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The Potential of Psidium Guajava as an Antidiabetic : a Review

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ABSTRACT

Psidium guava is known as a fruit that contains many bioactive compounds such as polyphenols, flavonoids, and heteropolysaccharides. This review presents the results of the latest research on the effect of guava fruit on type 2 diabetes mellitus. It is proven that guava fruit can act as an antihyperglycemic therapy through mechanisms that include repairing pancreatic cells, increasing insulin sensitivity, inhibiting α-glucosidase, and inhibiting SGLT1 and GLUT2 transporters. These results prove the potential of guava fruit as a functional food for glycemic control in patients with type 2 diabetes mellitus.

1. INTRODUCTION

Diabetes is one of the most common metabolic diseases worldwide. This disease is characterized by hyperglycemia resulting from insulin resistance or impaired insulin secretion, or both. Diabetes mellitus is a chronic non-communicable disease that can cause various complications in other organs including neuropathy, glaucoma, nephropathy, ischemic heart disease, ketoacidosis, and even limb amputation [1,2]. The latest data shows that in 2021, the total global prevalence of diabetes was 537 million sufferers which caused 6,7 million deaths. The incidence is expected to increase to 642 million in 2040 due to the high prevalence of unhealthy behavior, physical inactivity and increasing incidence of obesity [3].

Conventional treatment for diabetics usually includes oral hypoglycemic drugs, insulin injections, and diet therapy [4]. Oral therapy is usually indicated for patients who cannot control their glucose levels well. Although hypoglycemic drugs give a good initial effect, over time they can lose their effectiveness. Drugs such as sulfonylureas, thiazolidinediones, and biguanides cause a variety of unwanted side effects including weight gain, fatigue, nausea, vomiting, increased LDL cholesterol, and hypoglycemia [5,6,7]. These unwanted side effects increase the demand for safer and cheaper alternatives.

A potential alternative that can be used as an antihyperglycemic is to utilize bioactive compounds in plants. Several bioactive compounds extracted from plants can act as an alternative to lowering blood glucose levels by various mechanisms such as increasing the function of pancreatic beta cells, inhibiting glucose absorption, improving insulin resistance, or regulating GLP-1 homeostasis [8]. One of the plant products that have the potential as an anti-hyperglycemic agent is guava fruit (*Psidium Guajava Linn.*) which contains many bioactive compounds including polyphenols, flavonoids, and heteropolysaccharides.

This review will discuss the results of recent studies on the effect of bioactive substances in guava as antihyperglycemic agents. The purpose of this literature review is to present the latest information regarding the potential of guava as an antihyperglycemic for type 2 diabetes mellitus patients.

2. METHOD

The process of compiling this literature review is by tracing research articles on the PubMed electronic database. An article search was carried out with the keyword "Psidium guajava in diabetic". Articles were searched based on inclusion criteria: studies using guava fruit on diabetes mellitus both in vitro, in vivo, or in humans, published in 2013-2023, available in full text and in English. The articles

obtained were then synthesized in the following format: researcher's name, year, title and research results. The article synthesis step is carried out as follows:

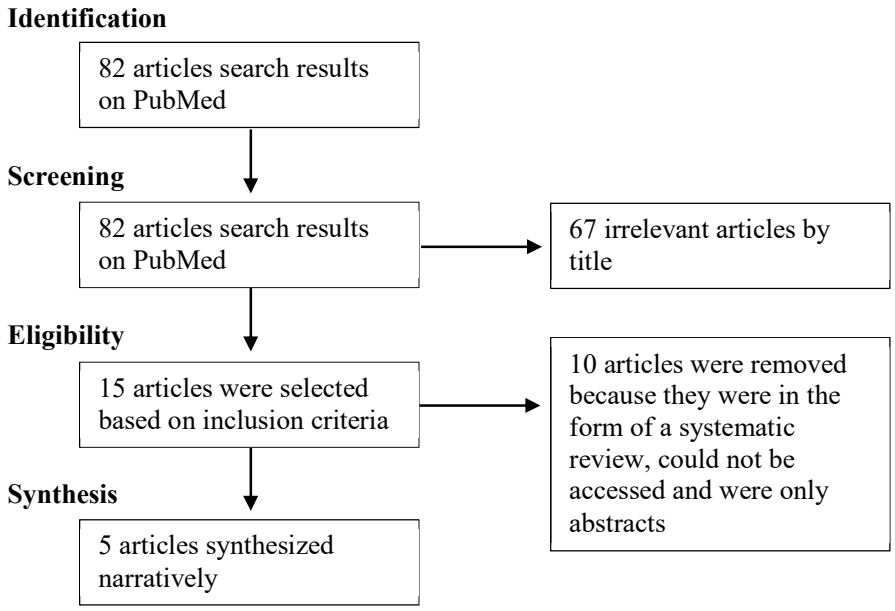

Figure 1. The article synthesis step

3. RESULTS AND DISCUSSION

Based on the results of the article search, 5 articles were found that were synthesized in a narrative manner. The description of the article is explained in Table 1 as follows:

Table 1. Article Synthesis Results

No	Author	Year	Research article	Results
1.	Li et al. [9]	2015	Protective Effects of Red Guava on Inflammation and Oxidative Stress in Streptozotocin-Induced Diabetic Mice	Streptozotocin (STZ)-induced diabetic rats were given red guava extract at doses of 1%, 2%, 5% and 5% + rosiglitazone for 8 weeks. The results showed that the intervention group experienced a significant increase in diabetes mellitus parameters such as blood sugar levels and insulin resistance. In addition, the intervention group also showed significant improvements in inflammatory mediators such as C-RP and TNF-α.
2.	Lin et al. [10]	2016	Quercetin-Rich Guava (Psidium guajava) Juice in Combination with Trehalose Reduces Autophagy, Apoptosis and Pyroptosis Formation in the Kidney and Pancreas of Type II Diabetic Rats	Quercetin extract from guava was given to rats with type 2 diabetes mellitus at doses of 4 ml, 8 ml, and 20 ml with a combination of trehalose per day for 4 weeks. The results show the effect of neutralizing the parameters of Reactive Oxygen Species (ROS), namely H2O2 and HOCl. Quercetin extract also improved the parameters of glucose tolerance test, plasma insulin, HOMA-IR, and HOMA-β.
3.	Jiao et al. [11]	2018	Characterization of a New	GP70 polysaccharide extract from guava tested in vitro showed strong inhibitory

			Heteropolysaccharide from Green Guava and its Application as an α-Glucosidase Inhibitor for the Treatment of Type II Diabetes	results against α-glucosidase. The degree of inhibition by polysaccharide GP70 was 1867 times stronger than inhibition by acarbose as a control.
4.	Müller et al. [12]	2018	In Vitro and In Vivo Inhibition of Intestinal Glucose Transport by Guava (Psidium Guajava) Extracts	In vitro studies on Caco-2 cells showed that guava leaf and fruit extracts could reduce the activity of SGLT1 and GLUT2 transporters. These findings were then followed by in vivo testing with the results that guava extract can reduce blood glucose levels in non-diabetic rats.
5.	König et al. [13]	2019	Guava (*Psidium guajava*) Fruit Extract Prepared by Supercritical CO2 Extraction Inhibits Intestinal Glucose Resorption in a Double-Blind, Randomized Clinical Study	Glucose solution and guava fruit extract were intervened to healthy people. The control group was given 75 g of glucose, while the intervention group was given 75 g of glucose solution and 2.5 ml of guava fruit extract. After overnight fasting, the intervention group resulted in increased postprandial glucose and lower insulin concentrations than the control group. These results indicate an inhibitory effect of glucose absorption by guava fruit extract.

Guava is a fruit that was first discovered in Central and South America. This fruit is often used as a dessert. Currently guava can be found throughout the tropics and some subtropical regions including Indonesia. Taxonomically guava can be classified as follows [14]:

Kingdom : *Plantea*
Division : *Spermatophyta*
Subdivision : *Angiospermae*
Class : *Dicotylodonae*
Order : *Myrtales*
Family : *Myrtales*
Genus : *Psidium*
Species : *Psidium Guajava Linn.*

Guava fruit contains many nutrients and bioactive compounds that are very important for human health. The nutrients include carbohydrates, vitamins, and minerals. While the bioactive substances include phenols, carotenoids, gallic acid, quercetin, myricetin, ascorbic acid, apigenin, and lycopene. These bioactive compounds have various physiological effects as antihypertensive, hypolipidemic, cardioprotective, antioxidant, and antidiabetic [15, 16]. Mechanisms of guava to improve the condition of diabetes mellitus can occur in various ways:

Improve pancreatic cells and insulin sensitivity

In type 2 diabetes mellitus, insulin is unable to do its job of transporting blood sugar into cells, causing blood sugar levels to increase. Then the body compensates by forcing the pancreatic β cells to increase insulin secretion. This leads to hyperglycemia and hyperinsulinemia which gradually reduces insulin receptor sensitivity and eventually leads to insulin resistance. This condition is explained by increased Homeostatic Model Assessment of Insulin Resistance (HOMA-IR). HOMA-IR is an examination used to assess insulin resistance in type 2 diabetes mellitus. Treatment of red guava in type II diabetes rats showed lower HOMA-IR values although insignificant. A low HOMA-IR test result indicates excellent high insulin sensitivity. This was also supported by the results of glucose levels in

the intervention group which were lower than those in the control group [9]. These results are in line with other studies that administered red guava extract and a combination of trehalose increased kidney and pancreatic β cells which were reflected in HOMA-β which increased within four weeks [10]. A high HOMA-β value indicates that pancreatic β cells produce sufficient amounts of insulin. This mechanism is mediated by the quercetin content in red guava which can neutralize reactive oxygen species (ROS) in the form of H2O2 and HOCl induced in mice. H2O2 and HOCl can trigger chronic inflammation which interferes with the work of pancreatic β cells resulting in insulin resistance [17]. The content of bioactive flavonoid glycosidase, quercetin, lycopene, and ursolic acid in the extract of red guava fruit increases insulin sensitivity and absorption of glucose in liver cells and contributes to improving conditions in diabetes [18, 19, 20].

α-glucosidase inhibitor

α-glucosidase is a group of enzymes that includes sucrase maltase and isomaltase which play an important role in glucose absorption. This group of enzymes works by hydrolyzing disaccharides into monosaccharides which can be absorbed in the small intestine. Inhibition of α-glucosidase activity has been used to control blood glucose levels in people with diabetes mellitus [21]. Among all available antidiabetic drugs, inhibition of α-glucosidase activity is the most effective drug in lowering postprandial blood glucose [22]. Guava also has α-glucosidase inhibitory activity through its polysaccharide content. Research by Jiao (2018) succeeded in exploring a type of polysaccharide in guava fruit called GP70. GP70 polysaccharide extracted from guava fruit showed stronger α-glucosidase inhibitor activity over acarbose which is an antidiabetic drug [11]. These results were also supported by other studies that GP70 polysaccharides reduced fasting blood glucose levels, glucosylated serum proteins, and improved insulin sensitivity in type 2 diabetes mellitus rat models [23].

Inhibits the SGLT1 and GLUT2 transporter

The food consumed will undergo a digestive process so that the nutrient content is hydrolyzed into a form that is ready to be absorbed by the small intestine. In the small intestine, glucose absorption is highly dependent on Sodium-dependent Glucose Transporter 1 (SGLT1) and Glucose transporter 2 (GLUT2) [24]. Therefore, it is necessary to approach the inhibition of SGLT1 and GLUT2 activity in people with diabetes mellitus to control postprandial glucose levels. Inhibition of SGLT1 and GLUT2 transporter activity can affect the amount of glucose absorbed to prevent a significant increase in glucose levels. Polyphenol and flavonoid compounds in guava have been shown in vitro and in vivo to inhibit SGLT1 and GLUT2 activities [25, 12]. These results were reinforced by studies in humans that the administration of guava fruit extract resulted in a controlled increase in postprandial glucose. The intervention group that was given glucose solution and guava fruit extract resulted in increased postprandial glucose and lower insulin concentrations compared to the control group [13]. These results can be used as evidence that the bioactive content in guava fruit can inhibit SGLT1 and GLUT2 activity properly.

4. CONCLUSION

Various studies have shown an antihyperglycemic effect on guava fruit through various mechanisms which include repairing pancreatic cells, increasing insulin sensitivity, and inhibiting α-glucosidase enzyme, SGLT1, and GLUT2 transporters. These results prove the potential of guava fruit as a antidiabetic agent for glycemic control in patients with type 2 diabetes mellitus.

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