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Original Research Article

Antidiabetic, Antioxidant, and PPAR-Gamma Modulating Effects of Extracts from the Leaves and Fruits of Jute Mallow (*Corchorus olitorius*) in High-Fat Diet-Fed, Streptozotocin-induced Diabetic rats

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ABSTRACT

Medicinal plants are increasingly gaining attention in diabetes management due to their cost-effectiveness and therapeutic potential. This study investigated and compared the antidiabetic, antioxidant, and anti-inflammatory effects of Jute (*Corchorus olitorius)* fruit and leaf extracts in rats fed with a high-fat diet, streptozotocin-induced diabetic rats. Rats received 1000 and 1800 mg/kg body weight (bw) of the extracts of the leaf and fruit of *Corchorus olitorius* for 28 days. Antidiabetic effects were assessed by measuring glucose levels and glucose metabolism-related gene expression. Antioxidant effects were evaluated by measuring antioxidant enzyme activities and TNF-α expression. Notably, the *C. olitorius* leaf extract exhibited more pronounced effects, including a 59.7% reduction in glucose concentration compared to 29.3% for the fruit extract, suggesting its potential as a more effective antidiabetic agent. However, weight gain was more significant with the fruit extract (14.1% vs. 8.9% for the leaf extract). The leaf extract increased the activities of catalase (CAT), glutathione peroxidase (GPx) and superoxide dismutase (SOD) in the liver, pancreas, and kidneys, and upregulated NRF-1 mRNA expression. Additionally, the leaf extract positively modulated glucose metabolism-related genes, including Akt, GSK-3β, and GLUT-2. Inflammation, a hallmark of diabetes, was relatively inhibited by the leaf extract, as evidenced by reduced TNF levels. Both extracts increased PPAR-γ expression and reduced inflammatory cytokine production, with the *C. olitorius* leaf extract exhibiting more pronounced effects. These findings unveil the therapeutic potential of *C. olitorius* leaf and fruit extracts in managing diabetes and related complications, with the leaf extract displaying better activity. The revealed nutraceutical potentials of *C. olitorius* leaf and fruits could enhance its utilization and large-scale production.

Keywords: Jute fruits, Antioxidant, Inflammation, Diabetes, Streptozotocin, Glucose Metabolism

Introduction

Diabetes mellitus (DM) is an inflammation-driven metabolic disorder that results either from weakened insulin action reduced insulin secretion, or a combination of conditions, leading to persistent hyperglycaemia.[1] Approximately a little more than half a billion individuals around the world are currently living with DM, which indicates that more than 10.5% of the adult community is currently affected by this ailment.[2] Research has shown that oxidative stress is a key factor which contributes to beta-cell dysfunction and insulin resistance, the features that characterize diabetes.[1]

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According to Antar and colleagues in 2023, hyperglycemia is involved in the development of vascular complications in diabetic patients, expressed through the increased production of reactive oxygen species (ROS), nitric oxide (NO), and nuclear factor kappa B (NF-κB).[1] Furthermore, oxidative stress is the mechanism by which environmental pollutants that cause diabetes, induce diabetes.[3] Therefore, therapeutically targeting oxidative stress may help ameliorate diabetes and its consequences.[4] In the face of oxidative stress, peroxisome proliferator-activated receptor-gamma (PPAR-γ) promotes the expression of antioxidant genes and also reduces the production of proinflammatory molecules. PPAR-γ, a nuclear receptor, is essential for controlling several essential biological functions, such as inflammation and glucose homeostasis. Additionally, it influences how antioxidant defence systems are modulated. Activation of PPAR-γ is associated with the improvement of oxidative damage in the liver caused by the consumption of a diet rich in fat by inducing an endogenous antioxidant defence system.[5,6,7] In diseases, the interactions between PPAR-γ, antioxidant enzymes, and pro-inflammatory cytokines are critical. Activation of PPAR-γ produces anti-inflammatory effects by reducing the expression of key pro-inflammatory cytokines, such as TNF-α, IL-6, and IL-1β.

Additionally, PPAR-gamma activation mitigates oxidative stress by upregulating the antioxidant enzymes gene level, including CAT, GPx, and SOD [8,9,10], emphasizing the potential of PPAR-γ modulation as a key approach in diabetes therapy.

Hypoglycemic agents such as insulin, thiazolidinediones, α-glucosidase inhibitors, sulfonylureas, and biguanides are medications used in the management of DM. One limitation of these drugs is their potential adverse effects, including kidney and liver complications, as well as the risk of hypoglycemic coma if not carefully managed and monitored.[11] As a result, efforts in recent decades have been concentrated on the identification of safer and more effective treatments, such as those employing bioactive chemicals derived from natural sources capable of alleviating diabetes. The most common type of the Traditional Medical System, which is used as complementary treatment throughout the world, is herbal therapy. Traditional medical systems based on plants still have a significant impact on healthcare. Consequently, there is a growing global demand for pharmaceuticals, food supplements, nutraceuticals, cosmetics, health goods, and medications based on herbs. Herbs, herbal preparations, and herbal products with various plant parts or other plant components as ingredients are all considered herbal remedies.[12] Several botanical drugs used in ethno-medicinal systems have been reported to be useful modern medications. Different parts of the medicinal plants were found to be responsible for various biological effects. The fruits of some medicinal plants are edible. For instance, the extracted juice leaf, seed fruit pulp and the whole plant of Kerala plant in ethno-medicine in the cure of diabetes. The fruit of *Gingko biloba* was reportedly used indigenously to treat asthma and infections with parasitic worms,[12,13,28] so all plant parts have their role.

Medicinal plants are plants that have been utilized for millennia in traditional healing practices across many countries due to their therapeutic properties. These plants can indeed be used as food, and many have been consumed for centuries for their nutritional and therapeutic benefits.[24] They contain active compounds that provide health benefits and are utilized to treat various ailments.[27] Jute, also known as *Corchorus* is a nutraceutical veggie that is native to the Asian and tropical African environments; that has a distribution that spans the whole pantropical region[14] It is consumed as soup in Southwestern Nigeria. It possesses antioxidant potential, which has been attributed to its hydrophilic and lipophilic phytoconstituents.[15] Its leaves possess various biological activities including antioxidant and antidiabetic activities which are linked to the presence of mucilaginous polysaccharides [16,17,18] and could be responsible for the viscosity.[19] Based on the biological activities linked to the mucilaginous substance in the leaf of *Corchorus olitorius*, there is a potential for the tender fruits of *Corchorus olitorius L*., which are also viscous, to exhibit various pharmacological activities similar to its leaves, as observed in other medicinal plants. Previous reports have indicated that the fruits possess nutritional benefits and contain a variety of phytochemicals, suggesting their potential for biological activities akin to those of the leaves.[20,21] Its viscous nature also suggests the presence of the phytochemicals implicated for its antioxidant and antidiabetic activities. The extracts were therefore screened for *in vivo* anti-diabetic activity in STZ-induced diabetes and high-fat-fed models to enhance the comparison of the modulation of diabetes-related biochemical markers regulated by both vegetable parts.

Materials and Methods

Materials

Drugs, Reagents and Chemicals

The study utilized streptozotocin (STZ), glibenclamide, hydrogen peroxide, NADP, and NADPH from Sigma Chemical Co. (USA), while other analytical-grade reagents were sourced from British Drug Houses (UK)

C. olitorius leaf and fruit Collection and Identification

C. olitorius leaf and tender fruits were collected from a *Corchorus* agronomic evaluation field in Ikole-Ekiti, Ekiti State, Nigeria in June 2022 and taxonomically verified by an expert at the Department of Plant Science and Biotechnology, Federal University Oye-Ekiti, where a voucher specimen with number FUOH 0145 exists in the department's herbarium.

Experimental animal

The anti-diabetic study employed male Wistar rats (*Rattus norvegicus*) of 180-200g body weight. The animals were used from the animal house of the Animal Facility Centre, Achievers University, Owo and kept in wooden cages at the Department of Biochemistry, Federal University Technology, Akure, Ondo State. Rats were kept under controlled laboratory conditions in stainless steel cages at a relative humidity of 45-55%, a temperature of 24 ± 2^0C, and a 12-hour light-dark cycle. They were fed rat feed and had free access to water.

Preparation of C. olitorius leaf ethanol extract

Following careful washing with running tap water, the *C. olitorius* leaves and fruits were thoroughly dried in a shaded environment. The dried material was then ground into a fine powder. Ethanol extraction involved soaking 2.5 kg of powdered plant material in 2.5 litres of ethanol for 24 hours. The extract was filtered, and the ethanol was removed through rotary evaporation to obtain the crude active ingredient.

Preparation of High-Fat Diet

The high-fat diet was formulated by weighing 7 kg of animal feed (finisher) and mixing it with 3 kg of cow fat. The cow fat was melted before being blended with the animal feed according to the modified version of Salma method.[64]

Experimental induction of Diabetes

This investigation utilized a cohort of fifty male Wistar rats fed a high-fat diet for four weeks. Subsequently, the rats received a single intraperitoneal injection of STZ (35 mg/kg) in citrate buffer (0.1 M, pH 4.5) after an overnight fasting period. The rats were then provided with food and water *ad libitum*. Twenty-four hours post-STZ administration, blood samples were collected via the vein in the tail, and the glucose levels were assessed using an Accu-check glucometer (Roche Diagnostics GmbH, Mannheim, Germany). Rats exhibiting fasting blood glucose levels above 230 mg/dl were defined as diabetic and included in the study.

Experimental procedure

Forty rats were divided into five groups of eight at random, and each group received the following treatment:

Group 1 - Normal (non-diabetic) control rats (NC)

Group 2 – Streptozotocin-induced diabetic control rats (PC) (35 mg/kg)

Group 3 - Glibenclamide (DGT) (0.6 mg/kg bw)-treated rats with Diabetes

Group 4 – *C. olitorius* Leaf extract (1000 mg/kg bw) + streptozotocin (35 mg/kg)

Group 5 - *C. olitorius* Leaf extract (1800 mg/kg bw) + streptozotocin (35 mg/kg)

Group 6 - *C. olitorius* Fruit extract (1000 mg/kg bw) + streptozotocin (35 mg/kg)

Group 7 - *C. olitorius* Fruit extract (1800 mg/kg bw) + streptozotocin (35 mg/kg)

The rats were euthanized at the expiration of the experiment, which lasted for four weeks (28 days)

Preparation of tissue homogenates

The liver, pancreas, brain, and kidney tissues were harvested, briefly washed in ice-cold 1.15% potassium chloride (KCl) solution, blotted to remove excess moisture, and weighed. Subsequent homogenization was performed in cold 0.1 M potassium phosphate buffer (pH 7.4). The homogenates were centrifuged at 3000 rpm for 10 minutes, and the resulting supernatants were collected, stored at 4°C, and later used for biochemical assays.

Determination of Body Weight

The body weights of the rats were measured on the day of commencement of treatment (D1), and D7, D14 and on the 28*th* day (D28) using an electronic weighing balance (Digital Precision Weighing Balance (Hansen, China).

Antioxidant enzyme assay
Superoxide dismutase
The superoxide dismutase (SOD) activity was evaluated using a modified version of the Mishra and Fridovich method.[22] This approach takes advantage of the activity of SOD in preventing the autoxidation of epinephrine at pH 10.2, allowing for a reliable and sensitive assessment of enzyme function.

Catalase
CAT was assayed using the methodology of Sinha.[23] This analytical method exploits the reduction of dichromate to chromic acetate in acetic acid, triggered by heating in the presence of hydrogen peroxide (H_2O_2). The reaction involves the brief formation of perchromic acid, and the chromic acetate generated is quantified using colourimetry.

Glutathione peroxidase
The activity of Glutathione peroxidase (GPx) was evaluated using a hydrogen peroxide-based analysis, as outlined by Hafeman et al.[24]

Molecular Analyses
Ribonucleic acid (RNA) Isolation and Quantification
RNA extraction from tissues was performed using TRIZOL reagent according to the manufacturer's instructions. The isolated RNA was then purified and its concentration and purity assessed by spectrophotometry at 260 nm and 260/280 nm. Only RNA samples with a purity ratio between 1.8 and 2.1 were used for subsequent gene expression analysis by PCR, following a previously established protocol Bando *et al.*,[25]

Complementary Deoxyribonucleic Acid (cDNA) Synthesis and Polymerase Chain Reaction
Reverse transcription of 2 µl extracted RNA was done using the Proto Script II First Strand cDNA Synthesis kit. The reaction involved a three-step protocol: denaturation at 65°C, reverse transcription at 42°C, and termination at 80°C. Subsequent PCR amplification was conducted using the Luna Mastermix kit and TaqMan probes. Gene expression analysis was normalized to the housekeeping gene, β-actin (*ACTB*), and the sequences of the primers used are listed in Table 1. Primers were sourced from Inqaba Biotech, while gel imaging was performed on an electrophoresis gel imager.

Agarose Gel Analysis of PCR product
Agarose (0.8g) was added to 50 ml of 1xTris-Borate-EDTA (TBE) buffer. Then, 4 µl of ethidium bromide, a staining dye was added to the mixture when warm, after which it was poured into a gel tray to solidify. It was then transferred to an electrophoresis tank. 5 µl of DNA ladder was added to the first well in the gel, after which 10 µl of the samples were also added to the same wells. It was then connected to an electrical outlet in the electrophoresis tank and allowed to run for 10-15 minutes. The gel was removed, and the density of the migrated fragment bands was estimated and then normalized β-actin gene.

Statistical Analysis
The results are presented as mean ± SEM (n = 5). One-way ANOVA and Student-Newman-Keuls post-hoc testing were used to compare groups, with $P \leq 0.05$ indicating statistical significance. The statistical interpretation was done by Graph Pad Prism 5.03.

Result and Discussion

Effects of C. olitorius Leaf on Blood Glucose Levels
In diabetes, the main observable characteristic or clinical feature is elevated blood glucose levels (hyperglycemia). Other associated phenotypic traits can include increased thirst, blurred vision, and unexplained weight loss.[35] The levels of glucose in the blood of the experimental rats at days 1, 7, 14, 21 and 28 of the research are presented in Figure 1. The effect of the various treatments on the blood glucose concentrations is presented as percentage changes in glucose concentration for 28 days. The diabetic group (2nd Group revealed a 29.6% increase in glucose concentration while the normal group (normal group) had a 2.3% increase. In contrast, all the treated groups had a reduction in the blood glucose level. Glibeclamide-treated group (3rd Group) had a 40.9% decrease in glucose concentration. The *C. olitorius* leaf extract treatment at 1,000 mg/kg bw (4th Group) and 1,800 mg/kg bw (5th Group) resulted in decreases in glucose concentration of 41.5% and 59.7%, respectively. The *C. olitorius* fruit extract treatment at 1,000 mg/kg bw (6th Group) resulted in a decrease in glucose level of 16.1%, while the 1,800 mg/kg bw treatment (7th Group) resulted in a decrease of 29.3%. These results suggest that there is a dose-dependent effect of the *C. olitorius* extracts on blood glucose concentration. It was also observed that *C. olitorius* leaf extract could be better at reducing glucose concentration in diabetic rats. Summarily, a notable decrease in glucose was detected in both the leaf and fruit extract-treated groups, though it was more observable in the *C. olitorius* leaf extract-treated group than the *C. olitorius* fruit extract-treated group as depicted in Figure 1. The observed variations in biological activity may be attributed to differences in both the qualitative composition and quantitative abundance of the mucilaginous polysaccharides present in these plant parts.[36,37] The antidiabetic capacity of the mucilaginous polysaccharides is likely attributable to a combination of mechanisms, including delayed gastric emptying, inhibited intestinal glucose absorption[29,30,31], stimulated insulin secretion, improved insulin sensitivity, and prebiotic modulation of the gut microbiome.[32,33,17,34] Further studies may analyze the components and the concentration of these polysaccharides in both plant parts.

Effects of C. olitorius Leaf in Body Weight
Body weight (bw) decreased due to a reduction in total body mass is linked to diabetes. High blood sugar levels normally lead to glucose in the urine (glycosuria), dehydration from increased urination, lipolysis and muscle wasting (catabolism) from inadequate insulin. [38] The effects of the treatments on body weight were assessed over 28 days and reported in Figure 2. The normal control group (NC) exhibited a significant weight gain of 14.5%. In contrast, the diabetic group (PC) showed a notable weight loss of -10%. The standard drug treatment (DGT) resulted in a modest weight gain of 4.8%. The *C. olitorius* leaf extract treatments at 1,000 mg/kg b.w (D1000JLT) and 1,800 mg/kg

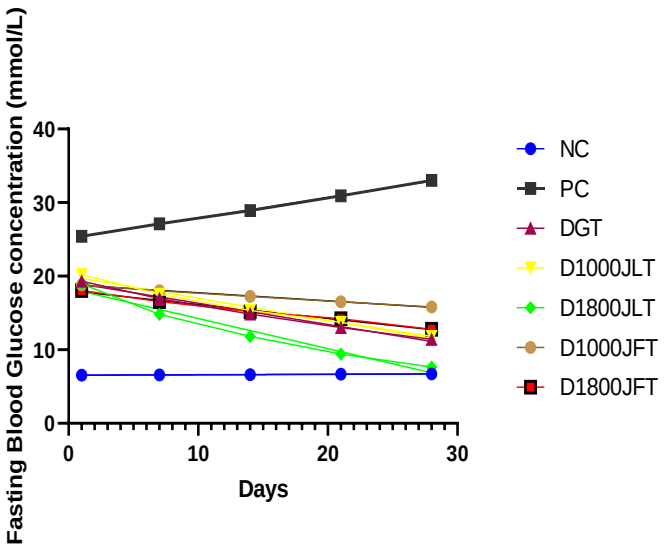

Figure 1: Effect of extracts of *C. olitorius* leaf and fruit on fasting blood glucose level in normal control and STZ-induced diabetes rats. Each point represents the mean of 5 values. NC: Normal control; PC: Positive control; DGT: Glibeclamide; D1000JLT: *C. olitorius* Leaf Extract at dose 1000 mg/kg bw; D1800JLF: *C. olitorius* Leaf Extract at dose 1800 mg/kg bw; D1000JFT: *C. olitorius* Fruit Extract at dose 1000 mg/kg bw; D1800JFT: *C. olitorius* Fruit Extract at dose 1800 mg/kg bw

b.w (D1800JLT) led to weight gains of 6.1% and 8.9%, respectively. The *C. olitorius* fruit extract treatments at 1,000 mg/kg b.w (D1000JFT) and 1,800 mg/kg body weight (D1800JFT) resulted in

weight gains of 10.5% and 14.1%, respectively. These findings suggest that *C. olitorius* leaf and fruit extracts may have the potential to promote weight gain, with the higher doses of *C. olitorius* fruit extract exhibiting the most pronounced effect. The extracts from the *C. olitorius* leaves and fruits produced a dose-dependent increase in the weight of the animals after intervention with them. A better weight redress of 14.1% was seen at 1800 mg/kg bw of *C. olitorius* fruit extract compared to 8.9 % in the *C. olitorius* leaf extract. The extracts could have addressed the weight loss observed in the diabetic groups due to their constituents' phytochemicals. In the opinion of Qiao, et al, [38] the presence of insulin-modulating phytochemicals in the plant extract must have been responsible.

Table 1: Sequences of the Primer Used

GENE PRIMERS	FORWARD	REVERSE
β- **ACTIN**	**5'-CCCGCGAGTACAACCTTCT-3′**	**5'-CGTCATCCATGGCGAACT-3′**
AKT	**5′-CCAAGGCCCAACAGTTTAT-3′**	**5′-AGCCCGAGTCCGTTATCT-3′**
GSK-3	**5'-GGAACTCCAACAAGGGAGCA- 3'**	**5'-TTCGGGGTCGGAAGACCTTA-3'**
GLUT-2	**5'-GTAACTTCATTGTCGGCATGG-3'**	**5'-AGCTGAGATCTGGTCAAACG-3'**
NRF-2	**5′-GGGGAACAGAACAGGAAACA-3′**	**5′-CCGTAATGCACGGCTAAGTT-3′**
PPAR-γ	**5'-TCATGACCAGGGAGTTCCTC-3′**	**5'-TCAGCGACTGGGACTTTTCT-3′**
TNF-α	**5'-CCAGACCCTCACACTCAGATCA-3'**	**5'-TCCGCTTGGTGGTTTGCTA-3'**

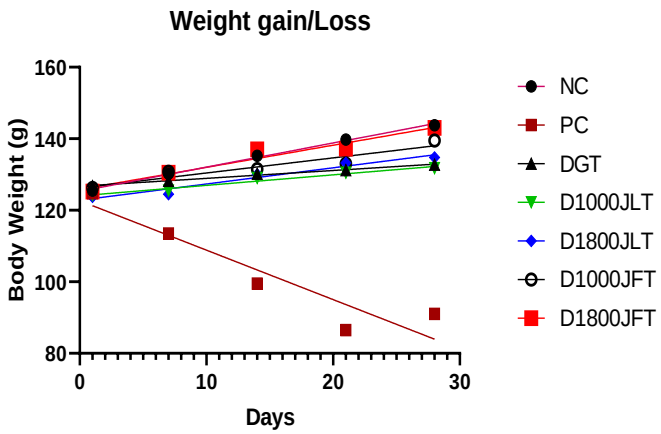

Figure 2: Body weight of diabetic rats after *C. olitorius* leaf and fruit extracts administration. Each point is a mean of 5 values. NC: Normal control; PC: Positive control; DGT: Glibeclamide; D1000JLT: *C. olitorius* Leaf Extract at dose 1000 mg/kg bw; D1800JLF: *C. olitorius* Leaf Extract at dose 1800 mg/kg bw; D1000JFT: *C. olitorius* Fruit Extract at dose 1000 mg/kg bw; D1800JFT: *C. olitorius* Fruit Extract at dose 1800 mg/kg bw

Antioxidant Effect Of Corchorus Olitorius Extracts In Diabetic Condition

Effects of C. olitorius Leaves and Fruit Extracts on the catalytic activity of GPx, CAT and SOD in the kidneys, pancreas and liver of high-fat-fed diabetic rats

Oxidative stress is implicated in βcell dysfunction and insulin resistance, the features that characterize diabetes. According to Antar and his team in 2023, hyperglycemia is crucial in the development of vascular impairments in patients with diabetes through enhanced production of Nuclear factor kappa light chain enhancer of activated B cells (NF-κB), nitric oxide (NO) and reactive oxygen species (ROS).[1] Furthermore, oxidative stress is the mechanism by which environmental pollutants that cause diabetes, induce diabetes.[3] Therefore, therapeutically targeting oxidative stress may help manage and prevent diabetes and its consequences.[4] In the present study, as depicted in Figure 3 (a-c) which presented the result on the enzymatic function of CAT, SOD and GPx in the kidneys, pancreas, and liver of the experimental animals in their various groups. The result revealed a significant decrease in the activities of these enzymes in the untreated diabetic rats compared to the normal rats. The rats that received the reference drug, glibenclamide (DGT), the *C. olitorius* fruit and leaf extracts showed an elevation in the activities of CAT, GPx and SOD in comparison with the untreated diabetic rats (PC). This result was in a dose-responsive manner in the plant extract-treated groups. A similar pattern of dose-dependent increase in the catalytic activity of GPx, CAT and SOD, was observed in the extract-treated groups with the leaf extract performing better at 1800 mg/kg b.w. Plant extracts have been shown to exhibit concentration-dependent biological effects, with varying phytochemical levels eliciting distinct physiological responses.[39] We have documented in this study that the leaves and fruit extracts of *C. olitorius* plants produced a dose-dependent improvement of the antioxidant status in diabetic rats.

Gene Expression of AKT, GSK-3β, and GLUT-2 in diabetic rats administered the extracts from C. olitorius Leaf and fruits.

In our research, the mRNA levels of genes associated with Akt signalling pathways to glucose metabolism were analyzed. These genes included the glucose transporter-2 (GLUT2), protein kinase B (AKT2), and glycogen synthase kinase 3 beta (GSK-3β) genes)[40.] In type 2 diabetes, impaired AKT signalling is a common occurrence, leading to decreased glucose uptake and metabolism due to reduced AKT activity, a crucial component of insulin signalling.[41] The AKT, GSK-3β and GLUT-2 mRNA expression levels in the different organs of the experimental animals are shown in Figure 4 (a-f) using β - actin as the housekeeping gene. All treatments were different at the significant level of ($p < 0.05$) from the untreated diabetes animals. The varying concentrations (1000 mg/kg b.w and 1800 mg/kg b.w) of the crude aqueous extract of *C. olitorius* leaf and fruit caused significant increase in the mRNA expression levels of AKT and GLUT-2 in the liver and pancreas of diabetic rats (Figure 4 (a-e),

while in contrast, the GSK-3 (Figure 4 f) mRNA expression was significantly reduced at 1000 mg/kg and 1800mg/kg in the liver of diabetes rats with increasing doses comparable to the standard drug. Both extracts of *C. olitorius* plant significantly increased the gene level of AKT genes with increasing doses, with the activity of the leaf extract on par with the standard drug. In addition, a sequel to impaired Akt signalling, the negative regulation of GSK-3β by AKT is disrupted, resulting in increased GSK-3β activity and contributing to insulin resistance and reduced glycogen synthesis. According to Srivani et al., GSK-3β inhibitors possess anti-diabetic

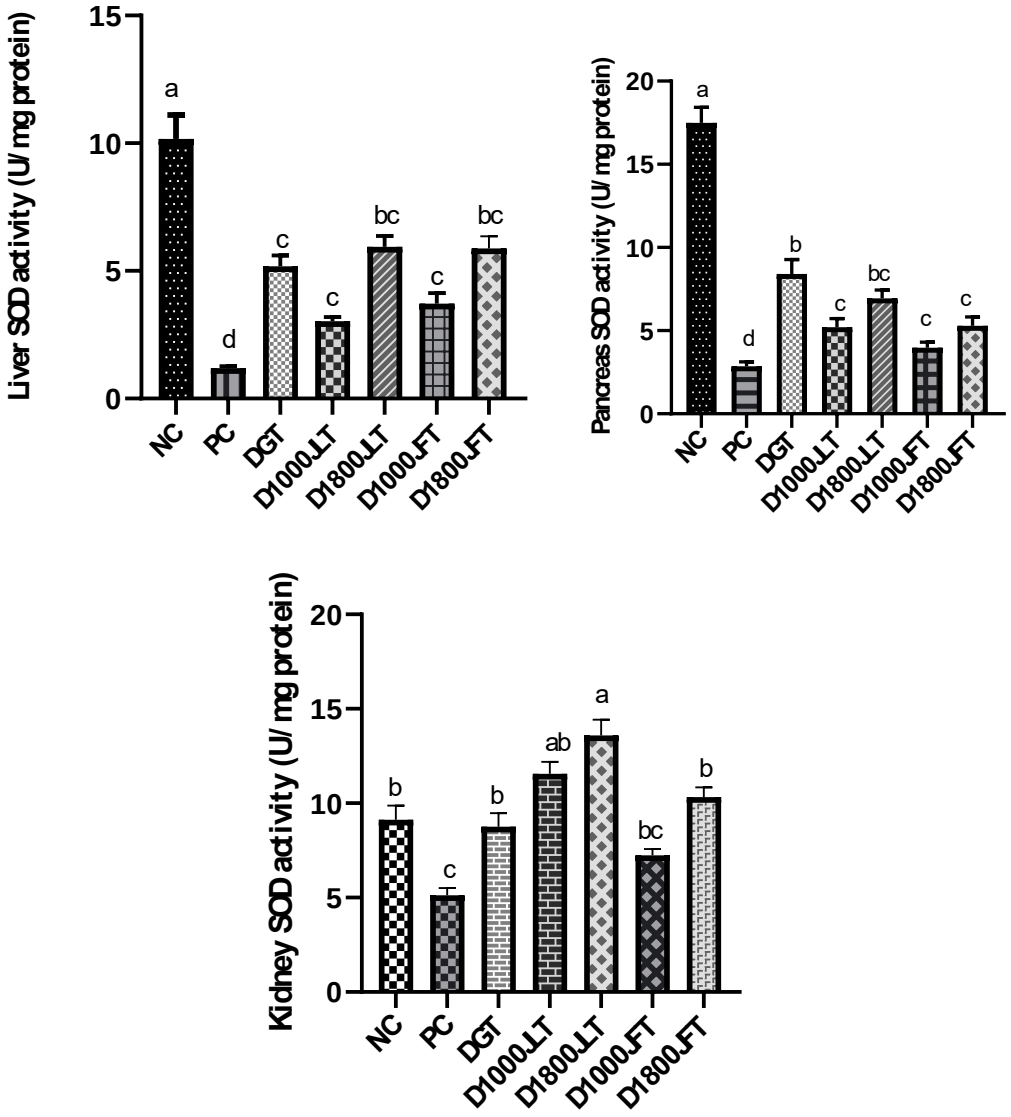

Figure 3a: SOD activity in the liver, pancreas and kidney of diabetic rats after *C. olitorius* leaf and fruit extracts administration. The results are presented as mean values ± standard error of the mean (SEM), based on five replicates. Significant differences between treatment groups ($p < 0.05$) are denoted by distinct letters (a, b, c, d). NNC: Normal control; PC: Positive control; DGT: Glibeclamide; D1000JLT: *C. olitorius* Leaf Extract at dose 1000 mg/kg bw; D1800JLF: *C. olitorius* Leaf Extract at dose 1800 mg/kg bw; D1000JFT: *C. olitorius* Fruit Extract at dose 1000 mg/kg bw; D1800JFT: *C. olitorius* Fruit Extract at dose 1800 mg/kg bw

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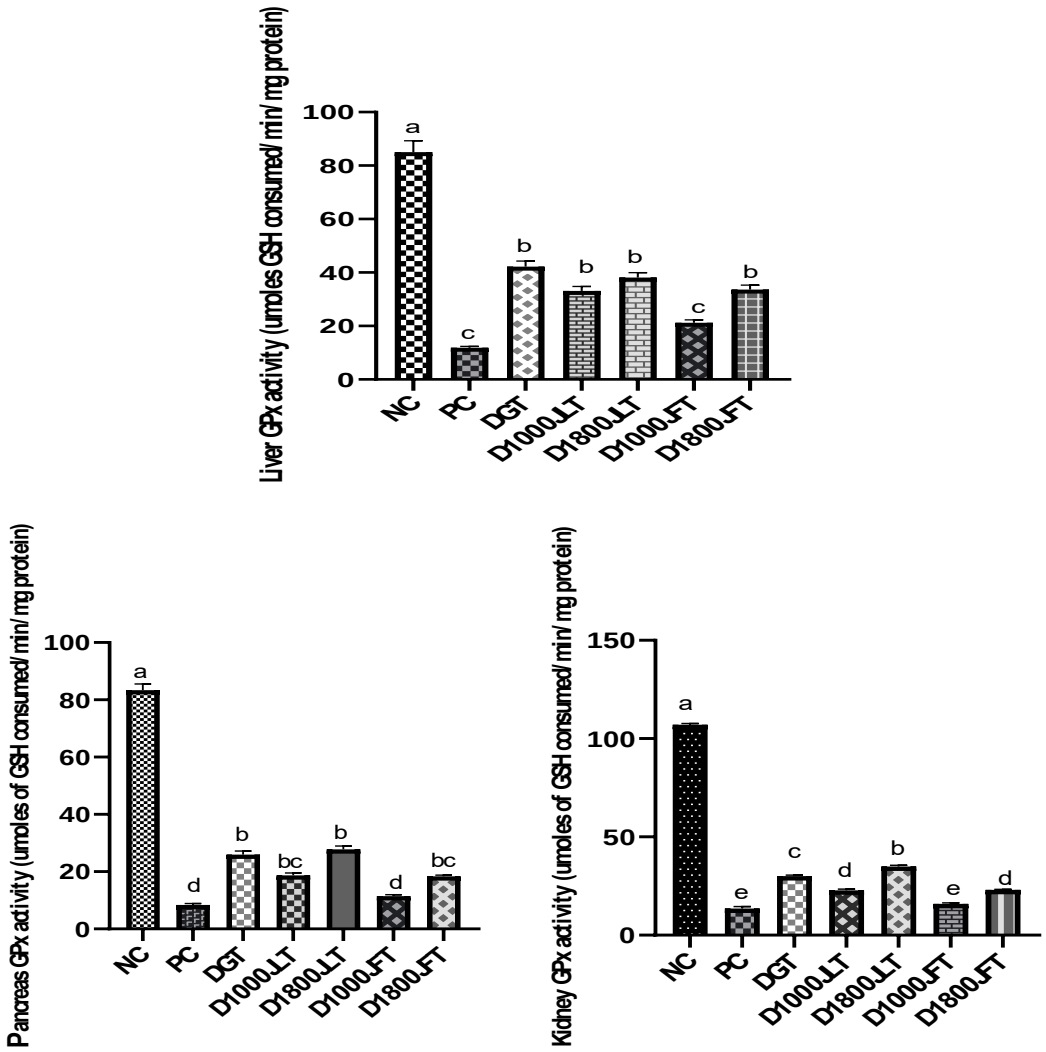

Figure 3b: GPx activity in the kidneys, pancreas and liver of diabetic rats after *C. olitorius* leaf and fruit extracts administration. The results are presented as mean values ± standard error of the mean (SEM), based on five replicates. Significant differences between treatment groups ($p < 0.05$) are denoted by distinct letters (a, b, c, d). NC: Normal control; PC: Positive control; DGT: Glibeclamide; D1000JLT: *C. olitorius* Leaf Extract at dose 1000 mg/kg bw; D1800JLF: *C. olitorius* Leaf Extract at dose 1800 mg/kg bw; D1000JFT: *C. olitorius* Fruit Extract at dose 1000 mg/kg bw; D1800JFT: *C. olitorius* Fruit Extract at dose 1800 mg/kg bw

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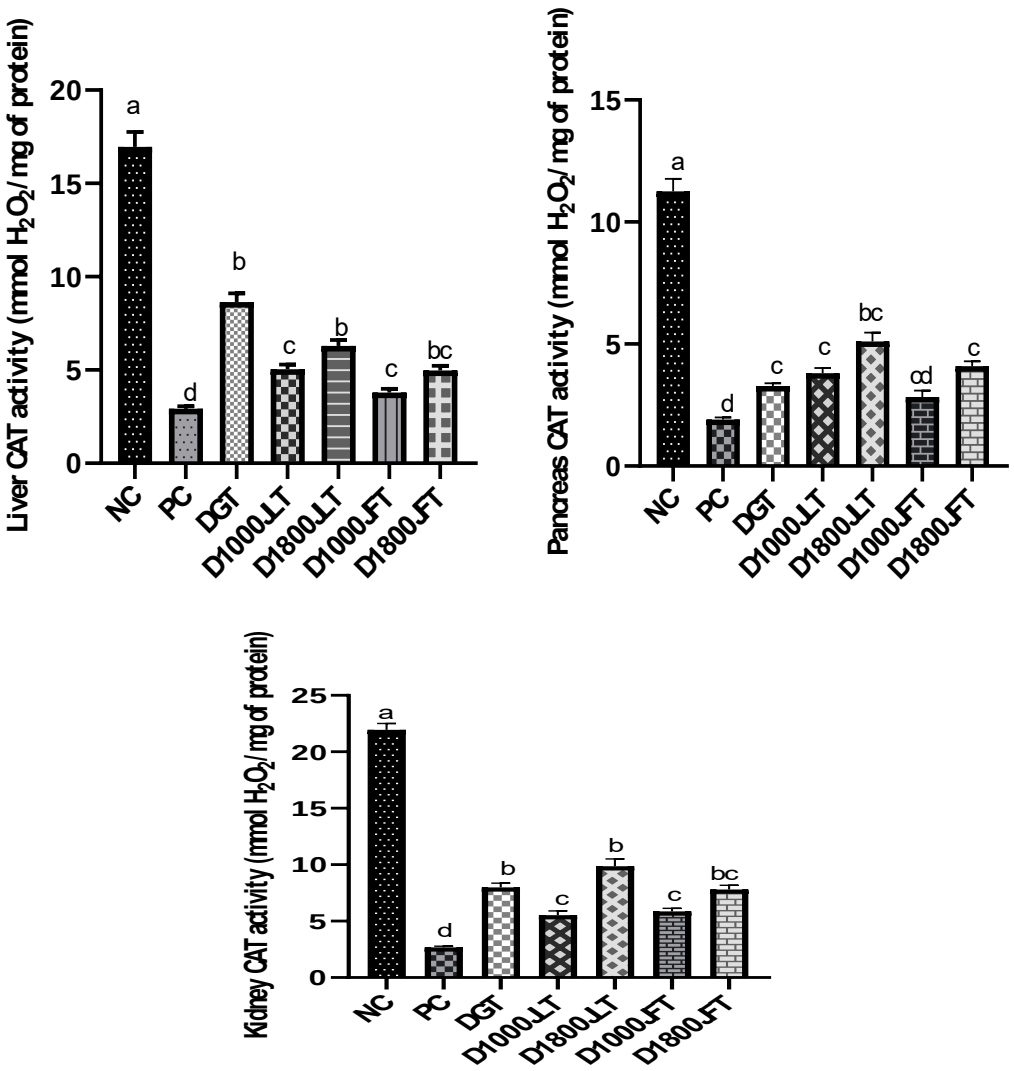

Figure 3c: CAT activity in the liver, pancreas and kidney of diabetic rats after *C. olitorius* leaf and fruit extracts administration. The results are presented as mean values ± standard error of the mean (SEM), based on five replicates. Significant differences between treatment groups ($p < 0.05$) are denoted by distinct letters (a, b, c, d). NC: Normal control; PC: Positive control; DGT: Glibeclamide; D1000JLT: *C. olitorius* Leaf Extract at dose 1000 mg/kg bw; D1800JLF: *C. olitorius* Leaf Extract at dose 1800 mg/kg bw; D1000JFT: *C. olitorius* Fruit Extract at dose 1000 mg/kg bw; D1800JFT: *C. olitorius* Fruit Extract at dose 1800 mg/kg bw

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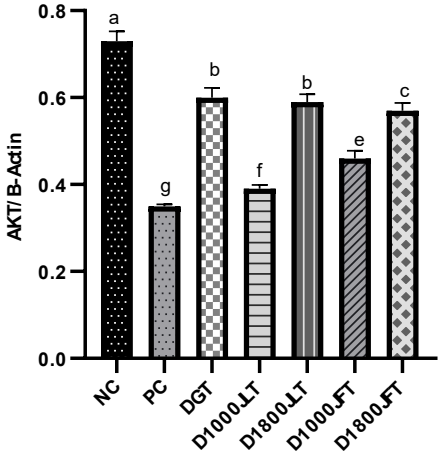
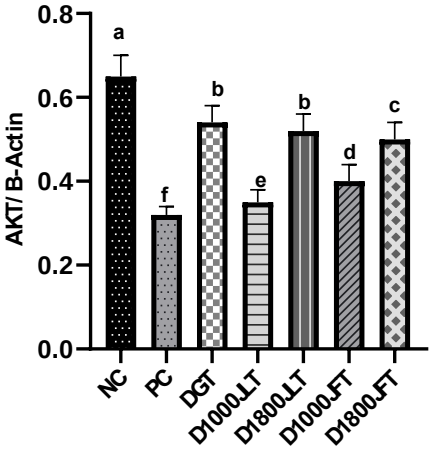


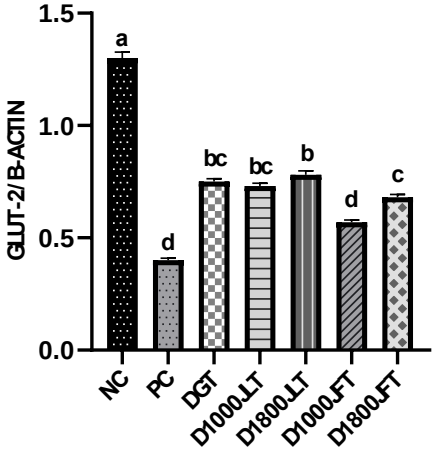
Liver AKT mRNA level quantified with RT-PCR

Figure 4a



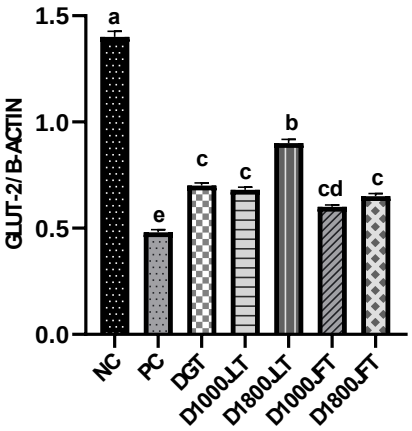
Pancreas AKT level quantified by RT-PCR

Figure 4b



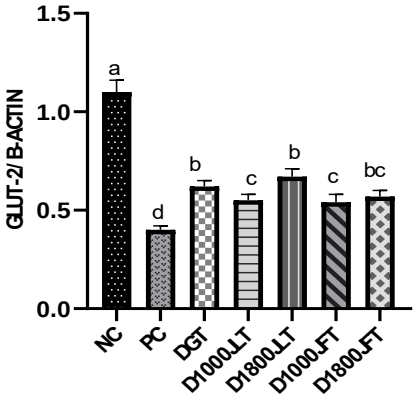
Kidney GLUT-2 mRNA levels quantified by RT-PCR

Figure 4c



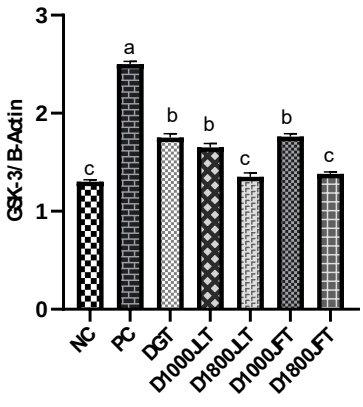
Liver GLUT-2 mRNA levels quantified by RT-PCR

Figure 4d



Pancreas GLUT-2 mRNA levels quantified by RT-PCR

Figure 4e



Liver GSK-3 mRNA levels quantified by RT-PCR

Figure 4f

Figure 4 (a-f): The mRNA expression levels of (a) liver AKT (b) pancreas AKT (c) kidney GLUT-2 (d) liver GLUT-2 (e) pancreas GLUT-2 (f) liver GSK-3 in diabetic rats after *C. olitorius* leaf and fruit extracts administration. The results are presented as mean values ± standard error of the mean (SEM), based on five replicates. Significant differences between treatment groups ($p < 0.05$) are denoted by distinct letters (a, b, c, d). NC: Normal control; PC: Positive control; DGT: Glibeclamide; D1000JLT: *C. olitorius* Leaf Extract at dose 1000 mg/kg bw; D1800JLF: *C. olitorius* Leaf Extract at dose 1800 mg/kg bw; D1000JFT: *C. olitorius* Fruit Extract at dose 1000 mg/kg bw; D1800JFT: *C. olitorius* Fruit Extract at dose 1800 mg/kg bw

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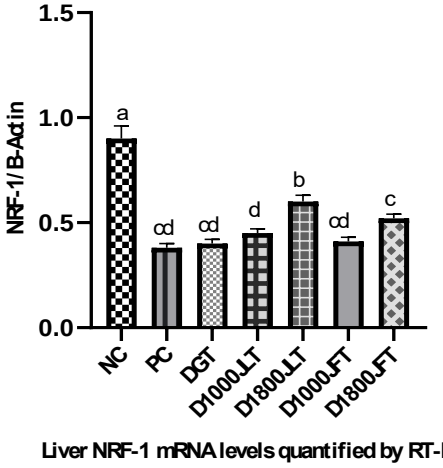


Figure 5a

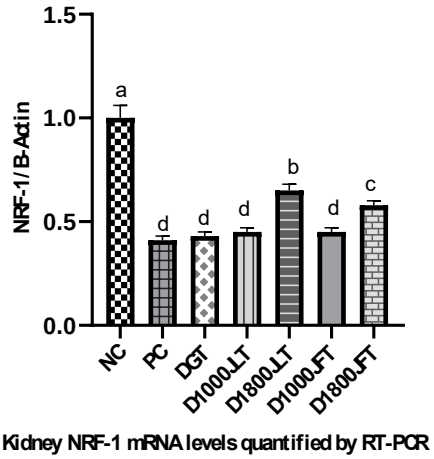


Figure 5b

Figure 5 (a, b): Effect of *C. olitorius* leaf and fruit Extracts on the mRNA expression levels of (a) liver NRF-1 and (b) kidney NRF-1 of diabetic rats. The results are presented as mean values ± standard error of the mean (SEM), based on five replicates. Significant differences between treatment groups ($p < 0.05$) are denoted by distinct letters (a, b, c, d). NC: Normal control; PC: Positive control; DGT: Glibeclamide; D1000JLT: *C. olitorius* Leaf Extract at dose 1000 mg/kg bw; D1800JLF: *C. olitorius* Leaf Extract at dose 1800 mg/kg bw; D1000JFT: *C. olitorius* Fruit Extract at dose 1000 mg/kg bw; D1800JFT: *C. olitorius* Fruit Extract at dose 1800 mg/kg bw

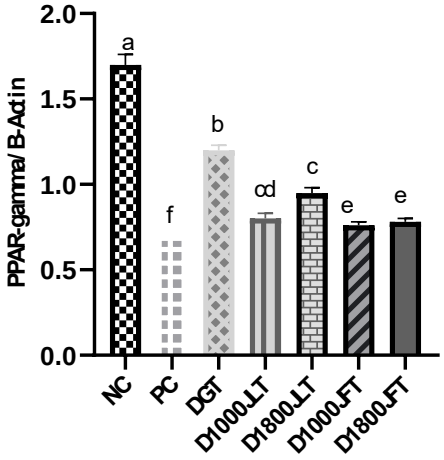


Figure 6a

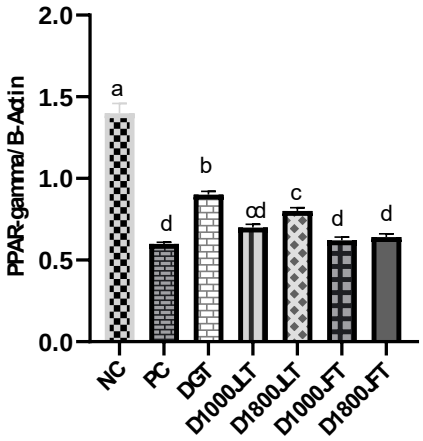
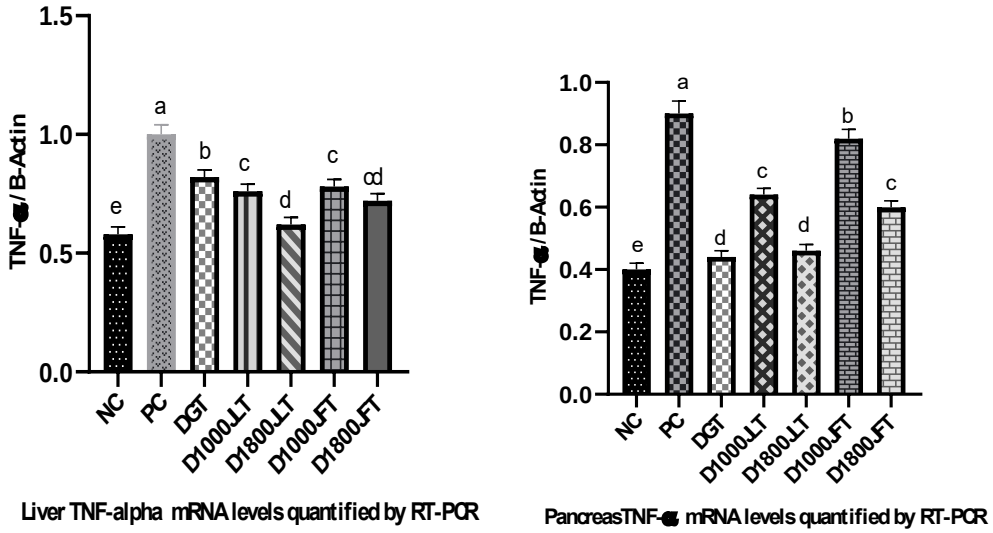


Figure 6b

Figure 6 (a-b): The mRNA expression levels of (a) liver PPAR-γ and (b) kidney PPAR-γ in diabetic rats after *C. olitorius* leaf and fruit extracts administration. The results are presented as mean values ± standard error of the mean (SEM), based on five replicates. Significant differences between treatment groups ($p < 0.05$) are denoted by distinct letters (a, b, c, d). NC: Normal control; PC: Positive control; DGT: Glibeclamide; D1000JLT: *C. olitorius* Leaf Extract at dose 1000 mg/kg bw; D1800JLF: *C. olitorius* Leaf Extract at dose 1800 mg/kg bw; D1000JFT: *C. olitorius* Fruit Extract at dose 1000 mg/kg bw; D1800JFT: *C. olitorius* Fruit Extract at dose 1800 mg/kg bw

effects. [42,43]. Our study revealed a significant, dose-dependent downregulation of GSK-3β mRNA levels following treatment with *C. olitorius* leaf and fruit extracts, with the leaf extract exhibiting a more pronounced effect. The ineffectiveness of glibenclamide in inhibiting GSK-3β activity is likely due to its unique mechanism of action, which targets insulin metabolism via binding to its receptor on pancreatic β-cells, thereby augmenting insulin release and subsequent glucose absorption into the peripheral tissues. This is in accordance with existing literature, which suggests that the glucose-regulating properties of glibenclamide are primarily interfered with by its insulinotropic effects, rather than direct modulation of GSK-3β activity[44]. Furthermore, impaired AKT signalling also leads to dysregulation of GLUT-2, exacerbating the pathological glucose metabolism characteristic of diabetes. GLUT-2 is involved in glucose uptake and metabolism in various tissues.[46] This metabolic activity influences and is influenced by insulin levels.[47] Glibenclamide enhances insulin response by improving peripheral glucose uptake and utilization, stimulating insulin secretion.[48] Our extracts could have influenced the secretion of insulin in the same manner as glibenclamide, thereby bringing about the modulation of GLUT-2 gene expression in the liver, kidney and pancreas. The increase in GLUT-2 gene levels in these organs has been reported in diabetes studies.[49] Comparatively, the *C. olitorius* fruit extracts exhibited reduced efficacy in mobilizing GLUT-2 compared to the leaf extracts, which demonstrated comparable activity to glibenclamide. Notably, at 1800 mg/kg b.w, the leaf extract surpassed the standard drug in terms

of GLUT-2 mobilization, indicating a dose-dependent enhancement of its activity. The flavonoids present in these plant parts might be responsible for this activity. In insulin-sensitive tissues, flavonoids can enhance insulin signalling, which in turn promotes the movement of GLUT-2 to the plasma membrane for the uptake of glucose. Insulin typically triggers the phosphoinositide 3-kinase pathway, which can increase the insertion of GLUT-2 into the membrane of target cells. [47]



A **B**

Figure 7 (a, b): Effect of *C. olitorius* leaf and fruit Extracts on the mRNA expression levels of (a) liver TNF-α and (b) kidney TNF-α of diabetic rats. The results are presented as mean values ± standard error of the mean (SEM), based on five replicates. Significant differences between treatment groups ($p < 0.05$) are denoted by distinct letters (a, b, c, d). NC: Normal control; PC: Positive control; DGT: Glibeclamide; D1000JLT: *C. olitorius* Leaf Extract at dose 1000 mg/kg bw; D1800JLF: *C. olitorius* Leaf Extract at dose 1800 mg/kg bw; D1000JFT: *C. olitorius* Fruit Extract at dose 1000 mg/kg bw; D1800JFT: *C. olitorius* Fruit Extract at dose 1800 mg/kg bw

Effects of C. olitorius leaf and fruit extract on NRF-1 expression in diabetic rats

NRF-1 transcription factor is crucial in the cellular antioxidant response by promoting the expression of antioxidant enzymes encoding genes, for example, glutathione peroxidase, superoxide dismutase and catalase.[50] It was identified as a key player, orchestrating crucial responses in both normal cellular function and pathological conditions including diabetes.[51] A significant downregulation of NRF-1 expression was reported by an earlier investigation done by Aslam et al.[s2] However, treatment with a polyherbal plant extract rich in polyphenols resulted in a marked upregulation of NRF-1 expression.[52] This up-regulation is likely attributed to these phytochemicals,[53] which have been previously identified in Jute plants (*Corchorus spp*.).[54] Various phytochemicals, like polyphenols such as resveratrol, and epigallocatechin gallate may have modulated the cellular defence pathway via the NRF-1 expression. The study's findings indicate that the extracts from the *C. olitorius* plants may have a beneficial effect on diabetic rats by increasing the expression of NRF-1. This may be a result of the antioxidant and anti-inflammatory properties of *C. olitorius* leaf extract. Figure 5 (a-b) illustrates the gene expression profiles of NRF-1 in the kidney and liver of diabetic rats given fruit and leaf extracts from *C. olitorius*. Notably, no significant effects in NRF-1 expression levels were recorded among diabetic animals, standard drug-treated animals, and those receiving plant extracts at 1000 mg/kg body weight. However, a significant up-regulation of NRF-1 expression was seen at 1800 mg/kg, indicating a dose-dependent effect of the plant extracts on NRF-1 expression. The findings of this study align with earlier investigations that have shown
that *C. olitorius* leaf extract has antioxidant, anti-inflammatory, and glucose-lowering effects in diabetic rats.[16,55] Our data indicate that both parts of the *C. olitorius* plant may be a promising treatment for diabetes

Effects of C. olitorius Leaf and fruit extract on PPAR-γ gene expression in STZ-induced diabetes rats

PPAR-γ is a key regulatory molecule in antioxidant and anti-inflammatory pathways, making it a vital component in maintaining cellular homeostasis and preventing disease progression. An effective strategy to trigger antioxidant/anti-inflammatory mediated pathways is through PPARγ agonist action.[56] PPAR-γ is one of the targets of the drugs for T2DM according to Guo et al. [49] It's involved in glucose homeostasis, and also influences how the antioxidant defence systems are modulated. PPAR-γ activation is involved in the improvement of oxidative injury in the liver caused by the intake of a high-fat diet by inducing an endogenous antioxidant defence system.[5,6,7] In diseases, the interactions between PPAR-γ, and antioxidant enzymes are critical. Activation of PPAR-gamma mitigates oxidative stress by upregulating antioxidant enzymes gene expression, including SOD, CAT, and GPx.[10,8,9] Figure 6 (a-b) reveals the gene expression analysis in the liver and kidney of STZ-induced rats with diabetes. It revealed a significant downregulation of PPAR-γ mRNA in untreated diabetic animals (PC) compared to normal controls. Treatment with *C. olitorius* leaf and fruit extracts resulted in a marked upregulation of PPAR-γ mRNA, except *C. olitorius* fruit extract in the liver, which, when compared to the group with diabetes, showed no discernible difference. Notably, the standard drug (DGT) exhibited an effect in upregulating PPAR-γ mRNA compared to both plant extracts. However, the *C. olitorius* leaf extract demonstrated better PPAR-γ expression ability than the fruit extract. From our result, both extracts modulated the expression of PPAR-γ mRNA in the treated groups compared to the diabetes group proportional to the dose. In a study carried out by Chae et al.,[55] the modulation of PPAR-γ was linked to anti-diabetic activity. Our results showed that it is more pronounced in the liver. PPAR-γ is a pivotal regulator of metabolic processes with distinct tissue-specific roles. In the liver, precisely, its modulatory function in lipid and glucose metabolism leads to the improvement in insulin sensitivity.[57]

Effects of C. olitorius Leaf and fruit extracts on the gene expression of TNF-α in STZ-induced diabetic rats

Peroxisome proliferator-activated receptor-gamma (PPAR-gamma) is one of the receptors to reckon with when it comes to inflammatory responses because of its capacity to reduce the production of proinflammatory molecules, stating its anti-inflammatory activity.[5,6,7] In diseases, the interactions between PPAR-gamma and pro-inflammatory cytokines are critical. By preventing the synthesis of proinflammatory cytokines like TNF-α IL-1β, and IL-6, and PPAR-gamma activation reduces inflammation. Figure 7 (a-b) illustrates the gene expression profiles revealing the impact of *C. olitorius* leaf and fruit extracts on TNF-α mRNA levels in diabetic rats' liver and pancreas. Notably, untreated diabetic rats (PC) exhibited a significant upregulation of TNF-α mRNA compared to normal control animals, indicating inflammation in these organs. In contrast, treatment with *C. olitorius* leaf and fruit extracts resulted in a marked downregulation of TNF-α mRNA levels, with both plant extracts doing significantly better compared to the standard drug at the concentrations tested. These findings suggest that *C. olitorius* leaf and fruit extracts may modulate TNF-α expression, potentially mitigating inflammation in diabetes. Tumour necrosis factor-α (TNF-α) levels in the treatment groups revealed statistically significant lower values than those in the diabetes control group. Interestingly, the *C. olitorius* leaf extract, when given at 1800 mg/kg body weight, was just as effective as the standard drug at lowering TNF-α levels. This finding is consistent with the prior study by Sen *et al.*,[56] who observed an upregulation of TNF-α mRNA expression in diabetic subjects, likely due to the inherent inflammatory nature of diabetes, as supported by Tsalamandris *et al*.[59.] The nutraceutical prospect of *C. olitorius* fruit has the potential of enhancing the utilization of *Corchorus olitorius* fruit, and increasing its production considering its huge nutrient-density and promising opportunity in it for food and nutrition security.[60-61] Similarly, African yam bean tubers and *Senecio biafrae* leaf have been reported to be nutrient-dense, with excellent opportunities for enhancing human nutrition and health.[62, 63]

Conclusion

Finally, our study illustrates the prospect of *C. olitorius* leaf and fruit extracts as antidiabetic and antioxidant agents. The extracts exhibited a dose-dependent increase in antioxidant enzyme expression, improved glucose metabolism, and reduced inflammatory cytokine production. Both the leaf and fruit extracts of *C. olitorius* significantly brought down the blood glucose levels in hyperglycemic rats and promoted weight gain comparable to the observed values in the normal control group. However, the leaf extract improved metabolic homeostasis, as well as enhanced anti-inflammatory and antioxidant activities. This study has revealed the nutraceutical potential of *C. olitorius* leaf and fruit. There is a need for awareness about its nutraceutical potential as this will enhance the utilization of this crop and its large-scale production.

Conflict of interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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