

Evaluation of Hypoglycemic and Hypolipidemic potentials of Aqueous Extracts of Guava and Mango leaves in Streptozotocin Diabetic Rats

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Abstract

The purpose of this study was to evaluate the hypoglycemic and hypolipidemic effects of aqueous extracts of Guava and Mango leaves either used separately or in a mixture in streptozotocin -induced diabetic rats. Thirty male adult rats were divided into five groups, each with six rats, and evaluated as follows: group 1 normal non diabetic rats (negative control); group 2 Diabetic untreated rats (positive control); group 3 diabetic treated with Guava leaves aqueous extract (GLAE) (500 mg/kg b.wt/day); group 4 :diabetic treated with Mango leaves aqueous extract (MLAE)(500 mg/kg b.wt/day); group five: diabetic treated with mixture of both tested plants extract. After four weeks of extracts administration, blood samples were taken to assess several biochemical markers. The results of the present study demonstrated a significant elevation in blood glucose levels, accompanied by a marked reduction in serum insulin concentrations in diabetic untreated rats, compared to normal (negative control) rats. Furthermore, the diabetic untreated group (positive control) exhibited a significant increase in serum levels of total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and very-low-density lipoprotein cholesterol (VLDL-C), along with a significant decrease in high-density lipoprotein cholesterol (HDL-C), compared to the negative control group. Streptozotocin administration also induced a noticeable loss in body weight gain in the diabetic untreated rats. In contrast, oral administration of aqueous extracts of guava and mango leaves, either individually or in combination, in diabetic rats resulted in significant reductions in blood glucose levels and significantly improved serum insulin concentrations. Moreover, notable improvements in the lipid profile were observed, as evidenced by a significant reduction in serum total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), and very low-density lipoprotein cholesterol (VLDL-C), along with a significant increase in high-density lipoprotein cholesterol (HDL-C), compared to diabetic untreated rats (positive control). Additionally, the weight loss induced by streptozotocin was ameliorated by treatment with guava leaf extract, mango leaf extract, or their combination. Both plant extracts demonstrated significant hypoglycemic and hypolipidemic effects in diabetic rats. These results highlight the therapeutic potential of aqueous extracts of guava and mango leaves either used separately or in a mixture for the management of type 2 diabetes accompanied by hyperlipidemia.

Keywords: Guava leaves, Mango leaves, Diabetes mellitus, Streptozotocin, glucose levels, insulin levels and rats.

INTRODUCTION

Diabetes mellitus (DM) is a major global health concern and one of the leading causes of morbidity and mortality worldwide (**Wang et al., 2019**). In recent years, its prevalence has increased markedly, reflecting a growing public health challenge. According to the International Diabetes Federation (IDF), an estimated 589 million people worldwide were living with diabetes in 2024, and this figure is projected to reach 853 million by 2050. Notably, Egypt ranked among the top ten countries globally in terms of diabetes prevalence in 2024 (**IDF, 2025**).

Diabetes is generally characterized by chronic hyperglycemia together with the disturbance of carbohydrate, fat, protein metabolism resulting from a defect of insulin secretion, insulin action or both (**WHO, 2019**). Diabetes is closely associated with an elevated risk for atherosclerotic cardiovascular disease (ASCVD), primarily due to dyslipidemia (**Maezawa et al., 2023**). Dyslipidemia associated with type 2 diabetes (T2D) is typically characterized by elevated triglyceride (TG) levels, reduced high-density lipoprotein cholesterol (HDL-C), and an increase in small, dense low-density lipoprotein cholesterol (LDL-C (**Yumiko et al., 2025**)). accordingly, the management of abnormal lipid profiles is essential to lower the risk of cardiovascular incidents and prevent microvascular complications in individuals with diabetes (**Maezawa et al., 2023**).

plants and plant-derived products have gained attention as potential therapeutic agents for managing diabetes due to their high antioxidant content, Studies have indicated that various plant-based byproducts—such as seeds, bark, roots, leaves, peels, and flowers—possess bioactive compounds with both antioxidant and anti-diabetic effects, which may rival those of existing pharmaceutical treatments (**Naveen & Baskaran, 2018**).

Psidium guajava (family: Myrtaceae) is a plant recognized for its considerable nutritional and medicinal value. It is cultivated in various regions across the world, particularly in South America and Brazil, and has a long

history of traditional use as a hypoglycemic agent. Supporting its traditional applications, numerous pharmacological studies have documented its wide range of therapeutic properties, including antacid and ulcer-protective effects, antioxidant activity, antihypertensive action, anti-allergic and antibacterial effects, hypolipidemic potential, as well as laxative, antispasmodic, antitussive, antidiabetic, and anti-inflammatory activities (**Raj et al 2022**).

Mangifera indica L., a member of the family Anacardiaceae, is a prominent tropical fruit species native to South and Southeast Asia. Phytochemical investigations of mango leaf (ML) extracts have led to the isolation and identification of diverse bioactive compounds, including five benzophenones and seventeen flavonoids. Extensive pharmacological studies have highlighted the broad spectrum of biological activities exhibited by ML extracts, encompassing anti-cancer, antidiabetic, antioxidant, antimicrobial, anti-obesity, lipid-lowering, hepatoprotective, and antidiarrheal properties. These multifunctional bioactivities position *M. indica* leaves as a valuable natural resource for potential therapeutic applications (**Thomas et al., 2025**).

Therefore, the aim of the present study was to investigate the hypoglycemic and hypolipidemic effects of aqueous extracts of guava and mango leaves, administered either individually or in combination, in streptozotocin-induced diabetic rats.

MATERIALS AND METHODS

1. Plant Material: The leaves of *Mangifera indica* (Mango) and *Psidium guajava* (guava) were collected freshly from Agriculture Research Center, Cairo, Egypt.

2. Chemicals: Streptozotocin (STZ) (Batch No.126k1174) were purchased from El-Gomhoriya Pharmaceutical Company, Cairo, Egypt.

3. Experimental animals: Thirty adult male albino rats with initial body weights ranging from 150 to 200g were purchased from Farm of experimental animals in Helwan, Egypt. Rats were kept in plastic cages under strict hygienic conditions ($24 \pm 1^\circ\text{C}$, $55 \pm 5\%$ humidity and 12-h light: 12- h dark cycle) and fed on the basal diet for one week before start of the experiment for

acclimatization. Water was provided ad libitum during experimental period (4 weeks).

4. Preparation of plant Extracts: Fresh leaves of *Mangifera indica* (mango) and *Psidium guajava* (guava) were collected from the Agricultural Research Center in Cairo, Egypt. The leaves were sorted to remove any dead matter and foreign particles, then thoroughly washed with tap water. After washing, the leaves were cut into small pieces, air-dried at room temperature, and subsequently ground into a fine powder using an electric grinder. The aqueous infusion was prepared according to the method described by **Swanston-Flatt et al. (1990)**. Briefly, the powdered plant material was added to boiling water and allowed to infuse for 15 minutes. The infusion was then filtered, and the filtrate was freshly used for experimental purposes.

5. Induction of Diabetes: Diabetes was induced by an intraperitoneal injection of freshly prepared streptozotocin at a dose of 45 mg/kg body weight dissolved in a citrate buffer (0.1M, pH 4.5) to the overnight fasted rats (**Burcelin et al., 1995**). After 72 hrs of STZ administration the rats with fasting blood-glucose levels more than 250 mg/dL were considered as diabetic and used for the study according to method of (**El-Sawi et al., 2017**).

6. Experimental design: Thirty rats were divided into five groups (6rats each).

Group 1: normal non diabetic rats were fed on basal diet only, (negative control).

Group 2: Diabetic untreated rats were fed on basal diet only, (positive control).

Group 3: diabetic rats were fed on basal diet and orally given aqueous extract of Guava leaves (500 mg/kg b.wt/once/day) for 4weeks.

Group 4: diabetic rats were fed on basal diet and orally given aqueous extract of Mango leaves (500 mg/kg b.wt/once/day) for 4weeks.

Group 5: diabetic rats were fed on basal diet and orally given a mixture of both plants aqueous extracts (500 mg/kg b.wt *M. indica* + 500 mg/kg b.wt. *guajava* once/day) for 4weeks.

7. Serum Biochemical analysis: Glucose was determined according to the method of described by **Asatoor and King (1954)**. Serum insulin was determined according to the method described by (**Temple et al., 1992**). total cholesterol (TC) was determined according to the method described by **Allain et al., (1974)**. Triglyceride (TG) was determined according to the method described by **Fossati and Prenape, (1982)**. High-density lipoprotein-cholesterol (HDL-C) was determined according to the method of (**Burtis and**

Ashwlood .,2001) .Low-density lipoprotein-cholesterol (LDL-C) and very low-density lipoprotein-cholesterol (VLDL-C) were calculated according to the method of (Friedwald et al ., 1972).

8. Statistical Analysis: All data obtained were analyzed using Statistical Package for the Social Sciences (SPSS) for Windows, version 20 (SPSS Inc., Chicago, IL, USA). Collected data were presented as mean± standard deviation (SD). Analysis of Variance (ANOVA) test was used for determining the significances among different groups according to (Armitage and Berry, 1987). The values were considered to be significantly different when the P value was less than 0.05.

RESLTS

Table (1) illustrates the changes in serum glucose levels in all experimental groups. In diabetic untreated rats (positive control group) there was significant elevation in glucose levels as compared with normal rats (negative control group). However, diabetic rats treated with aqueous extract of Guava and Mango leaves either individually or in a combination showed significant reduction in blood glucose levels ($p < 0.05$) as compared with diabetic untreated rats positive control group). The highest reduction in serum glucose levels in diabetic rats was achieved by using mixture of both plant extracts.

Table (1): Effect of oral administration of GLAE and MLAE on serum glucose (mg/dl) in STZ induced diabetic rats.

Groups	Glucose (mg/dl) Mean±SD	Glucose Reduction (%)
Normal rats	88.510±3.12 ^d	
Diabetic untreated rats	250.35±1.75 ^a	
Diabetic rats treated with GLAE	128.50±3.77 ^b	48.67
Diabetic rats treated with MLAE	132.11±3.19 ^b	47.22
Diabetic rats treated with a Mixture of GLAE & MLAE	108.24±1.65 ^c	56.78

Values with different superscript letters within a same column are significantly different at $p<0.05$, while those with similar or partially similar are not significant.

Results in **Table (2)** showed that the serum insulin level of the diabetic non-treated rats (positive control group) was significantly ($p < 0.05$) lower as compared to normal rats (negative control group). The oral administration of GLAE and MAE either separately or in combination to diabetic rats resulted in a significant ($p < 0.05$) increase in the serum insulin level compared with positive control group. However, the increase in insulin among treated diabetic rats was significantly lower ($p < 0.05$) than among normal rats (negative control group).

Table (2): Effect of oral administration of GLAE and MLAE on serum insulin (IU/L) in STZ induced diabetic rats.

Groups	Insulin (IU/L) Mean \pm SD
Normal rats	134.50 \pm 2.21 ^a
Diabetic untreated rats	77.76 \pm 3.17 ^e
Diabetic rats treated with GLAE	90.62 \pm 2.62 ^d
Diabetic rats treated with MLAE	101.28 \pm 1.49 ^c
Diabetic rats treated with a Mixture of GLAE & MLAE	120.26 \pm 1.49 ^b

Values with different superscript letters within a same column are significantly different at $p < 0.05$, while those with similar or partially similar are not significant.

As shown in **Table (3)**, body weight gain decreased significantly in diabetic untreated rats compared with normal rats. On the other hand, the oral administration of GLAE and MLAE either separately or in combination to diabetic rats caused significant ($P < 0.05$) increase in body weight gain compared to diabetic untreated rats (positive control group). While these increases in body weight gain among treated groups were significantly ($P < 0.05$) lower than among normal rats.

Table (3): Effect of oral administration of GLAE and MLAE on Body weight gain percent in STZ induced diabetic rats

Groups	IBW (g)	FBW (g)	BWG %
Normal rats	203.22±1.12 ^a	267.14±1.82 ^a	31.45±0.45 ^a
Diabetic untreated rats	204.13±1.02 ^a	223.33±1.12 ^e	9.40±1.03 ^e
Diabetic rats treated with GLAE	206.37±1.27 ^a	246.13±1.06 ^c	19.26±1.10 ^c
Diabetic rats treated with MLAE	205.30±1.30 ^a	230.96±1.54 ^d	12.49±0.81 ^d
Diabetic rats treated with a Mixture of GLAE & MLAE	206.78±1.07 ^a	254.26±1.18 ^b	22.96±0.97 ^b

Values with different superscript letters within a same column are significantly different at $p<0.05$, while those with similar or partially similar are not significant.

Results of the effect of daily treatment of GLAE and MLAE., for 4 weeks on serum total cholesterol (TC), triglycerides TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) and very low-density lipoprotein cholesterol (VLDL-C) levels in diabetic rats are presented in **Table (4)**.

Compared to normal rats (negative control group), the diabetic non-treated rats (positive control group), demonstrated a significant elevation ($p<0.05$) in serum TC and TG. Diabetic rats orally administered GLAE and MLAE either separately or in combination showed a significant decrease in serum TC and TG levels when compared to the positive control group ($p<0.05$). However, the decrease in serum TC and TG among treated groups was significantly lower than among normal rats (negative control rats). The effect of GLAE on TC and TG did not differ significantly from MLAE.

The data on the effect of daily treatment of GLAE and MLAE for 4 weeks on serum levels of HDL-c in diabetic rats is presented in Table (4). The results showed that there was a significant decrease ($p<0.05$) in the serum levels of (HDL-C) in diabetic non-treated group (positive control group) when

compared to normal rats (negative control group). The oral administration of GLAE and MLAE either separately or in combination to diabetic rats significantly increased ($p < 0.05$) the serum levels of HDL-C as compared to positive control group. However, the serum HDL-c level among treated groups was significantly lower than among normal rats (negative control rats). The GLAE and MALE did not differ significantly in the effect on serum level of HDL-c. Regarding the effect of daily treatment of GLAE and MLAE for 4 weeks on serum levels of LDL-c and VLDL-c in diabetic rats, the results are presented in Table (4). The diabetic untreated rats (positive control group) showed a significant elevation in serum levels of LDL-c and VLDL-c compared with the negative control group. Oral administration of GLAE and MLAE either separately or in combination to diabetic rats resulted in a significant decrease in the serum levels of LDL-c and VLDL-c ($p < 0.05$) compared with the diabetic untreated group. However, the improvement in serum levels of LDL-c and VLDL-c among diabetic rats orally given GLAE and/or MLAE was significantly ($p < 0.05$) lower than among the negative control group. Administration of GLAE and MLAE separately to diabetic rats resulted in a similar effect on LDL-c and VLDL-c.

Table (4): Effect of oral administration of GLAE and MLAE on serum lipid profiles (TC, TG, HDL-c, LDL-c & VLDL-c) in STZ induced diabetic rats.

Groups	TC (mg/dl)	TG (mg/dl)	HDL-c (mg/dl)	LDL-c (mg/dl)	VLDL-c (mg/dl)
Normal rats	130.40±4.27 ^d	90.00±1.870 ^e	65.19±2.68 ^a	47.21±3.37 ^d	18.00±0.37 ^e
Diabetic Rats	230.10±3.12 ^a	193.27±3.198 ^a	24.76±3.12 ^d	166.68±6.10 ^a	38.65±0.63 ^a
DR. Treated with GLAE	181.74±1.54 ^b	153.35±3.065 ^c	42.80±1.32 ^c	108.27±2.33 ^b	30.67±0.61 ^c
DR. Treated with MLAE	183.60±1.70 ^b	169.52±2.322 ^c	45.00±1.14 ^c	104.69±2.80 ^b	33.90±0.46 ^c
DR. Treated by Mixture of GLAE & MLAE	156.15±2.13 ^c	125.36±2.393 ^d	56.21±1.28 ^b	74.86±2.73 ^c	25.07±0.47 ^d

Values with different superscript letters within a same column are significantly different at $p < 0.05$, while those with similar or partially similar are not significant.

DISCUSSION

As evident from the present study, diabetic untreated rats exhibited a significant elevation in plasma glucose levels accompanied by a marked reduction in serum insulin levels, compared to normal (negative control) rats. these findings are consistent with previous studies. These findings are consistent with those of **El-Sawi et al., (2017)**, who observed that administration of STZ at a dose of 50 mg/kg body weight in normal rats effectively induced diabetes, as evidenced by a significant elevation ($p < 0.05$) in blood glucose levels compared to the control group. Similarly, **Sai Varsha et al., (2015)** demonstrated that intraperitoneal injection of STZ (35 mg/kg) into male albino Wistar rats led to a significant decrease in plasma insulin levels within 72 hours. In the same line with these results, **Nagrashi et al., (2015)** also confirmed that administration of STZ at 50 mg/kg body weight induced diabetes and significantly elevated serum glucose levels in rats.

Streptozotocin is a naturally occurring nitrosourea compound widely used to induce experimental diabetes due to its selective cytotoxic effects on pancreatic β -cells. Its diabetogenic action is believed to involve multiple mechanisms, including the generation of lipid peroxides and excessive reactive oxygen species (ROS), interference with the glucose transporter GLUT-2, and induction of DNA damage either through alkylation or peroxynitrite formation (**Turk et al., 2003**). The resulting DNA strand breakage activates poly (ADP-ribose) polymerase (PARP), leading to ATP depletion, β -cell death, and a consequent decline in insulin production (**Rupérez et al., 2008**).

In the present study, treatment with aqueous extract of guava leaves in diabetic rats, resulted in significant decrease in blood glucose levels accompanied with significant increase in serum insulin levels. These findings are in agreement with several previous studies. In the study conducted by **Luambia et al., (2024)** aqueous extract of *Psidium guajava* leaves lowered blood glucose levels more rapidly than metformin (hypoglycemic drug) in diabetic rats. Furthermore, it more effectively prevented disruptions in glucose metabolism, and the generation of reactive oxygen species. These protective effects were attributed to the extract's antioxidant constituents, including phenols, alkaloids, quercetin, and flavonoids. Also, **Tella et al., (2022)** evaluated the antidiabetic potential of *Psidium guajava* leaf aqueous extract in

streptozotocin-induced diabetic rats. Treatment with *Psidium guajava* aqueous extract significantly ameliorated pancreatic islet damage and improved glucose tolerance and increased skeletal muscle glycogen content as evidenced by reduced blood glucose levels., suggested that the antidiabetic properties of *Psidium guajava* may be attributed to its ability to modulate glycogen metabolism, likely by its phenolic and triterpenoid constituents **Tella *et al.*, (2022).**

Several studies demonstrated that the hypoglycemic effect of guava leaves may be attributed to its high content of flavonoids especially, quercetin (**Momtaz *et al.*, 2025; Ahmad et al 2025 and Luambia *et al.*, 2024).** (**Radwan et al., 2018**). Quercetin is potent antioxidant contributes to the regulation of blood glucose levels through multiple mechanisms. It mitigates oxidative stress by scavenging reactive oxygen species (ROS), commonly known as free radicals, thereby protecting pancreatic β -cells from damage and enhancing insulin secretion (**Zhang, et al., 2019**). Quercetin also inhibits the activity of α -glucosidase enzymes, thereby reducing postprandial blood glucose levels by limiting the breakdown of carbohydrates and their subsequent conversion into glucose. Additionally, it activates the AMP-activated protein kinase (AMPK) pathway, which facilitates glucose uptake in muscle and liver tissues and promotes its conversion into glycogen for storage (**Ahmad et al 2025**).

In addition to quercetin, guava leaves contain other bioactive flavonoids such as guaijaverin and avicularin, which contribute significantly to the preservation and functional improvement of pancreatic β -cells (islets of Langerhans) and exhibit antidiabetic properties. Guaijaverin has been shown to downregulate the activity of dipeptidyl peptidase-IV (DPP-IV), an enzyme involved in glucose homeostasis. Meanwhile, avicularin aids in preventing intracellular lipid accumulation by enhancing glucose uptake mechanism through the activation of the GLUT-4 (glucose transporter type 4) pathway, thus improving insulin sensitivity (**Ahmad et al., 2025**).

Results of the hypoglycemic effects of aqueous extract of Mango leaves which are in agreement with several previous studies carried on mango extracts. The study conducted by **Maghfuri *et al.*, (2022)** involved forty adult male albino rats, which were randomly divided into four groups (n=10 per group):

Group 1—healthy control (HC), Group 2—untreated diabetic (UD), Group 3—mango leaf extract-treated diabetic (MTD), and Group 4—mango leaf extract-treated non-diabetic (MT). Following eight weeks of mango leaf extract (MIL) administration, the results demonstrated that treatment with MIL extract in diabetic rats led to significant reductions in fasting blood glucose, glycated hemoglobin (HbA1c), and amylase enzyme activity. Additionally, there was a marked increase in serum levels of insulin.

Also, **Khan *et al.*, (2024)** evaluated the insulin-releasing and glucose-lowering potential of the extract of *Mangifera indica* leaves (EEMI) in streptozotocin-induced type 2 diabetic (STZ-T2D) rats, EEMI demonstrated a dose-dependent stimulation of insulin secretion from both clonal BRIN-BD11 β -cells and isolated mouse islets. It significantly inhibited starch digestion, glucose diffusion, and DPPH radical activity in vitro. The authors revealed that the ethanolic extract of *Mangifera indica* (EEMI) was found to contain a diverse spectrum of pharmacologically active constituents, including alkaloids, tannins, saponins, flavonoids, and reducing sugars. Notably, many of these bioactive compounds have been associated with enhanced glucose regulation in type 2 diabetes mellitus (T2DM) via multiple biological mechanisms (**Ansari, *et al.*, 2023 and Olasehinde *et al.*, 2018**)

Tannins and specific alkaloids have been demonstrated to promote glucose uptake and regulate glucose homeostasis through multiple signaling pathways, including the phosphatidylinositol 3-kinase (PI3K) and AMP-activated protein kinase (AMPK) pathways (**Muthusamy *etal.*, 2008 and Li *et al.*, 2017**). Additionally, the synergistic combination of triterpenoids and saponins has shown promising effects in inhibiting intestinal glucose absorption, thereby contributing to improved glycemic control (**Khan *et al.*, 2024**)

Four bioactive compounds isolated from MILs, norathyriol, mangiferin, and manindicins A and B—demonstrated significant antidiabetic activity. Notably, norathyriol exhibited potent α -glucosidase inhibitory activity, with an IC_{50} value of 4.22 ± 0.19 μ g/mL, making it approximately four times more effective than the widely used commercial α -glucosidase inhibitor, acarbose (IC_{50} : 16.28 ± 1.22 μ g/mL) (**Gu *et al.*, 2019**). Similar observations were obtained by **Saleem *et al.*, (2019)** who reported that the hypoglycemic effects of

Mangifera indica leaf extract are largely attributed to its rich composition of bioactive phytochemicals, including mangiferin, iriflophenone 3-C- β -D-glucoside, quercetin, gallic acid, and various polyphenolic constituents. Mangiferin has demonstrated notable antidiabetic activity by enhancing insulin sensitivity and inhibiting α -glucosidase. Iriflophenone 3-C- β -D-glucoside has also been reported to exert hypoglycemic effects (**Pranakhon et al., 2015**). Additionally, gallic acid has been shown to upregulate GLUT4 expression, thereby facilitating glucose uptake (**You et al., 2019**). Moreover, Quercetin, a prominent flavonoid in the extract, contributes to glycemic regulation by protecting pancreatic tissue and enhancing the activity of endogenous antioxidant enzymes (**Gupta., 2018**). Overall, phenolic compounds in the extract are known to lower blood glucose levels by inhibiting key metabolic enzymes such as α -glucosidase and pancreatic lipase (**Saleem et al., 2019**).

As clear from the present findings, the treatment with mixture of both aqueous extracts of *Psidium guajava* and *Mangifera*, possess a significant hypoglycemic action. These findings are in agreement with **Rawi et al., (2011)**, who similarly reported a significant reduction in blood glucose levels following the administration of *M. indica* and *P. guajava* water extracts. The hypoglycemic potentials observed was attributed to presence of several phytochemical constituents, including glycosides, alkaloids, saponins, tannins, resins, and triterpenes (**Rawi et al., 2011**).

In the study, body weight decreased significantly in diabetic untreated rats (positive control group) compared with normal rats. Similar findings were reported by number of researchers., **Yusuf et al., (2023)** reported that the diabetic group experienced a statistically significant reduction in body weight compared to the control group ($p < 0.05$). Also, **Ramakrishnan et al., (2017)** who indicated that streptozotocin induced diabetic rats significantly decreased the body weight when compared to normal rats.

The reduction in body weight observed in diabetic rats is primarily due to the accelerated catabolism of lipids and structural proteins, which are utilized as alternative energy sources in the absence of sufficient carbohydrates (**krishnasamy., 2013**). Furthermore, under conditions of insulin resistance or deficiency, muscle wasting and subsequent weight loss occur as a result of

increased protein degradation, supplying amino acids necessary for gluconeogenesis (Florence et al., 2014). In the same direction, **Frier and Fisher (2006)** stated that insulin deficiency leads to enhanced lipolysis and proteolysis, ultimately resulting in significant weight loss. In the absence of insulin, cells are unable to effectively utilize glucose, body's preferred energy source, thereby increased in lipolysis from adipose tissue and the degradation of proteins for energy. Similarly, **Vasudevan and Sreekumari, (2007)** postulated that insulin deficiency promotes lipolysis in adipose tissue and enhances protein catabolism. The characteristic reduction in body weight observed in streptozotocin-induced diabetic models may be attributed to increased muscle wasting and the depletion of tissue proteins (**Shirwaikar et al., 2004; Kato et al., 2008**)

In the current study, the oral administration of aqueous extract of guava leaves caused significant increase in body weight compared to diabetic non treated rats (positive control group). Similar observations were obtained by **Luambia et al., (2024)** who reported that diabetic rats treated with guava leaf extract-maintained body weight, which may be attributed to the presence of antioxidants such as flavonoids and other bioactive constituents within the extract. These compounds are believed to protect pancreatic islet β -cells from further damage and contribute to the reduction of blood glucose levels (**Diaz-de-Cerio et al., 2016**). Also, **Radwan et al., (2018)** indicated that treatment of the diabetic rat model with guava leaf extract, led to a restoration of body weight gain to normal values. This effect was closely associated with an improvement in insulin levels. The elevation in insulin facilitates the utilization of glucose as the primary energy source, thereby meeting the caloric requirements of cells. Consequently, the catabolic processes of proteolysis and lipolysis are reduced, which may account for the returning of weight gain to its normal level.

In the present study, diabetic untreated rats (positive control group) showed significant increase in serum total cholesterol (TC) , Triglycerides (TG) , low density lipo protein cholesterol (LDL-C) and very low density lipoprotein-cholesterol (VLDL-C) levels accompanied by a significant decrease in the serum levels of high density lipoprotein-cholesterol (HDL-C) when compared with normal rats (negative control group).

Diabetes is closely associated with significant alterations in plasma lipid and lipoprotein profiles, contributing to an elevated risk of coronary heart disease (**Atawodi et al., 2014**). The alterations in lipid profile parameters observed in streptozotocin-induced diabetic rats are likely attributable to insulin deficiency. The destruction of pancreatic β -cells leads to a marked reduction in plasma insulin levels, resulting in hyperlipidemia and hypercholesterolemia due to the disruption of normal metabolic processes (**Rasineni et al., 2010**). the elevation in serum total cholesterol level in diabetic rats may be due to the inability to metabolize carbohydrates as an energy source, thus, the subsequent use of free fatty acids for energy causes increase of cholesterol synthesis (**Yao et al., 2008**). Under normal conditions, insulin suppresses the production of very low-density lipoprotein (VLDL) by inhibiting the synthesis of apolipoprotein B (apoB), an essential structural component of VLDL (**Yumiko et al 2025**).

The results of the hypolipidemic effects of aqueous extract of guava leaves are in agreement with several previous studies. In the study conducted by **Mac-Kalunta et al., (2022)** the administration of guajava leaves extract resulted in significant reduction in low-density lipoprotein (LDL) levels. Triglyceride (TGC) levels and total cholesterol levels were also reduced. While, High-density lipoprotein (HDL) levels increased from 32 mg/dL to 57 mg/dL. The authors suggested that that *P. guajava* leaf extract exhibits anti-hyperlipidemic properties. **Akinloye et al., (2010)** investigated the effects of aqueous Psidium guajava leaf extract on diabetic rabbits fed a high-cholesterol diet. Administration of the extract resulted in a significant reduction in plasma cholesterol levels, alongside a notable increase in high-density lipoprotein (HDL) by 69% and a marked decrease in low-density lipoprotein (LDL) levels by 74%. Also, **Shabbir et al., (2020)** reported that the administration of polyphenols (200–250 mg/kg.bw) extracted from guava pulp, seeds, and leaves led to a significant improvement in blood lipid profiles. Specifically, total cholesterol (TC) and low-density lipoprotein (LDL) levels were significantly reduced ($p < 0.05$), while high-density lipoprotein (HDL) levels were elevated in the groups administered guava-derived polyphenols. These results may be attributed to the ability of polyphenols to reduce cholesterol absorption and biosynthesis, and also, enhancing fecal excretion of bile acids and cholesterol.

Rawi et al. (2011) demonstrated that treatment of streptozotocin-induced diabetic rats with *Psidium guajava* leaf extract resulted in a marked improvement in altered serum and hepatic lipid parameters. The leaves of *P. guajava* are known to be rich in bioactive compounds such as flavonoids—particularly quercetin—tannins, phenols, and triterpenes, which contribute to their antioxidant activity. The hypolipidemic effect of quercetin may be attributed to its capacity to stimulate insulin secretion, thereby reducing plasma cholesterol and triglyceride levels. Moreover, the extract's free radical-scavenging and antioxidant properties may further contribute to lipid-lowering effects by inhibiting hepatic 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, a key enzyme in the cholesterol biosynthesis pathway.

In the same cell line, **Constança et al., (2020)** revealed that the aqueous extract of guava leaves are rich in phenolic compounds. The extract demonstrated strong antioxidant activity and significant acetylcholinesterase inhibitory effects. The authors suggested that the extract of guava leaves exerts its lipid-lowering potentials by reducing cholesterol absorption across intestinal wall and by inhibiting cholesterol biosynthesis through suppression of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGR) activity and downregulated the expression of the cholesterol transporter NPC1L1. Also, limiting cholesterol permeation through the intestinal barrier.

The results of the present study demonstrated the hypolipidemic effect of aqueous extract of mango leaves which are in agreement with results of previous studies. The study conducted by **Liu et al., (2023)** demonstrated the anti-dyslipidemic effects of *Mangifera indica* leaf extract (MLE) in rats with high-fat diet-induced hyperlipidemia. The results indicated that high doses of MLE significantly improved serum lipid profiles by reducing total cholesterol (TC), triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C). Also, **Khan et al., 2024** reported that ethanolic extract of *Mangifera indica* (EEMI) significantly improved lipid profiles, indicating its potential to lower non-esterified fatty acids (NEFA) levels through multiple mechanisms. These include inhibition of HMG-CoA reductase activity, suppression of hepatic glucose production, and enhancement of peripheral glucose uptake.

In another investigation, the cholesterol-lowering effect of *Mangifera indica* leaf (MIL) extract was evaluated in vivo using female albino Wistar rats.

The methanolic extract of *M. indica* leaves demonstrated significant hypocholesterolemia activity in a high-cholesterol diet-induced hypercholesterolemia model when administered at a dose of 90 mg/kg body weight. A notable reduction in plasma triglyceride levels was also observed following treatment with the extract (Gururaja *et al.*, 2017).

Dineshkumar *et al.*, (2010) evaluated the hypolipidemic effects of mangiferin in both type 1 and type 2 diabetic rat models. Mangiferin was administered intraperitoneally at doses of 10 and 20 mg/kg daily for 30 days. The results demonstrated a significant reduction in fasting blood sugar (FBS), total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), and very-low-density lipoprotein (VLDL) levels, along with an increase in high-density lipoprotein (HDL) levels in type 2 diabetic rats.

The cholesterol-lowering effects *Mangifera indica* leaf (MIL) extract were believed to result from the combined actions of various phytoconstituents through multiple mechanisms. Water-soluble flavonoids in the extract may contribute by inhibiting HMG-CoA reductase, while nonpolar sterols such as 3 β -taraxerol are likely to compete with dietary cholesterol for intestinal absorption. Additionally, compounds such as rifampinone 3-C- β -D-glucoside and mangiferin, in conjunction with 3 β -taraxerol and other sterols, are considered major contributors to the hypocholesterolemic properties of *M. indica* leaf extract (Gururaja *et al.*, 2017). These findings are in the same line with Saleem *et al.*, (2019) who reported that the hypolipidemic effect observed following the administration of *Mangifera indica* leaf extract in alloxan-induced diabetic mice was attributed to the presence of bioactive phytochemicals. They indicated that catechin, epicatechin, chlorogenic acid, gallic acid, and mangiferin were likely responsible for the observed reduction in hyperlipidemia in diabetic animals. Therefore, the lipid-lowering activity of the *Mangifera indica* leaf extract may be attributed to the presence of these bioactive phytochemicals (Saleem *et al.*, 2019).

In the present study, the combination of aqueous extracts from *Psidium guajava* and *Mangifera indica* leaves produced significant hypolipidemic effects. This finding aligns with the results of Hammam *et al.*, 2023 who reported that treatment of both guava and mango leaf either individually or in a mixture resulted in a significant reduction in triglycerides, total cholesterol, and

LDL-cholesterol levels in experimental rats. Notably, Group E, which received a combination of guava and mango leaf extracts, exhibited the best lipid-lowering effects overall.

In conclusion, the findings of this study suggest that aqueous extracts of guava and mango leaves either individually or in a combination produced a significant hypoglycemic effect in diabetic rats and ameliorated diabetes-associated dyslipidemia.

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تقييم إمكانات خفض سكر الدم وخفض دهون الدم للمستخلصات المائية لأوراق الجوافة والمانجو في الفئران المصابة بالسكري باستخدام الستربتوزوتوسين

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الملخص العربي

الغرض من هذه الدراسة هو تقييم التأثيرات الخافضة لسكر الدم ونقص شحميات الدم للمستخلصات المائية لأوراق الجوافة والمانجو إما المستخدمة بشكل منفصل أو في خليط في الفئران المصابة بمرض السكري المستحث بالستربتوزوتوسين. تم تقسيم ثلاثين فأراً بالغاً من الذكور إلى خمس مجموعات، كل منها بستة فئران، وتم تقييمها على النحو التالي: المجموعة ١ فئران طبيعية غير مصابة بالسكري (مجموعة ضابطة إيجابية)؛ المجموعة ٢ فئران مصابة بالسكري غير معالجة (مجموعة ضابطة إيجابية)؛ المجموعة ٣ مصابة بالسكري عولجت بمستخلص مائي لأوراق الجوافة (GLAX) (٥٠٠ مجم / كجم من وزن الجسم / يوم)؛ المجموعة ٤: مصابة بالسكري عولجت بمستخلص مائي لأوراق المانجو (MLAE) (٥٠٠ مجم / كجم من وزن الجسم / يوم)؛ المجموعة الخامسة: مصابة بالسكري عولجت بمزيج من مستخلصي النباتات المختبرة. بعد أربعة أسابيع من إعطاء المستخلصات، تم أخذ عينات دم لتقييم العديد من العلامات الكيميائية الحيوية. أظهرت نتائج هذه الدراسة ارتفاعاً ملحوظاً في مستويات سكر الدم، مصحوباً بانخفاض ملحوظ في تركيزات الأنسولين في المصل لدى الفئران المصابة بداء السكري غير المعالجة، مقارنةً بفئران سليمة (مجموعة تحكم سلبية). علاوة على ذلك، أظهرت مجموعة مرضى السكري غير المعالجة (مجموعة تحكم إيجابية) زيادة ملحوظة في مستويات الكوليسترول الكلي (TC)، والدهون الثلاثية (TG)، وكوليسترول البروتين الدهني منخفض الكثافة (LDL-C)، وكوليسترول البروتين الدهني منخفض الكثافة جداً (VLDL-C) في المصل، إلى جانب انخفاض ملحوظ في كوليسترول البروتين الدهني عالي الكثافة (HDL-C)، مقارنةً بالمجموعة الضابطة السلبية. كما أدى إعطاء الستربتوزوتوسين إلى انخفاض ملحوظ في زيادة وزن الجسم لدى الفئران المصابة بداء السكري غير المعالجة. في المقابل، أدى تناول مستخلصات مائية من أوراق الجوافة والمانجو عن طريق الفم، سواء بشكل فردي أو مجتمعة، لدى الفئران المصابة بداء السكري إلى انخفاض كبير في مستويات سكر الدم وتحسين ملحوظ في تركيزات الأنسولين في المصل. علاوة على ذلك، لوحظ تحسن ملحوظ في مستوى الدهون، كما يتضح من انخفاض ملحوظ في الكوليسترول الكلي، والدهون الثلاثية، وكوليسترول البروتين الدهني منخفض الكثافة (LDL-C)، وكوليسترول البروتين الدهني منخفض الكثافة جداً (VLDL-C) في المصل، بالإضافة إلى زيادة ملحوظة في كوليسترول البروتين الدهني عالي الكثافة (HDL-C)، مقارنةً بالفئران المصابة بداء السكري غير المعالجة (مجموعة ضابطة إيجابية). بالإضافة إلى ذلك، تحسن فقدان الوزن الناتج عن الستربتوزوتوسين بالعلاج بمستخلص أوراق الجوافة، أو مستخلص أوراق المانجو، أو مزيج منهما. أظهر كلا المستخلصين النباتيين تأثيرات ملحوظة في خفض سكر الدم وخفض دهون الدم لدى الفئران المصابة بداء السكري. تُبرز هذه النتائج الإمكانات العلاجية للمستخلصات المائية لأوراق الجوافة والمانجو، سواء استُخدمت بشكل منفصل أو في خليط، لعلاج داء السكري من النوع الثاني المصحوب بفرط شحميات الدم.

الكلمات المفتاحية: أوراق الجوافة، أوراق المانجو، داء السكري، ستربتوزوتوسين، مستويات الجلوكوز، مستويات الأنسولين والفئران.