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Ethnobotanical Effect Of Psidium Guajava L. In Glucose Control In Patients With Type 2 Diabetes Mellitus

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ABSTRACT: Type 2 Diabetes Mellitus (DM2) is characterized by chronic hyperglycemia and metabolic disorders, resulting in costly treatments. Therefore, herbal medicine is suggested, specifically the use of Psidium Guajava L. (guava), as a sustainable alternative for prevention and treatment. This review aims to describe the parts of the plant and demonstrate their benefits to promote the consumption of its leaves in glycemic control. 532 original research articles were collected, selecting 70 where it is shown that guava leaf extract significantly contributes to the reduction of hyperglycemia, thanks to its active metabolites and mechanisms of action. In conclusion, new advances in the antidiabetic effects of guava leaf could be applied in the development of drugs, therapeutic diets, and functional foods. Further studies are recommended to demonstrate the efficacy, safety, and dosage of guava leaf extracts.

Keywords: Flavonoids; Hypoglycemia; Obesity; Diabetes mellitus; Triterpenoids

Resumen: La Diabetes Mellitus tipo 2 (DM2) se caracteriza por una hiperglucemia crónica y trastornos metabólicos, lo que resulta en tratamiento costosos, por lo tanto, se sugiere la herbolaria, específicamente el uso de Psidium Guajava L. (guayaba), como alternativa sostenible para prevención y tratamiento. Esta revisión pretende describir las partes de la planta y demostrar sus beneficios para fomentar el consumo de sus hojas en la prevención y control glucémico. Se recopilaron 532 artículos de investigación originales, seleccionando 70 donde muestran que el extracto de hojas de guayaba contribuye significativamente en la disminución de la hiperglucemia, gracias a los metabolitos activos y mecanismos que presenta. En conclusión, los nuevos avances sobre los efectos antidiabéticos de la hoja de guayaba podrían aplicarse en el desarrollo de fármacos, dietas terapéuticas y alimentos funcionales. Se recomienda ampliar más estudios para demostrar la eficacia, seguridad y posología de los extractos de hojas de guayaba.

Palabras clave: Flavonoides; Hipoglucemia; Obesidad; Diabetes mellitus; Triterpenoides

INTRODUCTION

Type 2 diabetes mellitus (DM2) is a public health problem that affects 9.3% of the world population, with a projection of 109 million cases by 2040, as estimated by the Pan American Health Organization/World Health Organization (OMS, 2016), with healthcare costs of 760 billion USD (Statista. 2022), urgently recommending prevention through a healthy lifestyle and high consumption of foods rich in high biological value proteins, polyunsaturated fats, and complex carbohydrates, especially emphasizing the consumption of carbohydrates devoid of empty calories, the intake of clean water, and daily exercise (Fuentes et al., 2021).

Within the risk factors for type 2 diabetes mellitus (DM2), we have obesity, physical inactivity, smoking, alcohol consumption, and a high-calorie diet (Miravet-Jiménez et al., 2020). Therefore, these risk factors must be modified through the implementation of certain strategies such as the use of integrative medicine, which suggests healthy lifestyles and healthy social environments, incorporating extracts from a variety of plants, including leaves, flowers, fruits, barks, among others. One of the plants used is guava, a fruit tree cultivated in Latin America and Asian countries (Caiza Chicaiza, 2019). Its ethnobotanical consumption focuses on glucose control using leaf extracts that exhibit hypoglycemic benefits (Rodríguez-Leyton, 2019).

The parts of the guava tree such as the root, bark, leaves, and fruits have traditionally been used to improve the digestive and respiratory systems (Amadike Ugbogu et al., 2022). Its fruits are rich in vitamins, minerals, ascorbic acid, catechin, epicatechin, shikimic acid, and quinic acid polyols, which provide certain antioxidant, antimicrobial, and anti-inflammatory properties, supporting a great therapeutic potential and a wide range of clinical applications (Vijaya Anand et al., 2020). The leaves of this plant contain triterpenoids, quercetin, flavonoids, tannins, alkaloids, among other secondary metabolites that help lower glucose levels (Rodríguez Amado et al., 2013).

Based on all of this, the present study aims to describe each part of the plant and demonstrate its benefits to promote the consumption of its leaves in the prevention and glycemic control in type 2 diabetic patients.

METHOD

Theoretical, analytical and interpretative methods were used on the information information obtained from original articles available in the Scopus and ScienceDirect databases were used. Keywords such as “Guayaba”,”Psidium guajava”, “Guayaba AND obesity”, “Psidium guajava AND obesity”, “Psidium guajava AND antidiabetic”, “Psidium guajava AND diabetes mellitus” and other words related to ethnopharmacological uses, phytochemical and bioactive constituents were used for the literature search. The search was conducted in the period of 2018 and 2022.

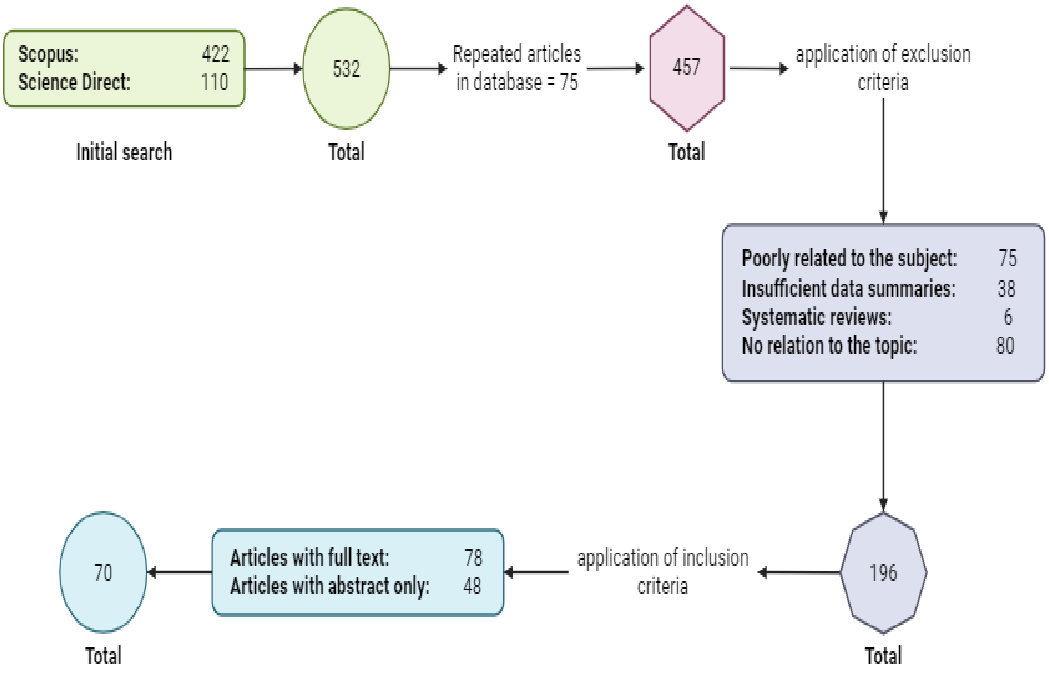

Figure 1. Flow chart of the literature search.

Repeated articles were eliminated; the remaining articles were classified by year of access, type of research and relevance, obtaining 70 research articles.

RESULTS

Table 1. Taxonomy of the plant Psidium Guajava L.

Reino	Plantae	Referens
Division	Magnoliophyta	
Class	Magnoliopsida	
Subclass	Rosidae	
Order	Myrtales	
Suborder	Myrtineae	(Gutierrez Devia, 2013)
Family	Myrtaceae	
Subfamily	Myrtoideae	
Genre	Psidium	
Species	Psidium guajava L.	

Its scientific name is Psidium Guajava L., also known as Psidium Pyriferum L. and Psidium Pomiferun L. The term “Psidium” comes from Greek and means pomegranate, being native to Tropical America and spread wild from Mexico to Brazil and the subtropical part of the world. On the other hand, the word "guajava" comes from its vernacular name in Taino (Gutierrez Devia, 2013).

Table 2. Morphological characteristics of the plant Psidium Guajava L.

Size	Seed	Leaves	Flower	Fruit	Referens
Evergreen shrub with a height of 5 to 10 and a diameter of 30-60 cm.	They are round from 3 to 5 mm	Simple, opposite leaves with fine, soft hairs. They are oblanceolate, oblong or elliptic in shape and are bright green to brownish green.	They measure between 3.5 and 5 cm. They are bisexual solitary or in bisexual cymes or dichotomous. They have 4 to 5 green sepals outside and white inside and four to five white petals.	The berries are 4 to 6 cm in diameter, globose to ovoid in shape, fleshy, juicy, sweet and sour, and creamy yellow to pink in color with a fragrant odor.	(Vijayakumar et al., 2020)

Table 3. In vivo ethnobotanical effect of the plant Psidium Guajava L.

Effect	Part	Route of administration	Method of preparation	Referens
Hepatoprotective	Leaves	Oral	-	(Vijayakumar et al., 2020)
Diabetes and hypoglycaemic	Leaves	Oral	-	(Rahayu et al., 2019)
Gastroenteritis, nausea, antidiarrhoea or dysentery	Leaves	Oral	-	(Mounica et al., 2020)
Cough, phlegm, anti-catarrhal, throat complaints	Leaves	Oral	-	(Cuellar Claros, 2018)
Antitussive	Leaves	Oral	Hydroalcoholic extract	(Naseer et al., 2018)
Alopecia	Leaves	Topic	-	(Patidar, 2018)
Antihaemolytic	Bark	Oral	Methanolic extract	(Durán et al., 2013)

Antidiarrhoeal	Leaves	Oral	-	(Chassagne et al., 2022)
Anti-inflammatory, antioxidant and hepatoprotective	Leaves	Oral	-	(Khedr et al., 2021)

Guava leaves, whether administered orally or topically, show positive effects against various pathologies. Therefore, it is a promising plant source for the prevention and control of the same (Camarena-Tello et al., 2018; Chassagne et al., 2022; Cuellar Claros, 2018; Durán et al., 2013; Khedr et al., 2021; Mounica et al., 2020; Naseer et al., 2018; Patidar, 2018; Rahayu et al., 2019).

Table 4. Use of the plant Psidium Guajava L.

Pharmacological effect	Study	Part of the plant	Method of preparation	Molecule and metabolic pathways involved	Response	Referens
Antioxidant	In vitro	Leaves	Organic extracts	Gallic acid, quercetin	Optimum	(Camarena-Tello et al., 2018)
Antidiabetic Pancreatic protector	In vivo	Leaves	Water extract	Glycogen synthase, muscle phosphorylase, triterpenes, phenolic compounds	Optimum	(Tella et al., 2019, 2022)
Antidiabetics Metabolic disorders	In vitro	Leaves	Methanolic extract	α-amylase, tyrosinase, hyaluronidase, quinalizarin, ellagic acid	Optimum	(Ahmed et al., 2021)
Anti-inflammatory Anticoagulant	In vitro	Leaves	Ethanolic extracts	Monoterpenoids	Optimum	(Yu et al., 2022)
Antibacterial	In vitro	Leaves	Ethanolic extracts	Psiflavonone	Optimum	(Huang et al., 2021)
Antioxidant	In vitro	Leaves with	Fungal extract	Secondary metabolites:	Optimum	(Ujam

Immuno suppressant		endophytic fungi		protocatechinic acid, asteric acid, citrinin, etc.		et al., 2021)
Antihyperglycaemics and liver protectors	In vivo	Leaves	Simple extract	Flavonoids	Optimum	(Zhu et al., 2020)
Healing Antimicrobial	In vitro	Leaves	Gel	Tannins, total phenols, gallic acids	Optimum	(Kumari et al., 2018)
Hepatoprotective	In vivo	Leaves	Ethanolic extract	Quercetin	Optimum	(Vijayakumar et al., 2018)
	In vitro	Leaves	Water extract	Polyphenols, flavonoids	Optimum	(Latha et al., 2018)
Antiangiogenic Antioxidant	In vivo	Leaves	Simple extract	Gluconeogenesis, glycogenesis	Optimum	(Vinayagam et al., 2018)
	In vivo	Leaves	Water extract	Glycogen synthase, glycogen phosphorylase	Optimum	(Tella et al., 2019, 2022)
	In vivo	Leaves	Ethanolic extracts	Glycogen	Doubtful	(Mounica et al., 2020)
Antidiabetic	In vivo	Leaves	Water extract	Glycogen synthase, muscle phosphorylase, pancreatic islets	Optimum	(Tella et al., 2019, 2022)
	In vitro	Leaves	-	Insulin, glucose	Optimum	(Jiang et al., 2021)
	In vitro	Leaves or fruits	-	Triterpenoids, α-glucosidase	Optimum	(Chao et al., 2020)
	In vitro and	Fruit	Supercritical CO2	Kojic acid, 5-Hydroxymethylfurfur	Optimum	(König

	in vivo		extraction	al		et al., 2019)
	In vivo	Leaves and fruits	Simple extract	Polyphenols	Optimum	(Müller et al., 2018)
	In vitro	Leaves	Infusions	α-glucosidase, chrysin, caffeoylquinic acid	Optimum	(Rahayu et al., 2019)
	In vivo	Leaves	Ethanolic extract	Aloxane	Optimum	(Rajput & Kumar, 2021)
	In vitro	Bark and leaves	Ethanolic extracts	α-glucosidase, α-amylase	Optimum	(Beidokhti et al., 2020)
	In vitro	Leaves	Methanolic extracts	Flavonoid	Optimum	(Adeniran & Gololo, 2022)
Antidiabetic Antioxidant	In vitro	Leaves	Ethanolic extracts	Phenolic compounds, α-glucosidase	Optimum	(Huang et al., 2021)
Antihyperglycaemics Hepatoprotectants	In vivo	Leaves	Simple extract	Flavonoids	Optimum	(Zhu et al., 2020)
Antioxidant Hypoglycaemic	In vitro	Root	Ethanolic extracs	α-glucosidase, α-amylase	Optimum	(Yuanbei et al., 2022)
	In vitro	Fruits	-	-	-	(Ismawanti et al., 2020)
Antidiabetic Hypoglycaemic	In vivo	Leaves	-	Metabolites, metabolic pathways	Optimum	(Xu et al., 2020)
	In vitro	Leaves	Methanolic	Adipogenesis,	Optimum	(Choi et al.,

			extracts	lipolysis		2021)
Antioxidants Antidiabetics Antibacterials	In vitro	Leaves	Essential oil	α-amylase, α-glucosidase	Optimum	(Zhang et al., 2022)
Antioxidants Antidiabetics Antilipidemics Antimicrobials	In vitro	Leaves	Water and methanolic extracts	Phenols, flavonoids, α-amylase, esculin, quercetin, gallocatechin, 3-synapoylquinic acid, gallic acid, citric acid, ellagic acid	Optimum	(Kumar et al., 2021)
Antioxidants Anti-inflammatory Hepatoprotector	In vivo	Leaves	Supplementation	-	Probable	(Debnath et al., 2021)
Hypoglycaemic Hepatoprotectors	In vivo	Leaves	Decoction	Ellagic acid, hyperoside, isoquercitroside, quercetin	Optimum	(Li et al., 2021)
Hypercholesterolemic	In vivo	-	Licopene extract (LRE)	Glutathione peroxidase, superoxide dismutase	Optimum	(Brito et al., 2019)
Antioxidants Hypercholesterolemic Anti-inflammation	In vivo	Leaves	Powdered supplements	Polyphenols, bioactive	Optimum	(Mamun et al., 2019)
Antioxidant Antidiabetic	In vitro	Leaves	Infusion	Free radicals, superoxide dismutase	Optimum	(Luo et al., 2019)
	In vitro	Fruits	-	Papaya (comparison)	Optimum	(Ismawanti et al., 2020)
Against oxidative stress	In vitro	Leaves	-	Polyphenols	Optimum	(Li et al., 2019)

Antidiabetic Hypolipidemic	In vivo	Leaves	Ethanolic extracts	-	Optimum	(Manikandan et al., 2017)
	In vitro	Leaves	Simple extract	Phenols, flavonoids	Optimum	(Sowmya & Usha Anandhi, 2020)
Antioxidants	In vitro	Husk	Ethanolic extracts	Total phenols, flavonoids	Optimum	(Liu et al., 2018)
	In vitro	Fruits	Simple extract	Ascorbic acid, catechin, epicatechin, shikimic acid, quinic acid, polyols	Optimum	(De Pradhan & De, 2020)
	In vitro	Leaves	Ethanolic and methanolic extracts	Phenols, flavonoids, flavonols, tannins	-	(Feudjio et al., 2020)
	In vitro	Leaves	Water extract	Polyphenols, gallic acid	-	(Zeng et al., 2019)
	In vitro	Leaves	Ethanolic extracts	Terpenoids, meroterpenoids	-	(Ryu et al., 2021)

The studies conducted on extracts from leaves of Psidium Guajava L. demonstrated that compounds such as phenols, flavonoids, meroterpenoids, kojic acid, aloxane, ellagic acid, and quercetin have antidiabetic effects. Likewise, they show that through different mechanisms their compounds can prevent or control hyperglycemia, due to the inhibition of α-glucosidase and α-amylase, effects on glucose uptake and transporters. Therefore, the plant Psidium Guajava L. is a promising source of new compounds applicable to the treatment of type 2 diabetes (Ríos et al., 2016).

DISCUSSION

The medicinal properties of the leaf of Psidium Guajava L. (guava) are relevant in the prevention and control of Type 2 Diabetes Mellitus (DM2). These medicinal properties are associated with the hypoglycaemic action generated by the various constituent metabolites of the guava plant (Jiang et al., 2021). Therefore, it is becoming increasingly important to promote the use of herbal medicine, rather than pharmacological treatment, for the prevention and control of blood glucose levels in patients with DM2 (Ahmed et al., 2021; Tella et al., 2022) .

The mechanism by which guava leaf exhibits potential properties against DM2 (Mounica et al., 2020) operates through two pathways: the PI3K-AKT signaling pathway, which facilitates the synthesis and transport of GLUT 4 in myocytes and hepatocytes. Additionally, at a dose of 200 mg/kg body weight administered to laboratory rats, it regulates proteins in this pathway by stimulating the translocation of GLUT 2 to the cell membrane, thereby facilitating glucose entry into the cell, consequently reducing blood glucose levels and regulating insulin resistance. Furthermore, it regulates cell growth cycle and gluconeogenesis/glycolysis metabolism (Vinayagam et al., 2018). The other pathway involves the regulation of genes (INS, INSR, TNF, PEPCK, NFKB, AKT) that reduce insulin resistance (Jiang et al., 2021). Moreover, the extract of Psidium Guajava L. leaf significantly decreases the activity of glycogen synthase, a key enzyme in glycogen synthesis, and increases the activity of glycogen phosphorylase, which degrades glycogen (Tella et al., 2022).

The medicinal plant guava, specifically its leaves, are considered a source of polyphenols, meroterpenoids, flavonoids such as gallic acid and quercetin in various forms. Utilizing appropriate methods alongside extracts that aid in the revelation of bioactive compounds, they are considered functional against multiple chronic metabolic disorders, such as in the case of diabetes (Latha et al., 2018; Y. Li et al., 2019).

In in vitro studies, metabolites such as flavonoids were identified through HPLC, among which guaijaverin and avicularin are the main contributors to the hypoglycemic effect of this plant. Studies revealed that guaijaverin inhibits the activity of dipeptidyl peptidase IV, which is an important enzyme in blood glucose homeostasis. It was also observed that avicularin suppresses the accumulation of intracellular lipids by repressing glucose uptake mediated by glucose transporter 4 (GLUT4) (Zhu et al., 2020). Furthermore, an in vivo study demonstrated that guava flavonoids significantly decrease glucose tolerance, insulin resistance index, serum total cholesterol, triacylglycerols, and low-density lipoproteins (LDL) (Luo et al., 2019; Tella et al., 2019; Vinayagam et al., 2018; Zhu et al., 2020).

In an experimental in vivo study, aloxane was induced in diabetic mice, and the antidiabetic activity of the ethanolic extract of Psidium Guajava L. leaves was compared with the drug Glibenclamide (5mg/kg), resulting in guava producing a better reduction in glucose levels (Rajput & Kumar, 2021) .

Similarly, in another in vivo study, crude ethanolic extracts of leaf and bark of Psidium Guajava L. were analyzed, along with compounds from metformin and insulin to stimulate glucose uptake in skeletal muscle cells. The result showed that glucose absorption was significantly elevated in the presence of the leaf extract of Psidium Guajava L., but not with the bark extract. Furthermore, when comparing glucose uptake in the presence of the leaf extract of Psidium Guajava L. with uptake measured in the presence of metformin and insulin (separately), it was detected that they exhibit the same level of stimulation of glucose uptake in skeletal muscle cells (Beidokhti et al., 2020).

Obesity and overweight are risk factors for developing type 2 diabetes (DM2), a study demonstrated the anti-obesity effects of guava polysaccharide by alleviating body weight gain from a high-fat diet, preventing hepatic lipid accumulation, and inflammation in hepatocytes and adipose tissues in obese mice, thus demonstrating that guava consumption prevents DM2 (Manikandan et al., 2017; Sowmya & Usha Anandhi, 2020).

CONCLUSION

This review served to compile new advances on the antidiabetic effects of guava leaf that could be applied in the development of new bioactive drugs and therapeutic diet strategies, possible prebiotic ingredients in the nutraceutical and food industry, as well as functional foods. Therefore, it is suggested to carry out new studies that demonstrate the efficacy, safety, and appropriate dosage of guava leaf extract to be implemented in the prevention and control of diabetes in humans.

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