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Expression of Cytochrome P450 Pathway Genes CYP3A4 and CYP2D6 in the Liver and Pancreas of STZ-Induced Diabetic Rats

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ABSTRACT

Diabetes mellitus disrupts metabolism and can alter hepatic drug-metabolizing enzymes, including CYP450 isoforms. Medicinal plants like *Eucalyptus globulus* and *Psidium guajava* exhibit antihyperglycemic effects, but their impact on CYP3A4 and CYP2D6 expression in diabetes is not well understood. **Objectives:** To evaluate the antihyperglycemic effects of *Eucalyptus globulus* and *Psidium guajava* extracts and to investigate the expression of CYP3A4 and CYP2D6 genes in the liver and pancreas of streptozotocin (STZ)-induced diabetic rats. **Methods:** This controlled experimental laboratory animal study was conducted on 36 male albino rats divided into six groups (n=6). Diabetes was induced using streptozotocin (STZ)–nicotinamide. Diabetic groups were treated with stem and leaf extracts of *Eucalyptus globulus* and *Psidium guajava* for 15 days. Blood glucose levels were monitored using a glucometer. Expression of CYP3A4 and CYP2D6 in liver and pancreatic tissues was analyzed by RT-PCR, and histopathological examination was performed. **Results:** STZ administration significantly elevated blood glucose levels compared to controls, confirming successful induction of diabetes. Treatment with plant extracts, particularly *Eucalyptus globulus* stem extract, significantly reduced hyperglycemia. In liver tissue, CYP3A4 expression was downregulated in diabetic rats, while CYP2D6 expression was upregulated. Plant treatment tended to restore expression levels toward normal. In pancreatic tissue, *Cyp3a1/2* and Cyp2d expression were not detected by semi-quantitative RT-PCR under the present experimental conditions. **Conclusions:** STZ-induced diabetes alters hepatic CYP450 gene expression, potentially affecting drug metabolism. *Eucalyptus globulus*, particularly the stem extract, demonstrated notable antihyperglycemic activity and partially normalized hepatic CYP expression.

INTRODUCTION

In research, diabetes is commonly induced in animal models using streptozotocin (STZ), a glucosamine-nitrosourea compound produced by the soil bacterium Streptomyces achromogenes, which selectively damages insulin-producing pancreatic β-cells [1]. STZ selectively targets pancreatic β-cells, causing their destruction, reducing insulin production, and thereby inducing hyperglycemia that closely resembles type 2 diabetes. Its reproducible effects across various rodent strains make STZ a widely employed tool for studying the mechanisms, complications, and potential therapies for diabetes [2]. *Psidium guajava*, the scientific name of Guava, has leaves rich in proteins, carbohydrates, fiber, minerals, carotene, nicotinic acid, Vitamin C, vitamin A, and potassium, and is known as a medicinal plant that improves digestion and appetite. Extracts of the leaves have been tested for hypoglycemic activity, and treatment with *P. guajava* not only restores blood glucose homeostasis but also reverses physiological and inflammatory alterations in pancreatic islets. In diabetic albino rats, administration of *P. guajava*

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reduced mean blood glucose by 18.88%, with glycemic assessments and electron microscopy studies suggesting that its beneficial effects are mediated through the rejuvenation, regeneration, and functional activation of pancreatic β-cells [3, 4]. Eucalyptus globulus, commonly known as eucalyptus, has leaves rich in bioactive compounds, including eucalyptol (cineol), rutin, terpineol, sesquiterpenes, various alcohols, aliphatic aldehydes, isoamyl alcohol, ethanol, terpenes, and tannins. Studies in STZ-induced diabetic mice show that *E. globulus* extracts lower blood glucose, demonstrating significant antihyperglycemic effects [5]. Cytochrome P450 (CYP) enzymes, mainly in the liver but also in the small intestine, lungs, placenta, kidneys, and pancreas, metabolize most drugs, with CYP3A4 and CYP2D6 being the most significant [6]. Genetic variations or drug interactions can alter CYP activity, affecting drug efficacy or toxicity. In diabetes, hepatic and pancreatic CYP expression is modified, exposing metabolically active pancreatic β-cells to xenobiotics and reactive intermediates, potentially causing cellular damage [7]. CYP2A6 activates many procarcinogens, with higher activity linked to increased pancreatic cancer risk[8].

Despite known antihyperglycemic effects of *E. globulus* and *P. guajava*, their influence on rat homologs of human CYP enzymes in diabetic conditions remains unclear. This study aimed to evaluate these extracts' effects on blood glucose and expression of rat Cyp3a1/2 and Cyp2d subfamily in the liver and pancreas of STZ-induced diabetic rats.

METHODS

This controlled experimental animal study was conducted at The University of Lahore. The study duration was from February 2021 to February 2022. Thirty-six male albino rats were randomly divided into six groups (n = 6 per group) using a computer-generated sequence. The protocol was approved by the Institutional Animal Ethical Committee (IRB Approval No. COE/Evaluation/IMBB/2021/1009) and conducted according to institutional guidelines for laboratory animals. All occurrences of CYP3A4 and CYP2D6 were replaced with their rat orthologs, Cyp3a1/2 and the Cyp2d subfamily. Based on a priori power analysis (G*Power 3.1, α=0.05, power=0.80), 6 rats per group were sufficient to detect a large effect size (Cohen's d = 0.8). The study evaluated the effects of *Psidium guajava* and *Eucalyptus globulus* extracts on blood glucose and cytochrome P450 gene expression (Cyp3a1/2 and Cyp2d) in a streptozotocin (STZ)-induced diabetes model over 22 days: 7 days of acclimatization, 1 day for diabetes induction, and 15 days of treatment. Rats were housed individually under controlled temperature (20–25°C) with a 12-hour light/dark cycle and free access to standard feed and water. Groups were as follows: Group I: negative control; Group II: positive control (STZ only); Group III: guava stem extract; Group IV: guava leaf extract; Group V: eucalyptus stem extract; Group VI: eucalyptus leaf extract. All rats were confirmed healthy before STZ administration. STZ was given intraperitoneally to Groups II–VI, and Group I received no STZ. The STZ dose was 55 mg/kg body weight, and Nicotinamide (NA) was administered 30 min later at 120 mg/kg body weight. Blood glucose was monitored to confirm diabetes. *E. globulus* and *P. guajava* were authenticated by a botanist. Leaves and stems were shade-dried for 10 days, ground into powder, macerated in distilled water (100 g in 500 mL) for 48 h, filtered, and lyophilized. The dried extracts were reconstituted in olive oil and administered intraperitoneally at 250 mg/kg/day for 15 days. Preliminary phytochemical screening confirmed tannins, flavonoids, and saponins. Blood glucose was monitored periodically. On day 15, rats were euthanized, and the liver and pancreas were collected, each divided into TRIzol (for RNA) and formalin (for histology). RNA was extracted, purity assessed (A260/A280 ≈1.8–2.0), and cDNA synthesized using M-MLV reverse transcriptase (Invitrogen, USA). Semi-quantitative RT-PCR was performed using rat-specific primers (Cyp3a1, Gapdh as control). PCR: 94°C for 3 min, 30 cycles of 94°C 30 s, 58°C 30 s, 72°C 30 s, final extension 72°C 5 min. Products were resolved on 2% agarose gels, stained, visualized under UV, and band intensities quantified using ImageJ, normalized to Gapdh. Tissues were fixed in 10% formalin, processed, stained with hematoxylin and eosin (H&E), and examined under high-power microscopy. GAPDH was used as an internal control for gene expression normalization.

Data normality was assessed using the Shapiro-Wilk test. Given the presence of six experimental groups, a one-way analysis of variance (ANOVA) was performed, followed by Tukey's post-hoc test for multiple comparisons.

RESULTS

A significant increase in the level of blood glucose was observed in STZ-induced diabetic rats when compared to control rats. Administration of Guava (leaves plus stem), and *Eucalyptus globulus* decreased the blood glucose at a significant level (Figure 1).

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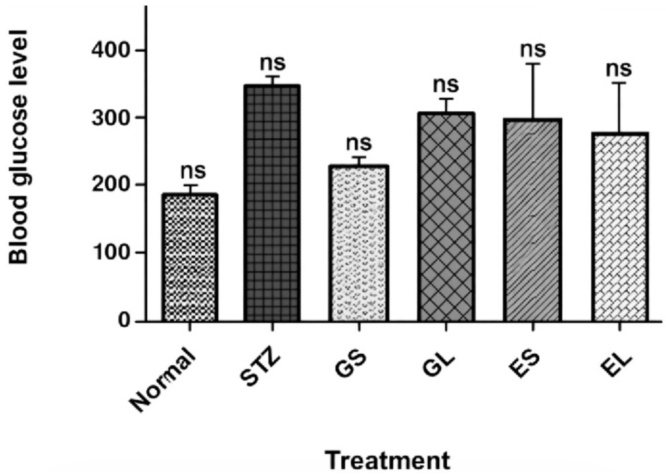

Figure 1: Blood Glucose Level in STZ-Induced Diabetic Rats

(a) Liver of control rat: Histology shows normal hepatic architecture with no signs of inflammation, degeneration, fibrosis, necrosis, steatosis, atypia, or malignancy. (b) Pancreas of control rat: The pancreatic tissue displays normal exocrine and endocrine elements. Islets of Langerhans contain a normal concentration of β-cells, and acinar cells appear healthy. Histological analysis revealed an absence of tissue degeneration, inflammatory infiltration, calcification, granuloma formation, or malignancy. (c) Liver of STZ-induced diabetic rat: The liver shows dense mononuclear infiltration in the portal tract. Hepatocytes exhibit cytoplasmic vacuolation, peripheral nuclei, apoptotic changes, and some hydropic and ballooning degeneration. Early cirrhotic changes are noted in one section. No atypia or malignant changes are present. (d) Pancreas of STZ-induced diabetic rat: The pancreas shows marked fatty infiltration and reduced islet size. Islets of Langerhans have below-normal β-cell density, with inflammatory cell aggregation around β-cells. Acinar cell necrosis is also evident. No atypia or malignancy is observed. (e) Liver of STZ-induced diabetic rat treated with guava leaves: Liver architecture appears normal. Tubular hyperplasia with peritubular lymphocyte cuffing is observed. No degeneration, fibrosis, necrosis, inflammation, atypia, or malignancy is noted. (f) Pancreas of STZ-induced diabetic rat treated with guava leaves: Exocrine pancreas appears normal, while islets show slightly reduced β-cell numbers. Minimal β-cell degeneration is present. No inflammation, calcification, granuloma, or malignancy is observed. (g) Liver of STZ-induced diabetic rat treated with guava stem: Dense mononuclear infiltration is noted in the portal area, with focal tubular hyperplasia and peritubular lymphocyte cuffing. Hepatic tissue shows no degeneration, fibrosis, necrosis, atypia, or malignancy. (h) Pancreas of STZ-induced diabetic rat treated with guava stem: Exocrine pancreas appears normal. Islets contain a moderate number of β-cells and acinar cells, with minimal β-cell degeneration. No inflammation, calcification, granuloma, or malignancy is observed. (i) Liver of STZ-induced diabetic rat treated with eucalyptus stem: The liver shows moderate hepatocyte degeneration and inflammatory cell aggregates, particularly around the hepatic rim. Overall hepatic structure remains intact. No atypia or malignancy is detected. (j) Pancreas of STZ-induced diabetic rat treated with Eucalyptus stem: Histological examination of the pancreas reveals moderate grade islet cell degeneration. The cleavage of inflammatory cells is seen encircling pancreatic lobules. No atypia or malignancy seen. (k) Liver of STZ-induced diabetic rat treated with Eucalyptus leaves: Histological examination of the submitted liver reveals moderate hepatocytic degeneration. The inflammatory cell aggregates are present prominently around the hepatic rim. No atypia or malignancy seen. (l) Pancreas of STZ-induced diabetic rat treated with Eucalyptus leaves: Histological analysis of the pancreatic tissue showed well-preserved exocrine structures. The islets of Langerhans within the endocrine portion contained β-cells and acinar cells at nearly normal levels. No signs of tissue degeneration, inflammation, calcification, granuloma formation, or malignancy were observed (Figure 2).

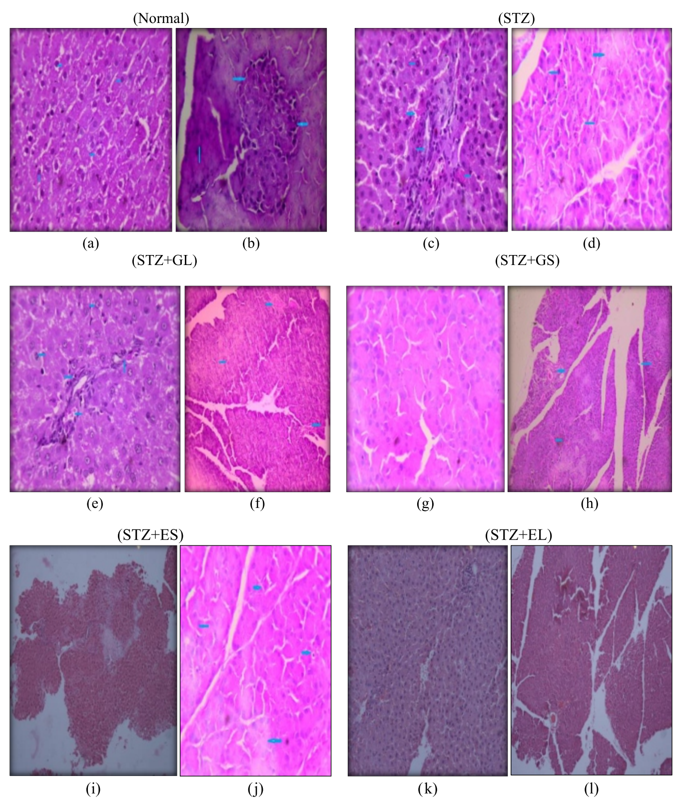

Figure 2: Histopathological Examination of Liver and Pancreas Tissues

After STZ induction, GAPDH was used as an internal control to assess normalization effects (Figure 3).

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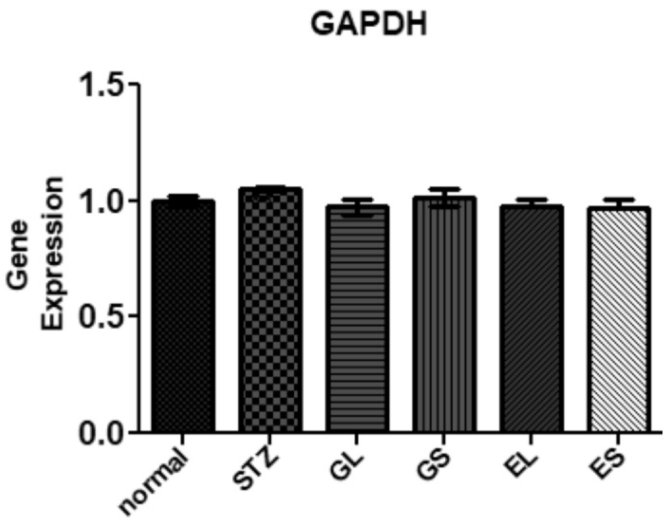

Figure 3: GAPDH Gene Expression in Liver and Pancreas of STZ-Induced Diabetic Rats

CYP3A4 was downregulated in diabetic liver, and Eucalyptus globulus stem extract partially restored it. CYP2D6 was upregulated in diabetic liver, and *Eucalyptus globulus* stem extract partially normalized it. Effect of diabetes and *E. globulus* stem extract on hepatic Cyp3a1/2 and Cyp2d expression. Cyp3a1/2 was downregulated, and Cyp2d was upregulated in diabetic rats; treatment partially restored both expressions(Figure 4).

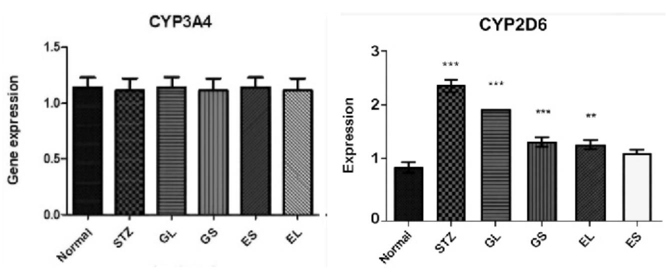

Figure 4: Hepatic CYP3A4 and CYP2D6 Expression in STZ-Induced Diabetic Rats

CYP3A4 expression was absent in diabetic pancreas but partially restored after treatment with Psidium guajava and *Eucalyptus globulus.* CYP2D6 expression was absent in diabetic pancreas and showed partial restoration with the same plant extracts(Figure 5).

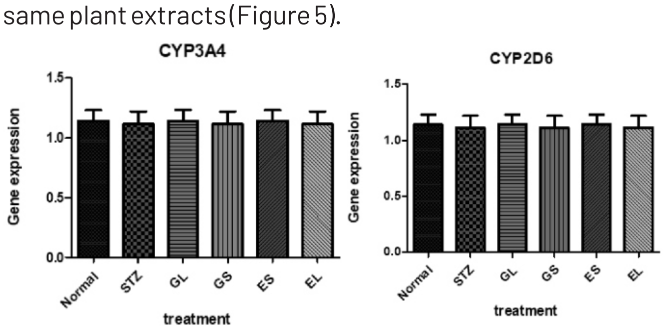

Figure 5: CYP3A4 and CYP2D6 Expression in Pancreas of STZ-Induced Diabetic Rats

DISCUSSION

Diabetes mellitus disrupts blood glucose regulation due to progressive dysfunction or loss of pancreatic β-cells, leading to persistent hyperglycemia and metabolic complications. Pathogenic mechanisms include autoimmune β-cell damage, causing insulin deficiency and defects in insulin signaling, causing resistance [9, 10]. Streptozotocin (STZ), a product of Streptomyces achromogenes, is commonly used to induce experimental diabetes in animals by damaging β-cell membranes, inducing DNA strand breaks, and generating reactive oxygen species (ROS), resulting in oxidative stress and hyperglycemia[11]. The level of glucose in the blood of mice was significantly increased after streptozotocin (STZ) administration compared to untreated control mice. The control animals kept the glucose levels within the normal range. Even the low dose of STZ caused an important hyperglycemic effect, which gradually accumulated with time, until the development of insulin-dependent (type I) diabetes. Histopathological examination of the treated liver using STZ showed dense mononuclear cell infiltration in portal tracts, hepatocyte cytoplasmic vacuolation, apoptotic alterations, and, at times, hydropic or balloon degeneration with some areas showing initial signs of cirrhosis [12]. Similarly, STZ-treated mice showed a significant degeneration and depletion of islet cells in the pancreatic tissue compared to controls. The exposure to STZ caused structural alteration of the lobules of the pancreas with a decrease in the size and number of cells in the islets of Langerhans [13]. Similarly, the pancreas of STZ-treated mice demonstrated loss or degeneration of islet cells compared to controls [2]. The exposure to STZ caused structural alteration of the lobules of the pancreas with a decrease in the size and number of cells in the islets of Langerhans[14]. After STZ induction, high blood glucose levels were observed in Albino rats. Hyperglycemia is a key contributor to the life-threatening complications associated with diabetes mellitus. In this study, *Eucalyptus globulus* and *Psidium guajava* extracts were evaluated for their effects on STZ-induced diabetic rats, and treatment resulted in a significant reduction in blood glucose levels. Although native to Tasmania, *Eucalyptus globulus* (blue gum tree) has been traditionally used for diabetes management in regions of South America and Africa [15]. Its extract is reported to contain high levels of manganese, which may contribute to its hypoglycemic effect [16]. Guava leaves contain numerous bioactive compounds, including various terpenoids. Among these, quercetin, a major flavonoid, exerts spasmolytic effects through a calcium-mediated mechanism [17]. Additionally, the butanol-soluble fraction of a 50% ethanol extract from guava leaves has been shown to prevent increases in plasma glucose levels in diabetic rats and improve glucose

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tolerance [18]. In normal rats, the liver exhibits typical hepatic architecture with no signs of inflammation, hydropic degeneration, fibrosis, necrosis, steatosis, atypia, or malignancy. The pancreas shows normal exocrine tissue, and the Islets of Langerhans contain a healthy concentration of β-cells, with no evidence of degeneration, inflammation, calcification, granuloma, or malignancy. The pancreas of the STZ-induced diabetic rat shows significant fatty infiltration and atrophy of the islet cells. The concentration of β-cells in the diabetic rats was below normal in the Islets of Langerhans following the induction of STZ, and the islets were surrounded by an aggregation of inflammatory cells. Diabetic rats were subsequently treated with stem and leaf extracts of *Eucalyptus globulus* and *Psidium guajava*. In STZ-diabetic rats treated with guava leaves, the liver displayed normal architecture with tubular hyperplasia and peritubular lymphocyte cuffing. The pancreas showed normal exocrine tissue, while the islets contained slightly reduced β-cell numbers, with minimal β-cell degeneration and fewer acinar cells. Administration of guava leaf extract markedly suppressed STZ-induced activation of pancreatic nuclear factor-kappa B (NF-κB) and restored the activities of key antioxidant enzymes, including superoxide dismutase, catalase, and glutathione peroxidase. These findings indicate that the antihyperglycemic effects of *Psidium guajava* are largely mediated through its antioxidant mechanisms [18]. In rats treated with Eucalyptus globulus stem extract, the liver showed moderate hepatocyte degeneration with inflammatory cell aggregates, particularly around the hepatic rim. *Eucalyptus globulus* is recognized for its antihyperglycemic potential and may serve as a valuable dietary supplement for diabetes management, as well as a promising candidate for the development of new orally active antidiabetic agents [19]. The results of this study indicate that diabetes markedly reduces hepatic CYP3A4 activity. Given the liver's central role in drug metabolism, impaired CYP3A4 function may lead to increased bioavailability of its substrate drugs and extend their elimination half-life [20]. The current study shows that antidiabetic plant extracts administered to diabetic rats try to normalize the diabetic level along with the activity of the CYP3A4 gene. As the recent study shows, in STZ-induced diabetic rats, the CYP2D6 gene was upregulated, but the plant extracts, particularly Eucalyptus globulus stem, tried to normalize it back to the normal sample. Thus, it is shown that *Eucalyptus globulus* is the most effective antidiabetic plant among all the plant extracts used. In the pancreas, CYP3A4 and CYP2D6 were not expressed, indicating their absence in the pancreas. However, some data represent the presence of CYP genes in the pancreas. CYP2A6 activity may play a role in carcinogenic pancreatic disease. CYP2A6 has been reported to influence smoking behavior [21], and its enzymatic activity can increase in response to inflammatory conditions [22]. In the endocrine pancreas, CYP1A enzymes are inducible; however, it remains unclear whether CYP1A1 or CYP1A2 are upregulated or functionally active in pancreatic islets, particularly in human tissues. Studies have shown that CYP1A genes can be induced in mouse and human islets following direct in vitro exposure to xenobiotics [23]. While CYP1A2 contributes to the metabolism of several widely used drugs, CYP1A1 and CYP1B1 play a comparatively minor role in drug biotransformation [24]. Interestingly, some environmental contaminants can amplify the genotoxic effects of polycyclic aromatic hydrocarbons (PAHs) through aldo-keto reductases while simultaneously inhibiting CYP1A activity [23]. Tobacco smoke, a known risk factor for pancreatic cancer, is also associated with higher incidences of pancreatitis and diabetes. Many toxic compounds in cigarette smoke reach the pancreas, where cytochrome P450–mediated metabolism is required for their activation. Among human P450 enzymes, CYP2A13 efficiently activates the tobacco-specific carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). Immunohistochemical studies have shown that CYP2A13 is expressed specifically in pancreatic islets, with dual immunofluorescence labeling indicating predominant expression in α-cells rather than β-cells [25].

This study is limited by a small sample size, use of semi-quantitative RT-PCR, and lack of phytochemical profiling, which may affect reproducibility and interpretation. CYP absence in the pancreas may reflect low method sensitivity. Future studies should use qPCR, larger groups, detailed phytochemical analysis, and protein-level assessments.

CONCLUSIONS

STZ-induced diabetes greatly increased the level of blood glucose and brought about histopathological changes in the hepatic and pancreatic tissues. Diabetes was also linked with the change in hepatic expression of CYP3A4 (down-regulation) and CYP2D6 (up-regulation), which might indicate the possibility of altering drug-metabolizing ability in diabetic conditions. *Eucalyptus globulus* stem extract and *Psidium guajava* extract treatment of hyperglycemia and partial restoration of hepatic CYP expression to normal levels, respectively. Under the current experimental conditions, no pancreatic tissue expression of CYP3A4 and CYP2D6 could be detected. Further quantitative and mechanistic studies are required to clarify tissue-specific CYP regulation in diabetes and the pharmacological implications of herbal therapies.

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Authors' Contribution

Conceptualization: NI
Methodology: NI, FI, SA, AA, TAF, EIO
Formal analysis: NI
Writing and Drafting: NI, FI
Review and Editing: NI, FI, SA, AA, TAF, EIO

All authors approved the final manuscript and take responsibility for the integrity of the work.

Conflicts of Interest

All the authors declare no conflict of interest.

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