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HYPOGLYCEMIC AND ANTIHYPERGLYCEMIC EFFECT OF LEAVES EXTRACTS OF *PSIDIUM GUAJAVA* IN NORMOGLYCEMIC AND STREPTOZOTOCIN-INDUCED DIABETIC MICE

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ABSTRACT: Introduction: Diabetes mellitus is a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia. As morbidity and mortality rate from diabetes is increasing on the one hand and the cost of modern medicine is getting higher on the other in low - and middle - income countries, it is necessary to evaluate medicinal plants for their potential therapeutic effects against diabetes. The present study was, therefore, undertaken to evaluate the hypoglycemic and anti-hyperglycemic activity of the leaf extracts of *Psidium guajava* in normoglycemic and streptozotocin-induced diabetic mice, respectively. **Materials and Methods:** The aqueous and ethanol extracts of *Psidium guajava* leaves were prepared following standard procedures. Swiss albino mice of either sex weighing 20-30 grams were used for the experiments. Normal mice were grouped into eight groups to carry out the hypoglycemic effect of the extracts, whereas mice that were made diabetic were grouped into nine groups to study the antihyperglycemic effect of the extracts. Diabetes was induced by streptozotocin (STZ). Blood glucose levels were measured using the glucose oxidase method. **Results:** A significant decrease in blood glucose levels ($P < 0.05$) was observed after administering for 21 days treatment of the aqueous and ethanolic extracts of *Psidium guajava* leaf to streptozotocin-induced diabetic mice. The aqueous and ethanol extracts of *Psidium guajava* leaves, however, did not show a hypoglycemic effect on normoglycemic mice. Guava leaf extracts were found to contain alkaloids, phenols, flavonoids, tannins, and saponins which might be responsible for the observed antihyperglycemic effect. It was also observed that the extracts had shown no acute toxicity. **Conclusion:** The aqueous and ethanol extracts of *Psidium guajava* leaves are effective in lowering blood glucose level in diabetic mice without causing hypoglycemia. Further studies are warranted to elucidate the possible mechanism(s) of action of the plant material.

INTRODUCTION: Diabetes mellitus (DM) is a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both.

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The effects of DM include long term damage, dysfunction, and failure of various organs. DM may present with characteristic symptoms such as thirst, polyuria, blurring of vision, and weight loss. In its most severe forms, ketoacidosis or a non-ketotic hyperosmolar state may develop and lead to stupor, coma and, in the absence of effective treatment, death [1].

According to the report of the International Diabetes Federation (IDF), 387 million people have diabetes all over the world. About 77% of people with diabetes live in low- and middle-income countries. Besides, 4.9 million people died, and 612

billion USD was spent due to diabetes in 2014. Africa has the highest mortality rate due to diabetes compared to other parts of the world [2]. The goal of diabetes treatment is to secure a quality of life and lifespan comparable to those of healthy people, and a prerequisite for attaining this goal is the prevention of onset and progression of vascular complications [3]. Pharmacological interventions in the treatment of diabetes mellitus include insulin therapy, oral antidiabetic drugs such as sulfonylureas, biguanides, thiazolidinediones, aldose reductase and alpha-glucosidase inhibitors; and herbal treatment modalities [4]. For diabetes mellitus, therapies developed along the principles of western medicine (allopathic) are often limited in efficacy, carry the risk of adverse effects, and are often too costly, especially for the developing world. Therefore, treating diabetes mellitus with plant-derived compounds which are accessible and do not require laborious pharmaceutical synthesis seems highly attractive [5].

One of the plants used for the treatment of diabetes is *Psidium guajava* which is commonly known as Zeytuna in Amharic, Guava in English, Guayaba in Spanish and Goiaba in Portuguese. It is a common shade tree in door-yard gardens in the tropics. It belongs to the family of Myrtaceae, genus: *Psidium, species*: guajava and common names of the plant are guava, goiaba, guayaba, *etc.* [6] It is originated in tropical South America and grows widely in Bangladesh, India, Thailand, Brazil, Florida, and West Indies, California and also in several other countries [7]. Generally, guava plant has spread widely throughout the tropics because it thrives in a variety of soils, propagates easily, and bears fruit relatively quickly. The guava berry is an important tropical fruit that is mostly consumed fresh [8].

The aim of this study was, therefore, to investigate whether or not the aqueous and ethanolic extracts of *Psidium guajava* leaves have hypoglycemic and antihyperglycemic effect in normoglycemic and streptozotocin-induced diabetic mice.

MATERIALS AND METHODS:

Collections and Preparation of Plant Materials: Fresh leaves of *Psidium guajava* were collected from Wolaitta Zone, South Nation's and Nationalities Peoples Region located about 330 kilometers south of the capital city, Addis Ababa, Ethiopia. After collection, the plant materials were identified and authenticated by a taxonomist and deposited with a voucher number AG001 at Ethiopian Public Health Institute. The guava leaves were then dried under shade and crushed to powder for extraction.

Chemicals: Streptozotocin (STZ) was purchased from [S0130 Sigma - Aldrich, USA]. Glibenclamide was obtained from [Cadila Pharmaceuticals (Ethiopia) PLC, Ethiopia]. Senso Card - blood glucose meter and test strips were purchased from (77 Electronic Kft, Hungary). All other chemicals used were of analytical grade.

Extraction: For ethanol extract, the powdered leaves (300 g) were extracted by maceration in 70% ethanol, and the mixture was filtered using Whatman filter paper no. 1. The extract was made ethanol free by evaporating it using rotary vaporizers under reduced pressure. The extract was made solvent free by keeping it in a water bath at 400°C. The yield obtained was 7.5% (w/w). Then, it was kept in the refrigerator at 8-degree centigrade, and fresh stock solution was prepared for the experiment whenever required. The aqueous extract was prepared by maceration of the powdered leaves (300 g) in distilled water. Subsequently, the mixture was filtered using Whatman filter paper no. 1. The extract was set to water free by using Lyophilizer. The yield obtained was 8.5% (w/w).

Animal Preparation: Healthy, Swiss albino mice of either sex weighing 20-30 grams were brought from Experimental Animal Breeding Unit, Ethiopian Public Health Institute: the animals were bred using a standard diet and tap water *ad libitum* in an environment of a 12-h light/dark cycle. Then, the mice were acclimatized before use for the study.

Preparation of Diabetic Mice: Mice fasted for four hours with free access to water, and then injected intraperitoneally twice on successive days with streptozotocin dissolved in 2.94% sodium citrate solution (50 mg/kg body weight). All animals had free access to water and pellet diet after thirty minutes of administration of streptozotocin.

After 72 h, blood glucose level was measured in mice fasted for four hours using glucometer; mice with greater than 200 mg/dl was defined as DM. Streptozotocin-induced diabetic mice were selected and divided into eight groups; one negative control, one positive control, and six test groups.

Administration of Extract to Streptozotocin-Induced Diabetic Mice: Streptozotocin-induced diabetic mice were administered (orally) 250 mg/kg, 500 mg/kg and 750 mg/kg of the ethanol and aqueous extracts of *Psidium guajava* for test groups; 0.66 mg/kg glibenclamide for positive control group; and distilled water (1 ml) for negative control group. There was also normal control group that received distilled water (1 ml) orally. Extract, standard drug, and water were administered once daily for 21 days. Blood glucose level was measured on 0 days, 7th day, 14th day and the 21st day following the induction. The blood glucose level was measured using glucometer blood drawn from the tail of the mice.

Administration of Extract to Normoglycemic Mice: Mice were divided into eight groups (six test groups and two control groups), each group comprising a minimum of six mice (n = 6). The mice were starved overnight before experimenting. The positive control group received glibenclamide, while the negative control group received distilled water, and the test groups were administered aqueous extracts of 250 mg/kg, 500 mg/kg and 750 mg/kg; and ethanol extract of 250 mg/kg, 500 mg/kg and 750 mg/kg of *Psidium guajava*. The extract was administered orally using gavage. The effects of the plant extract were compared with that of the control groups. A blood sample from the control and test animals was collected after 0, 30, 60, 90, 120 and 180 min following extract or water administration. Blood glucose level was measured using glucometer on blood drawn from the tail of the mice.

Phytochemical Analysis of *Psidium guajava* Leaf Extracts: Qualitative preliminary phytochemical screening test was carried out for *Psidium guajava* leaf extracts as per the standard methods [9, 10, 11] to confirm the presence of alkaloids, phenols, flavonoids, tannins, and saponins.

Acute Toxicity Study: Acute toxicity study was performed on 30 female mice. The animals were kept fasting overnight, but the water was provided *ad libitum*. They were divided into six groups, five animals in each group, and the aqueous and alcohol extracts of *Psidium guajava* were administered orally in an increased dose level of 300, 2000, and 5000 mg/kg *via* oral gavage according to the guidelines of the Organization for Economic Cooperation and Development [12]. Animals were kept under close observation for 4 h after administering the extracts for behavioral, neurological and autonomic symptoms and then were observed for any change in the general behavior and other physical activities within 24 h. After that, the observation continued daily for a total of 14 days.

Statistical Analysis: The data were expressed as mean ± standard error of the mean (SEM). Differences between means of all parameters were carried out using analysis of variance (ANOVA). Subsequently, the Tukey post-hoc tests with multiple comparisons were used to determine the source of significant differences. $P<0.05$ was considered to be statistically significant. GraphPad InStat 3 and SPSS Version 20 Software were used for statistical analysis. Percent reduction of blood glucose level was calculated using the following formula:

$$= G_0 – G_{21} / G_0$$

Where, G_o is blood glucose level on day 0; G_{21} is blood glucose level at day 21.

RESULTS AND DISCUSSION: In the present study, the hypoglycemic and antihyperglycemic effects of the aqueous and ethanol extracts of *P. guajava* were performed in normoglycemic and streptozotocin-induced diabetic mice, respectively. STZ is one of the most commonly used substances to induce diabetes in rodents. STZ (2-deoxy-2-(3-methyl-3 -nitrosourea)-1-D -glucopyranose) is a broad-spectrum antibiotic produced by the bacterium Streptomyces achromogenes in 1959.

The diabetogenic effect of STZ was first reported in 1963 by Rakieten *et al.*, [13] after injection of a single intravenous dose in rats and dogs. STZ-induced diabetes is associated not only with hyperglycemia but also with marked necrotic changes in endocrine cells of pancreatic islets, decreased β-islet cell area accompanied by

hyperplasia of their nuclei, increased α-endocrine cell area, as well as increased apoptotic index [14].

Antihyperglycemic Effect of Aqueous and Ethanolic Extract of *Psidium guajava* Leaves: The blood glucose levels of the whole groups were measured once weekly during the three weeks treatment course as shown in **Table 1**. Before the induction of diabetes, the treatment groups had no statistically significant difference in their blood glucose levels. The blood glucose levels were not significantly different between the standard and test groups before initiating the treatment. The standard group and the test groups that received 500 mg/kg (aqueous), 750 mg/kg (aqueous) and 750 mg/kg (ethanol) showed statistically significant variation in their blood glucose level within the first-week treatment (P<0.05 for all). In addition to the above groups, the blood glucose level of the test group that received 500 mg/kg (ethanolic extract) was significantly different at the end of the second week of treatment course (P<0.05). On day 21st, the test group which received 250 mg/kg (aqueous) also showed a statistically significant difference (P< 0.05) in their blood glucose level.

Across the experimental period, the normal control (non-diabetic) group and the negative control (diabetic) group did not show any significant difference in their blood glucose level. The present study reveals that both the aqueous and ethanolic extracts of *Psidium guajava* have anti-hyperglycaemic effect in diabetic-induced mice.

TABLE 1: ANTIHYPERGLYCEMIC EFFECT OF EXTRACTS OF *PSIDIUM GUAJAVA* LEAVES IN STREPTOZOTOCIN-INDUCED DIABETIC MICE

Groups	Blood Glucose Level (mg/dl)				Percent Reduction
	Day 0	Day 7	Day 14	Day 21	
Normal control group (without streptozotocin)	129.33± 3.20	134.50± 2.89	135.33± 1.94	136.17± 1.94	-5.23
Negative control group (diabetic mice)	275.80±6.90	280.40±5.51	280.80±4.37	276.80±5.45	-0.36
Positive control group [Glibenclamide (0.66 mg/kg)]	263.20± 5.94	228.00± 5.61***	205.60± 4.85***	180.00± 6.59***	31.61
Aqueous extract of 250 mg/kg	267.00±12.29	262.33±9.97	250.17±10.12	245.00±7.98*	8.24
Aqueous extract 0f 500 mg/kg	272.67±9.05	246.00±8.56*	230.17±9.08***	208.83±7.52***	23.41
Aqueous extract of 750 mg/kg	261.33±7.92	230.17±7.88***	209.33±8.11***	186.17±7.50***	28.76
Ethanol extract of 250 mg/kg	274.00±7.80	267.67±6.78	260.17±6.45	256.00±5.94	6.57
Ethanol extract of 500 mg/kg	257.50±4.55	247.67±5.06	234.00±4.08**	221.83±4.84***	13.85
Ethanol extract of 750 mg/kg	249.33±6.53	231.67±6.21**	212.67±5.30***	195.33±5.90***	21.66

*P < 0.05, **P < 0.01, ***P < 0.001 *vs.* negative control (diabetic mice); Mean ± Standard Error of Mean, n=6

After administration of leaf extract of *Psidium guajava* (250 mg/kg) to alloxan and STZ-induced diabetic mice, the blood glucose level began to decline within one hour and continued to decline up to 6 hr on alloxan-induced diabetic mice; but the blood glucose levels declined to their lowest level after an interval of 4 h on STZ-induced diabetic mice [15]. The ethanolic extract of *Psidium guajava* leaf has a marked hypoglycemic and hypolipidemic effect on alloxan-induced diabetes [16]. In this study, the significant reduction of the blood glucose levels of the mice was observed gradually from the first-week end to the last week of treatment in the group receiving aqueous extract (250 mg/kg, 500 and 750 mg/kg) and ethanol extract (500 and 750 mg/kg). The present study revealed that both the aqueous and ethanolic extracts of *Psidium guajava* leaves have a significant antihyperglycemic effect on STZ-induced diabetic mice.

The aqueous extract of *Psidium guajava* leaf (750 mg/kg) reduced the blood glucose level efficiently by 28.76 percent on the 21st day which is almost comparable with the dose of glibenclamide treated group which showed a significant fall of 31.61 percent.

Hypoglycemic Effect of Aqueous and Ethanolic Extract of *Psidium guajava* Leaves: After administering the test substance and the standard, the blood glucose levels were measured every 30 min for 3 h. The results are summarized in **Table 2**. Before initiating the treatment, there were no statistically significant differences in blood glucose level among the whole groups; this insignificant change continued for 30 min. After 1 h, the blood glucose level of the standard substance showed a statistically significant difference from the negative control group and the test groups (P<0.05).

TABLE 2: HYPOGLYCEMIC EFFECT OF EXTRACTS OF *PSIDIUM GUAJAVA* LEAVES IN NORMOGLYCEMIC MICE

Groups	Blood Glucose Level (mg/dl)						Percent Reduction
	0'	30'	60'	90'	120'	180'	
Negative control group (distilled water)	167.0± 5.28	195.7± 10.71	195.7± 8.77	196.2± 10.80	194.2± 12.33	147.0± 10.73	11.98
Positive control group Glibenclamide (0.66 mg/kg)	178.0± 3.28	166.7± 6.84	128.8± 7.48*	113.8± 7.11*	113.7± 3.46*	113.3± 10.91*	36.35
Aqueous extract of 250 mg/kg	185.0±5.39	195.5±5.55	192.0±4.81	186.3±4.90	169.8±6.75	161.5±2.98	12.70
Aqueous extract 0f 500 mg/kg	169.2±4.40	195.3±6.25	183.2±6.37	162.8±7.07	157.5±4.44	171.0±12.38	-1.06
Aqueous extract of 750 mg/kg	174.5±3.17	185.8±4.85	179.5±6.75	197.8±7.85	181.2±7.45	166.8±6.25	4.41
Ethanol extract of 250 mg/kg	173.5±10.45	182.2±5.97	179.7±7.44	192.0±10.90	176.1±8.65	161.8±9.87	6.74
Ethanol extract of 500 mg/kg	187.3±10.94	204.0±18.38	194.8±16.09	197.5±16.80	187.0±20.73	171.7±16.30	8.33
Ethanol extract of 750 mg/kg	185.8±11.25	200.5±9.42	191.2±11.47	180.8±9.60	167.8±9.24	174.2±6.61	6.24

*P < 0.05, Mean ± Standard Error of Mean, n = 6.

The negative control group and the whole test groups did not show any significant differences in blood glucose level within 3 h, whereas the blood glucose level of the positive control group showed statistically significant variation after 3 h of administration (P<0.05). The present results indicate that both the aqueous and ethanolic extracts of *P. guajava* have no hypoglycaemic effect in normoglycemic mice. The previous study done on normoglycemic mice with ethanolic extract of the stem bark of *Psidium guajava* was devoid of significant hypoglycemic effect [17] which is in agreement with the results of the present study. However, the acute oral administration of aqueous extract of *Psidium guajava* leaves (dose ranging from 50-800 mg/kg) showed the hypoglycemic effect on normoglycemic mice [18] which is not in agreement with the present study.

In the present study, the leaf extracts of *Psidium guajava* showed an antihyperglycemic effect in STZ-induced diabetic mice without causing hypoglycemia on normoglycemic mice while glibenclamide showed both hypoglycemic and anti-hyperglycemic effects on normoglycemic and STZ-induced diabetic mice. This might suggest that the mechanism of antidiabetic action of leaf extracts of *Psidium guajava* might be different from the standard drug glibenclamide, which acts by increasing insulin secretion from the pancreas and should be used with caution in patients with cardiovascular disease or in elderly patients, in whom hypoglycemia would be especially dangerous [19].

However, wide-ranging pharmacological and biochemical researches are required to address the detailed mechanism and active principles responsible for the antihyperglycemic effects observed in the study.

Phytochemical Composition of *Psidium guajava* Leaf Extracts: As the phytochemical screening tests showed in our study, both the aqueous and ethanolic extracts of *Psidium guajava* leaves comprise many secondary metabolites (see **Table 3**). The result revealed that the guava leaf extracts are good sources of alkaloids, phenols, flavonoids, tannins, and saponins. The aqueous extract contains a higher amount of phenols and saponins than the ethanolic extract, whereas the ethanolic extract contains larger amount of alkaloids and tannins than aqueous extract.

Most of the drugs have definite specific chemical constituents which might attribute to their biological or pharmacological activity. Qualitative and quantitative characterization of the active ingredient should be assayed using biomarkers. A defining biomarker has to be very specific, and a lot of insight has to go into it before declaring any distinct molecule [9].

Ethanolic leaf extracts of *Psidium guajava* (guava) produced the highest percentage of the phytochemical constituents than the aqueous leaf extracts. Tannins, alkaloids, total polyphenols, saponins and oxalate found in both extracts may be responsible for the folklore and scientifically documented medicinally beneficial effects of the plants [20]. Phytochemical screening analysis done on leaves of *Psidium guajava* revealed the presence of flavonoids, tannins, reducing sugars, terpenes, saponins, anthraquinones, and alkaloids. The chemical constituents present in the extracts have some therapeutic values [21]. One or more of these

secondary metabolites may be responsible for the anti-diabetic effect observed in the present study.

Acute Toxicity of Aqueous and Ethanolic Extracts of *Psidium guajava* Leaves: In the present study, signs of toxicity were not observed. No changes were observed in behaviors or autonomic activities following administration of graded doses of both aqueous and ethanol extracts of *Psidium guajava* (up to a dose of 5000 mg/kg) within 24 h, as shown in **Table 4**. Besides, there were no delayed deaths within 14 day observation period up to the dose of 5000 mg/kg body weight, indicating that the medium lethal dose (LD_{50}) is greater than 5 g/kg body weight. These results indicate that there is very low potential for acute toxicity from oral ingestion of aqueous and ethanol extracts of *Psidium guajava*. The extracts were, therefore, found to be relatively safe on acute exposure up to a single oral administration of 5000 mg/kg.

TABLE 3: PHYTOCHEMICAL SCREENING OF AQUEOUS AND ETHANOLIC EXTRACT OF *PSIDIUM GUAJAVA* LEAVES

Chemical Compounds Class	Test Performed	Expected Outcome	Result	
			Aqueous Extract	Ethanol Extract
Alkaloids	Dragendorff's Test	Yellow-orange precipitate	Positive	Positive
	Hager's Test	Yellow precipitate	Positive	Positive
Phenols	Ferric chloride test	Blue black coloration	Positive	Positive
Flavonoids	Lead acetate test	Yellow color precipitate	Positive	Positive
Tannins	Ferric chloride (0.1%) test	Blue black coloration	Positive	Positive
Saponins	Foam formation test	Foam formation	Positive	Positive

TABLE 4: ACUTE ORAL TOXICITY OF AQUEOUS AND ETHANOLIC EXTRACT OF *PSIDIUM GUAJAVA*

Group	No. of mice	*Psidium guajava* leaf extract Dose (mg/kg)	Toxicity observed		Number of deaths
			Within 24 h	After 14 days	
1	5	300 mg (Aqueous extract)	No	No	0*
2	5	2000 mg (Aqueous extract)	No	No	0*
3	5	5000 mg (Aqueous extract)	No	No	0*
4	5	300 mg (Ethanol extract)	No	No	0*
5	5	2000 mg (Ethanol extract)	No	No	0*
6	5	5000 mg (Ethanol extract)	No	No	0*
7	5	1 ml of water (control)	No	No	0*

* At $P < 0.05$, there is no statistically significant difference among test and control groups.

CONCLUSION: In conclusion, this study revealed that the aqueous and ethanolic extracts of *Psidium guajava* leaves are effective in lowering blood glucose level on diabetic mice, but lack hypoglycemic effect on normoglycemic mice. Therefore, *Psidium guajava* leaves can be used as an alternative herbal remedy for the treatment/ prevention of diabetes. Further studies are warranted to isolate and identify the exact molecules which are responsible for the antidiabetic effect.

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COMPETING INTEREST: The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTION: AG conceived the idea, drafted the proposal and involved in all implementation stages of the project and write up. EM and NM reviewed the proposal, and involved in all implementation stages of the project and write up. All authors read and approved the final manuscript.

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