Diabetes is driven by chronic low-grade inflammation; IL-6 is a consistent predictor and mediator of insulin resistance and T2D risk. As shown in Figure 3, the downregulation of IL-6 gene expression following treatment with the fortified biscuits indicates attenuation of inflammatory tone, which helps preserve β-cell function and insulin signaling. Researchers have linked the pro-inflammatory cytokine interleukin-6 (IL-6) to the progression of diabetes nephropathy (DN), observing elevated levels in DN patients compared to those without DN [24]. GLUT-4 is the key insulin-responsive transporter that translocate to the membrane in muscle and adipose tissue to clear blood glucose. Restoration/upregulation of GLUT-4 gene expression, as shown in Figure 4, is a canonical molecular sign of improved insulin sensitivity and trafficking. Recent overviews of GLUT-4 biology and insulin signaling confirm that increasing GLUT-4 availability/trafficking is central to improving whole-body glucose disposal [27].

Taken together, the molecular changes observed upregulated GLP-1, GLUT-4 and downregulated DPP-4, IL-6 indicates that fortified biscuits improved glycemic regulation through multiple pathways. These directions map neatly onto established diabetes biology: higher GLP-1 with lower DPP-4 sustains incretin signaling; higher GLUT-4 supports insulin-stimulated glucose uptake; lower IL-6 indicates attenuated low-grade inflammation. The significant increase in GLP-1 gene expression observed with 20g fortification of *Ficus exasperata* and 40g *Sphenostylis stenocarpa* (Table 1) highlights the potential of this formulation to enhance incretin activity. GLP-1 plays a critical role in glucose homeostasis by stimulating glucose-dependent insulin secretion and improving pancreatic β-cell function [2]. The phytochemical profile of Ficus exasperata, rich in flavonoids, phenolics, and organic acids, likely contributes to this upregulation by stimulating enteroendocrine cells or by preserving GLP-1 activity through inhibiting its degradation [14]. In addition, Oboh et al. (2010) found that African Yam Bean (AYB) has the lowest glycemic index (GI) among Nigerian legumes, with a GI of 17, compared to cowpea (41), pigeon pea (24), and groundnut (24) [28]. Legumes generally elicit low glycemic responses in both healthy individuals and diabetics (Gbenga-Fabusiwa et al., 2018a, 2019)" [29,30].

Factors such as dietary fiber, protein, and starch type in legumes affect glucose release and absorption. AYB, due to its low GI, is effective in managing postprandial blood glucose levels and has been associated with disease management and prevention. The medicinal properties of plants secondary metabolites are many and well documented [32,36]. The nutritional value of AYB, combined with the pharmacological potential of *Ficus exasperata*, reinforces the observed therapeutic efficacy and nutritional benefit of fortified biscuits in this study, which could help alleviate diabetes prevalence when effectively utilized. This offers a promising complementary approach (due to its synergistic blend of nutrients from AYB, *Ficus exasperata*, and other ingredients, nutritional value, and potential for improved glycemic control) to synthetic GLP-1 receptor agonists used in diabetes therapy [4].Conversely, downregulation of DPP-4 gene expression at higher 40g fortification of *Ficus exasperata* and 20g *Sphenostylis stenocarpa* indicates dose-dependent enzyme inhibition that helps sustain active incretin hormone levels. The inhibition of DPP-4 gene expression suggests that the biscuits could mimic pharmacological DPP-4 inhibitors such as sitagliptin, enhancing incretin-mediated glycemic control. The observed downregulation of IL-6 at higher fortification with *Ficus exasperata* further indicates pronounced anti-inflammatory actions, which are likely to mitigate the chronic low-grade inflammation characteristic of diabetes and its vascular complications [9]. Anti-inflammatory effects have been attributed to the suppression of NF-κB signaling and cytokine production by bioactive compounds in Ficus exasperata, strengthening its therapeutic profile [37].

Interestingly, biscuits fortified with fermented Ficus exasperata leave augmented GLUT-4 gene expression at both dose levels. GLUT-4 is central to insulin-stimulated glucose uptake in muscle and adipose tissue, and its diminished expression or translocation is a hallmark of insulin resistance in diabetes [6]. Fermentation alters phytochemical composition and enhances the production of bioactive compounds, which may enhance GLUT-4 expression via improved oxidative stress modulation and signaling pathway activation [8,13]. This effect synergizes with the macronutrient profile of Sphenostylis stenocarpa, which serves as a source of protein, dietary fiber, and resistant starch, further improving insulin sensitivity and glycemic regulation [16].

The reciprocal proportions used in the biscuit formulations (Table 1), 20g *Ficus exasperata* to 40g Sphenostylis stenocarpa, and vice versa underscore a dose-dependent synergism between these botanicals. Higher concentrations of *Ficus exasperata* promote anti-inflammatory and enzymatic inhibitory actions, while increased *Sphenostylis stenocarpa* content supports enhanced glucose transport and insulin responsiveness. This balance optimizes the modulation of multifaceted diabetes pathways, reducing hyperglycemia and inflammation simultaneously. These findings are consistent with combined herbal strategies in functional food development, where phytochemical diversity and macronutrient supplementation jointly contribute to metabolic regulation [14,15].

The present study also highlights the superiority of unfermented *Ficus exasperata* in attenuating pro-inflammatory markers, DPP-4 enzyme activity and ameliorating GLP-1. However, fermentation improves bioactive compound bioavailability favoring glucose transporter modulation. Hence, formulation optimization should consider processing impacts to maximize multi-targeted therapeutic effects. This investigation is limited and focused on mRNA expression without concomitant characterization of biscuits bioactive profile which future work should address to affirm mechanistic insights. Furthermore, long-term effects and clinical translation remain to be explored through extended animal studies and human trials.

5. Conclusion

This study illustrates that biscuits containing *Sphenostylis stenocarpa* and *Ficus exasperata* positively influence molecular biomarkers related to diabetes. The observed upregulation of GLP-1 and GLUT-4 genes expression alongside downregulation of DPP-4 and IL-6 genes expression suggests improved glycemic control through better incretin signaling, increased glucose uptake and reduced inflammation. The results emphasize the need to optimize both the proportions of these herbs and their processing methods to enhance therapeutic effects. The findings advocate for these functional biscuits as innovative dietary options for diabetes management, highlighting the potential advantages of combining plant-derived compounds with legumes. Future research should aim at detailed phytochemical analyses and clinical studies to validate these insights in practical treatment approaches.

Authors' contribution: S.A designed the study. L., S.O., O.V., V. O., D. O., B. K., P. O., B., O. A., P. O., and S. O. conducted the methodology. S.A. and L. provided the materials. L. and O. V. conducted the analysis and interpretation of the results. L. prepared the initial draft of the manuscript. All authors have thoroughly reviewed and approved the final version and take responsibility for its content and similarity index.

References

1. Mobasseri, M., Shirmohammadi, M., Amiri, T., Vahed, N., Fard, H. H., & Ghojazadeh, M. (2020). Prevalence and incidence of type 1 diabetes in the world: a systematic review and meta-analysis. *Health promotion perspectives, 10*(2), 98.
2. Drucker, D. J. (2018). Mechanisms of action and therapeutic application of glucagon-like peptide-1. *Cell metabolism, 27*(4), 740-756.
3. Drucker, D. J. (2016). The cardiovascular biology of glucagon-like peptide-1. *Cell metabolism, 24*(1), 15-30.
4. Demuth, H. U., McIntosh, C. H., & Pederson, R. A. (2005). Type 2 diabetes—therapy with dipeptidyl peptidase IV inhibitors. *Biochimica et Biophysica Acta (BBA)-Proteins and Proteomics, 1751*(1), 33-44.
5. Asano, T., Fujishiro, M., Kushiyama, A., Nakatsu, Y., Yoneda, M., Kamata, H., & Sakoda, H. (2007). Role of phosphatidylinositol 3-kinase activation on insulin action and its alteration in diabetic conditions. *Biological and Pharmaceutical Bulletin, 30*(9), 1610-1616.
6. Huang, S., & Czech, M. P. (2007). The GLUT4 glucose transporter. *Cell metabolism, 5*(4), 237-252.
7. Suárez, E., Bach, D., Cadefau, J., Palacín, M., Zorzano, A., & Gumà, A. (2001). A novel role of neuregulin in skeletal muscle: Neuregulin stimulates glucose uptake, glucose transporter translocation, and transporter expression in muscle cells. *Journal of biological chemistry, 276*(21), 18257-18264.
8. Shan, W. F., Chen, B. Q., Zhu, S. J., Jiang, L., & Zhou, Y. F. (2011). Effects of GLUT4 expression on insulin resistance in patients with advanced liver cirrhosis. *Journal of Zhejiang University SCIENCE B, 12*(8), 677-682.
9. Scheller, J., Chalaris, A., Schmidt-Arras, D., & Rose-John, S. (2011). The pro-and anti-inflammatory properties of the cytokine interleukin-6. *Biochimica et Biophysica Acta (BBA)-Molecular Cell Research, 1813*(5), 878-888.
10. Lowe, G., Woodward, M., Hillis, G., Rumley, A., Li, Q., Harrap, S., ... & Chalmers, J. (2014). Circulating inflammatory markers and the risk of vascular complications and mortality in people with type 2 diabetes and cardiovascular disease or risk factors: the ADVANCE study. *Diabetes, 63*(3), 1115-1123.
11. Ahmed, F., Ahmed, K. M., Abedin, M., & Karim, A. (2012). Traditional uses and pharmacological potential of Ficus exasperata Vahl. *Systematic Reviews in Pharmacy, 3*(1), 15.
12. Shodehinde, S.A., Awojulu, V.O., Nwanna, E.E., Olubode, S.O., Bello, L., Akinnusi, P.A., Adefolalu, A., Awelewa, O.V., Olubode, S.O., Bakare, O.S., Adetokunbo, T., & Egunjobi, G.D. (2025). Multimodal Assessment of Ficus exasperata in Diabetic Drosophila. *International Journal of Biological Chemistry, 19*(1), 36-61.
13. Bello, L., Shodehinde, S. A., Arowolo, K. G., Arowolo, B. D., Adegnenga, A. G., Ayodeji, R. D., ... & Sabitu, A. S. (2025). Phytochemical Analysis and Antioxidant Activity of Ficus exasperata.
14. Ajibola, C. F., Fashakin, J. B., Fagbemi, T. N., and Aluko, R. E. (2016). Effect of African yam bean seed-based diets on blood glucose, antioxidant status, and lipid profile of diabetic rats. *Plant Foods for Human Nutrition, 71*(1), 41–47.
15. Jeff-Agboola. (2007). Nutritional value of African yam beans. Retrieved from
16. Emiola, I. A. (2011). Processed african yam bean (Sphenostylis stenocarpa) in broiler feeding performance characteristics and nutrient utilization. *Journal of Environmental Issues and Agriculture in Developing Countries, 3*(3), 123-131.
17. Arámburo-Gálvez, J. G., Beltrán-Cárdenas, C. E., Geralda André, T., Carvalho Gomes, I., Macêdo-Callou, M. A., Braga-Rocha, É. M., ... & Cabrera-Chávez, F. (2020). Prevalence of Adverse Reactions to Glutenand People Going on a Gluten-Free Diet: A Survey Study Conducted in Brazil. *Medicina, 56*(4), 163.
18. Anania, C., Pacifico, L., Olivero, F., Perla, F. M., & Chiesa, C. (2017). Cardiometabolic risk factors in children with celiac disease on a gluten-free diet. *World Journal of Clinical Pediatrics, 6*(3), 143.
19. Bengi, G., Cıvak, M., Akarsu, M., Soytürk, M., Ellidokuz, E., Topalak, Ö., & Akpınar, H. (2019). Prevalance of celiac disease in patients with inflammatory bowel disease in Turkish population. *Gastroenterology Research and Practice, 2019*(1), 6272098.
20. Shodehinde, S. A., Bello, L., Awojulu, O. V., Ayejuni, V. O., Omoyajowo, F. E., Fagbohun, O., & Zauka, R. (2025). Phenolics, Antioxidants and Minerals in Fermented vs Unfermented Terminalia catappa.
21. Elekofehinti, O. O., Onunkun, A. T., & Olaleye, T. M. (2020). Cymbopogon citratus (DC.) Stapf mitigates ER-stress induced by streptozotocin in rats via down-regulation of GRP78 and up-regulation of Nrf2 signaling. *Journal of ethnopharmacology, 262,* 113130.
22. Elekofehinti, O. O., Lawal, A. O., Ejelonu, O. C., Molehin, O. R., & Famusiwa, C. D. (2020). Involvement of fat mass and obesity gene (FTO) in the anti-obesity action of Annona muricata Annonaceae: in silico and in vivo studies. *Journal of Diabetes & Metabolic Disorders, 19*(1), 197-204
23. Marzook, A., Tomas, A., & Jones, B. (2021). The interplay of glucagon-like peptide-1 receptor trafficking and signalling in pancreatic beta cells. *Frontiers in endocrinology, 12*, 678055.
24. Rondas, D., D'Hertog, W., Overbergh, L., & Mathieu, C. (2013). Glucagon-like peptide-1: modulator of β-cell dysfunction and death. *Diabetes, Obesity and Metabolism, 15*(s3), 185-192.
25. Mulvihill, E. E., & Drucker, D. J. (2014). Pharmacology, physiology, and mechanisms of action of dipeptidyl peptidase-4 inhibitors. *Endocrine reviews, 35*(6), 992-1019.
26. Ahrén, B., & Schmitz, O. (2004). GLP-1 receptor agonists and DPP-4 inhibitors in the treatment of type 2 diabetes. *Hormone*

and metabolic research, 36(11/12), 867-876.
27. Reddy, V. K. K., Shiddapur, G., Jagdale, N., Kondapalli, M. P., & Adapa, S. (2024). Investigating Interleukin-6 levels in type 2 diabetes mellitus patients with and without diabetic nephropathy. *Cureus, 16*(8), e67014.
28. Klip, A., McGraw, T. E., & James, D. E. (2019). Thirty sweet years of GLUT4. *Journal of Biological Chemistry, 294*(30), 11369-11381.
29. Oboh H, Osagie A, Omotosho A (2010). Glycemic response of some boiled legumes commonly eaten in Nigeria. *Diabetologia Croatica 39*(4):125-131.
30. Gbenga-Fabusiwa FJ (2019). Proximate, mineral and physicochemical properties of starch extracted from pigeon-pea (*Cajanus cajan*) and varieties of African yam beans (*Sphenostylis sternocarpa*). *Journal of ChemResearch 1*(1):121-131.
31. Gbenga-Fabusiwa, F. J., Oladele, E. P., Oboh, G., Adefegha, S. A., Fabusiwa, O. F., Osho, P. O., ... & Oshodi, A. A. (2019). Glycemic response in diabetic subjects to biscuits produced from blends of pigeon pea and wheat flour. *Plant Foods for Human Nutrition, 74*(4), 553-559.
32. Frank UE, Rita NO, Chukwuemeka SA (2016). Effect of African yam bean (Sphenostylis stenocarpa) on serum calcium, inorganic phosphate, uric acid, and alkaline phosphatase concentration of male albino rats. *Journal of Agricultural Science 8*(1) ISSN 1916-9752 E-ISSN 1916-9760
33. Michael ON, Etim EE, Innocent OO (2018). Investigation on the anti-diabetic activity of Sphenostylis stenocarpa seed milk extract in alloxan-induced diabetes rats. *International Journal of Scientific and Research Publications* 8(8):824 ISSN 2250-3153
34. Okonkwo CC, Njoku UO, Mbah AM (2013). Anti-anaemic effect of methanol seed extract of Sphenostylis stenocarpa (African yam bean) in Wistar albino rats. *African Journal of Pharmacy and Pharmacology* 7(45):2907-2913
35. Sarwar, N., Gao, P., Seshasai, S. R., Gobin, R., Kaptoge, S., Di Angelantonio, E., ... & Danesh, J. (2010). Emerging Risk Factors Collaboration Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet, 375*(9733), 2215-2222.
36. Akpan, I. P., Ebenso, I. E., Effiong, O. O., & White, E. E. (2012). Performance and organoleptic properties of edible land snail fed Chromolaena odorata. *Nigerian Journal of Agriculture, Food and Environment, 8*(2), 5-8.
37. Jimoh-Abdulghaffaar, H. O., Ajibare, A. J., Akintoye, O. O., Jimoh, O. S., Ananias, E. N., Owoyemi, J. O., ... & Ojulari, L. S. (2023). Ficus exasperata leaves aqueous extract influences pathophysiolgic mechanisms of diabetic peripheral neuropathy in a rat model. *Journal of Applied Pharmaceutical Science, 13*(9), 077-083