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A SYSTEMATIC REVIEW ON PSIDIUM GUAJAVA IN THE MANAGEMENT OF DIABETES MELLITUS

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ABSTRACT

The current study was undertaken to explore and compile the research evidence on *Psidium guajava* in the management of diabetes. To undertake the said aim, peer-reviewed literatures were retrieved during January 2023 from PubMed, Science Direct and Springer databases. The obtained literature was initially subjected to title and abstract screening, followed by full-text screening. The study includes eight articles that used *in vivo* research on animal models. In these researches, the antidiabetic property was evaluated using either leaf or fruit. The available evidence conclusively demonstrates the potential of *Psidium guajava* against diabetes as it holds significant glucose-lowering effects in the reported screened models. Bioactivity-guided fractionation followed by elucidation of the mechanism of action will be useful in establishing the application of the plant species in diabetes.

Keywords: ***Psidium guajava*, systematic review, diabetes, *in vivo* model**

INTRODUCTION

Diabetes mellitus is a long-term disease of glucose metabolism with substantial clinical repercussions. Microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (ischemic heart disease, stroke, peripheral vascular disease) outcomes are included in the multi-system consequences of diabetes. In recent decades,

there has been an increase in the prevalence of diabetes, which has been fueled by the global rise in obesity rates. Diabetes is a significant public health issue because to the early morbidity, mortality, shortened life expectancy, and associated financial and other expenses to the patient, their carers, and the healthcare system **[1]**.

Nearly 422 million people have been reported with diabetes worldwide, majority living in low and middle income countries. Diabetes is directly responsible for 1.5 million fatalities annually and both the number of cases and prevalence are increasing steadily over the past few decades **[2]**. Feet and eyes are only two bodily areas that high blood sugar levels can gravely harm. These are referred to as diabetes complications. However, many of these diabetes side effects are preventable or can be postponed with action. Acute complications are those that can occur at any time, whereas chronic complications are dangerous ones that develop over time. These are long-term issues that may appear gradually and, if left addressed, may cause significant harm **[3]**. In order to manage and treat diabetes, there are numerous treatments available. Because each person is unique, each person's needs will dictate the specific treatment they receive.

The management of blood glucose (sugar) levels requires the administration of insulin to all type 1 diabetics and some type 2 diabetics. Since the pancreas cannot produce insulin, people with type 1 diabetes must take it via injection. Diabetes medications must also be taken by many patients with type 2 diabetes **[4]**. Synthetic drugs which are used for treatment of diabetes are associated with various adverse effect such as sickness, vomiting, dysentery, alcohol flush, migraine, swelling, malignant anemia and faintness. Herbal drugs are proved to be a better choice over synthetic drugs because of less side effects and toxicity **[5]**.

Many preclinical studies have been carried out on several traditional medicinal plants including *Psidium guava* for diabetes, both type 1 and 2.

Guava's nutritional worth is sometimes compared to that of super fruits because of its abundance in dietary fibre, vitamins A and C, folic acid, and dietary minerals including potassium, copper, and manganese. A single common guava fruit has nearly four times as much vitamin C as an orange and a generally broad, low-calorie profile of vital elements. Psidium guajava (PG) is known as the "poor man's apple" since it is a tropical and subtropical country's staple food and therapeutic plant. Traditionally the plant is used in gastrointestinal infections such as diarrhea, dysentery, stomach aches, and indigestion. Its leaf's extract is being used as a medicine in cough, diarrhea, and oral ulcers and in some swollen gums wound **[6, 7]**.

Several phytoconstituents have been reported from Psidium guajava leaves namely gallic acid, pedunculagin, casuariin, prodelphinidin, gallocatechin, catechin, chlorogenic acid, rutin, vanillic acid, quercetin, P-hydroxy benzoic acid, syringic acid, Kaempferol, Myricetin, Isoquercetin, apigenin, cinnamic acid, luteolin, Reynoutrina (quercetin-3-O-β-D-xylopyranoside), Guajaverina (quercetin-3-O-α-L-arabinopyranoside), Morin, Ellagic acid, Myrciaphenone B, Vescalagin, Hyperoside, Quercetin-3-O-β-glucoside, Guaijaverin, Pedunculoside, Madecassiac acid, Asiastic acid, Ursolic acid, Oleanolic acid, Beta-sitosterol glucoside, Methyl gallate, Epicatechin, Procyanidin, Protocatechuic acid, Caffeic acid [8], two new benzophenone galloyl glycosides (guavinosides A and B) and one quercetin galloyl glycoside (guavinoside C) **[9]**, diphenylmethane **[10]** sesquiterpenoid-diphenylmethane meroterpenoids (psiguadials A and B) **[11]** and psiguanins A–D (1–4) **[12]**.

Because of its pharmacologic properties, *Psidium guajava* Linn. is utilized both as a food and a traditional medicine in subtropical regions all over the world. In instance, in East Asia and other regions, guava leaf extract has been used for centuries to treat diabetes. In several animal models, the extract's anti-hyperglycaemic efficacy has also been documented. But little is understood about the extract's therapeutic activity in human clinical studies, as well as its underlying therapeutic mechanisms and safety.

The aim of the present study is to identify, collect and summarize the research work carried on *Psidium guajava* plant on diabetes, which will provide an overall research insights on the medicinal properties and work done on the plant.

MATERIALS AND METHODS

Search strategy

Data related the selected study were obtained from three major data bases namely PubMed, Science Direct and Springer. The search was carried out by using the keywords *Psidium guava* or guava or anti-diabetic or Hypoglycaemia or blood glucose or diabetes mellitus.

Selection of Research articles

The selection were limited to original articles published in English and included abstracts. Review articles, case studies and other research articles not related to PG and diabetes were excluded from the selection.

Inclusion and Exclusion criteria

For the present systematic review, studies related to PG and diabetes were included. The inclusion criteria were as follows: i) Studies involving animal experimentation ii) studies reported at least one criteria such as fasting blood glucose, plasma insulin, OGTT iii) Studies that evaluated the anti-diabetic effect of PG in any part of the plant

(leaf, fruit etc) iv) studies evaluating the effect of crude plant part extracts and not its isolated phytocompounds.

The following were the exclusion criteria i) Studies on cell lines ii) studies on humans iii) studies investigating the effect of isolated PG phytoconstituents iv) studies of PG in combination with other plant material against diabetes.

Data extraction

Three independent authors scrutinized the title and abstract of the retrieved studies and the relevant articles were included for further analysis. These three authors extracted the data from the full text selected for analysis. Any difference among these three authors were resolved by the other two authors.

RESULTS

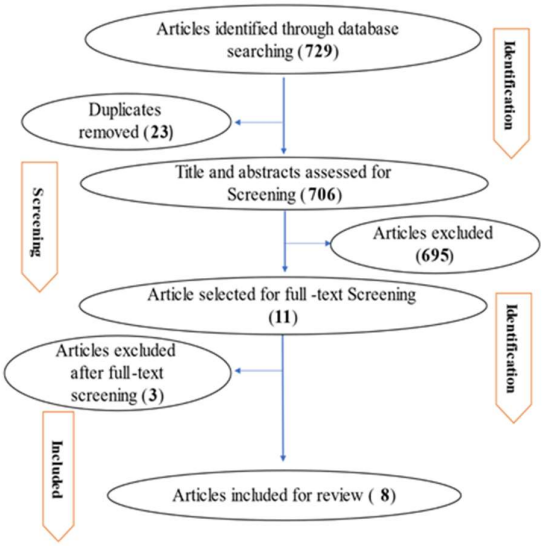

Figure 1: Study flowchart describing the results of the database

Table 1: Characteristics of the included studies

Author (year)	Plant part	Place of collection	Extract type	Animal	Diabetes inducing agent with dose and RoA	Extract dose and RoA	Duration of study
Toluwani Tella, Bubuya Masola, Samson Mukaratirwa [13] (2022)	Leaves	Durban, South Africa	Aqueous extract (Freeze dried)	Male Sprague-Dawley rats	Streptozotocin (40 mg/kg. body weight), Intraperitoneal route	400 mg/kg body weight, oral route	14 days
Sowmya Soman *et al.* [14] (2013)	Budding leaves	Trivandrum	Methanol (80%) extract fractionated with n-hexane, chloroform, ethyl acetate, butanol and water. Ethyl acetate fraction was selected based on its maximum *in*	Female Sprague–Dawley rats	Streptozotocin (55 mg/kg body weight) intraperitoneal route	25 and 50 mg/kg body weight /day, Intragastric administration	30 days

			vitro **anti-oxidant potential.**				
Won Keun Oh *et al*, [15](2005)	**Dried leaves**	**Kyung-gi province, South Korea**	**Methanol extract fractionated with water, n-hexane, ethyl acetate butanol and water. Butanol soluble extract was used for the study**	**$Lepr^{db}$/$Lepr^{db}$ diabetic mice**	**-**	**10 mg/kg fraction, intraperitoneal route**	**4 weeks**
Chin-Shiu Huang, Mei-Chin Yin, Lan-Chi Chiu [16](2011)	**Freeze dried ripe Fruit(seedless)**	**Yanchao, Kaohsing, Taiwan**	**Polyphenolic fraction of dried fruit powder eluted from silica gel column with 1% acidified ethanol**	**Adult male Sprague–Dawley rats**	**Streptozotocin (55 mg/kg body weight),intraperitoneal route**	**125 and 250 mg/kg body weight, Oral route**	**4 weeks**
Dan Li, Sen Yang *et al*, [17] (2021)	**Dried and rice fried Leaves**	**Procured from Chengdu Tongling Chinese Medicine Pieces Selection Co. China**	**Decoction**	**Sprague Dawley (SD) male rats**	**Streptozotocin (45.0 mg/kg) Iintraperitoneal**	**2.5.g/kg body weight**	**49 days**
Szu-Chuan Shen *et al*, [18] (2008)	**Leaf**	**Hu-Shan farm (Yuanshan township, Yilan Prefecture, Taiwan)**	**Aqueous and ethanol extract (Freeze dried)**	**Sprague-Dawley rat**	**Intraperitoneal administration 230 mg/kg body weight Nicotinamide and Intravenous administration 65 mg/kg Streptozotocin (STZ)**	**200 and 400 mg/kg**	**6 weeks**
Prashant K. Rai *et al*, [19] (2009)	**Unripe fruit peel**	**Khushrobagh, Allahabad**	**Aqueous extract (Freeze dried)**	**Male albino Wistar rat**	**Streptozotocin 45 mg/kg**	**300, 400 and 500 mg/kg**	**21 days**
Juei-Tang Cheng and Ren-Shaw Yang [20](1983)	**Fruit**	**Department of Pharmacology, Tajen Pharmaceutical College, Ping-Tong City, Taiwan 900**	**Fruit juice**	**Mice**	**Alloxan monohydrate (150 mg/kg) Subcutaneous administration**	**1g/kg body weight, Oral administration**	**7 days**

Table 2. Effect of *Psidium guava* on FBG and OGTT

Author (year)	Effect on fasted normal animals	Effect on GTT
Toluwani Tella, Bubuya Masola, Samson Mukaratirwa [13]	**Not reported**	**At the end of the study there was a significant reduction in the glucose level ($P<0.05$) in the group treated with PG compared to the diabetic control group, the mean glucose levels being 9.3 and 13.9 mM respectively. The study indicates the enhanced glucose tolerance activity of PG which is evident at 120 min where the blood glucose returned to initial values in contrast to control animals where the percentage is 13 at the same time interval.**
Sowmya Soman *et al* [14]	**There was a significant increase in blood glucose level in the diabetic induced group whereas animals in all groups treated with PG extracts showed a significant reduction in the blood glucose level compared to diabetic control**	**Not reported**
Won Keun Oh *et al* [15]	**Treatment with 10 mg of butanol-soluble fraction of the leaves in 1 month old diabetic Leprdb/Leprdb mice for 14 days significantly reduced the glucose level to 127+ 29 mg/dl from 412+45 mg/dl of the control animals. similarly treatment of butanol-soluble fraction on three**	**Not reported**

	months Leprdb/Leprdb old mice showed a significant reduction from 587+29 to 246+35mg/dl in treated groups	
Chin-Shiu Huang, Mei-Chin Yin, Lan-Chi Chiu [16]	Treatment with STZ showed a 8 fold increase in blood glucose level compared to normal control group Treatment with high dose of PG significantly (P<0.001) lowered the blood glucose by 74 % with a glucose value of 152 mg/dl compared to 574 mg/dl in diabetic control animals at 5 weeks	Not reported
Dan Li *et al*, [17]	Administration of HFD/STZ significantly increased the blood glucose level after 7, 21, 35 and 49 days. After 35 days of administration , the FBG levels in animals treated with metformin and PGLD (Psidium guajava Leaves Decoction) showed an obvious lowering effect while the group treated with RPGLD (Rice fried Psidium guajava Leaves Decoction) significantly (P<0.05) reduced FBG level. After 49 days, metformin and RPGLD treated groups showed a significant blood glucose lowering effect.	Not reported
Szu-Chuan Shen *et al*, [18]	Acute treatment of guava leaf extracts showed a lower glucose level and there were no significant differences between aqueous, ethanol extracts and normal control groups. The long term treatment of guava leaf extracts (aqueous and ethanol extract) for 6 weeks showed a significant (P<0.05) lowering in the blood glucose level than the control group	Long term treatment of PG aqueous and ethanol extract for six weeks showed a significant lowering of blood glucose level compared to control diabetic group (P< 0.05)
Prashant K. Rai *et al* [19]	In severe diabetic rats 400 mg/kg of aqueous extract showed a significant reduction of 20.8 % in FBG level and 17.5 % in PPG (Post Pranadial Glucose) level, whereas tolbutamide treated groups showed a reduction of 23.1 % in FBG and 20.6 % in PPG levels.	After single administration of 300, 400 and 500 mg/kg of aqueous extracts, normal healthy rats showed a decrease in blood glucose level during GTT. Administration of 400 mg/kg aqueous extract for 21 days in normal healthy rats showed a fall of 21.2 %, while the same dose in mild diabetic rats exhibited a maximum fall of 26.9 % in blood glucose level.
Juei-Tang Cheng and Ren-Shaw Yang [20]	Hypoglycemic effect was found in both normal and diabetic mice. Administration of 1g/kg of guava juice resulted in lowering of FBG level. In diabetic mices, the FBG was found to be 132.1±16.5 mg/dl. After treatment with guava juice 1g/kg the blood glucose level reduced to 100.7±12.7 mg/dl which was statistically significant P<0.01	Not reported

DISCUSSION

After thorough screening of three databases namely PubMed, Science Direct, Springer, eight research articles were finally shortlisted and selected. Out of this eight articles, five authors have worked on leaves in various forms (dried, fresh, rice dried, budding stage) and other three authors have worked on ripe seedless fruit, unripe fruit peel and fruit juice respectively.

Oral glucose tolerance test (OGTT)

From the eight studies reviewed, only three studies measured the oral glucose tolerance (OGTT). Toluwani Tella *et al*, (2022) evaluated the effect of aqueous extract of PG on 12 hrs fasted normal and diabetic rats at 0, 15,30,60,90 and 120 mins interval. The normal control animals showed 4.76±0.1208 % glucose concentration, diabetic rats 13.92 ± 0.3470 whereas the normal animals treated with PG showed 5.5 ±0.1183 and diabetic animals treated with PG showed 9.280 ±0.8434%. The study

showed that PG has enhanced the glucose tolerance **[13]**. Szu-Chuan Shen *et al*. (2008), reported the effect of PG aqueous and ethanol extract on normal and diabetic rats for six weeks. Both the leaf extracts showed a significant lowering of blood glucose than the control group **[18]**. Prashant Rai *et al*. (2009), reported that 400 mg/kg of aqueous extract showed a significant glucose lowering effect compared to other concentrations **[19]**.

Fasting Blood Glucose (FBG)

Out of the eight studies, seven studies reported FBG level. According to Sowmya Soman *et al*. (2013), FBG levels significantly reduced after treatment with ethyl acetate fraction of the methanol extract (budding leaves) for 30 days **[14]**. Won Keun Oh *et al*. (2005), showed a significantly decreased the FBG level after treatment with butanol soluble fraction of methanol extract (dried leaves) for four weeks **[15]**. Chin-Shiu Huang *et al*. (2011), explained a significant decrease in FBG levels by treatment with freeze dried ripe seedless fruit for a duration of four weeks **[16]**. Dan Li *et al*. (2021), established that the FBG levels was significantly decreased by treatment with aqueous extract of rice fried and dried leaves for a period of 49 days **[17]**. Szu-Chuan Shen *et al*. showed a significant decrease in FBG level by treatment with freeze dried powders of aqueous and ethanol extract (leaves) for 6 weeks. No significant difference was found among the extracts in reducing the FBG level **[18]**. Prashant K. Rai *et al*. (2009), showed a significant decrease in FBG levels after administration of aqueous extract of PG unripe fruit peel for 21 days **[19]**. Juei-Tang Cheng *et al*. (1983), reported the significant lowering of FBG levels by administration with PG fresh fruit juice for 7 days **[20]**.

CONCLUSION

All the studies reviewed in the present study showed a positive effect of *Psidium guajava* on diabetes. The plant was found to be effective in lowering the FBG level. Further studies are required to identify the phytomolecules responsible for the action and its mechanistic study.

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Conflict of interest: None.

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Ethics statement: None.

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