STEVIA REBAUDIANA AS A NATURAL ANTIDIABETIC AGENT: CURRENT EVIDENCE AND MECHANISTIC PERSPECTIVES

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Abstract

The aim of this review is to provide a comprehensive evaluation of stevia in relation to diabetes, focusing on its mechanisms of action and therapeutic potential. Sugar, particularly sucrose, has long been a staple in human diets due to its sweetness and energy-providing properties. However, excessive consumption of sugar is strongly linked to obesity, type 2 diabetes, cardiovascular diseases, and metabolic syndrome. High intake of refined sugars can lead to hyperglycemia, insulin resistance, and chronic inflammation, creating a cascade of health complications. In recent years, attention has shifted toward natural sweeteners derived from plants, including stevia, monk fruit, and sugar alcohols (e.g., xylitol, erythritol). Among these, stevia (Stevia rebaudiana) stands out due to its rich content of bioactive compounds (phytochemicals) such as steviol, steviosides, and rebaudiosides, which exhibit strong anti-hyperglycemic activity. These compounds make stevia a safe and effective substitute for sucrose in diabetic patients.The active compounds in stevia not only lower blood sugar levels but also support pancreatic tissue health by enhancing insulin secretion and promoting anti-diabetic effects. Additionally, stevia contributes to maintaining normal glucose levels by reducing inflammation and oxidative stress, making it a highly effective natural sweetener for the growing demand in the herbal and natural food market.

Keywords: Diabetes, stevia, Antidiabetic, Bioactive compounds

Introduction

Diabetes is a common metabolic disorder caused by cellular insulin resistance or insufficiency. It is linked to a number of noncommunicable diseases (NCDs), including dysfunction or failure of organs such as the heart, kidneys, or blood vessels, making it susceptible to heart failure, obesity, stroke, hypertension, renal disease, and ophthalmic illnesses (Mellitus, 2005). Approximately 90–95% of people with diabetes worldwide are thought to have Type 2 diabetes (T2D), among various forms of the disease (Issa & Hussen Bule, 2015). A number of indicators, including glucose intolerance, fasting blood glucose (FBG), insulin secretion level, and serum glucose level (SGL), are used to diagnose type 2 diabetes in patients (Rahmani et al., 2018). Diabetes management is complicated and requires a number of techniques, including eating a balanced diet, being aware of food-related factors that may assist control blood glucose levels (BGL), exercising, and, if necessary, using insulin as directed. Diabetes is being treated with natural antihyperglycemic medications (Gaudel et al., 2013; Milani et al., 2016). When compared to pharmaceutical medications used to treat diabetic patients, natural medicines with antihyperglycemic activity are thought to be safer, less toxic, and more affordable. In addition to these advantages, compared to pharmaceutical medications, natural substances like stevia leaves have fewer negative side effects (Dhasarathan & Theriappan, 2011; Li et al., 2008). Sweet tulsi leaf, or *Stevia rebaudiana* (Bertoni), is a type of antihyperglycemic plant that has been used for many years as a safe sweetener (Barriocanal et al., 2008). Stevia is frequently utilized as a sugar substitute in foods, drinks, and medications in many nations, and stevia derivatives have been used to create

commercial products (Abbas et al. 2017). Numerous significant phytochemicals found in stevia, including as rebaudiosides, steviol, and steviosides, have the ability to lower blood sugar levels. It has a strong anti-hyperglycemic effect and can replace saccharose in diabetics. By raising insulin levels and strengthening anti-diabetic qualities, it has positive effects on pancreatic tissue (Jan et al., 2021). It's interesting to note that stevia leaves have better functional and sensory qualities than many other high-potency sweeteners. In the future, stevia is probably going to be a significant source of high-potency sweetener for the expanding natural food market (Goyal et al., 2010). Numerous research have demonstrated that stevia has numerous health benefits in addition to its industrial uses, such as anti-diabetic, anti-obesity, anti-tumor, anti-hypertensive, anti-microbial, anti-caries, and antioxidant qualities (Abbas et al., 2017; Ruiz-Ruiz et al., 2015). Furthermore, steviol glycosides from stevia leaves have been shown in numerous investigations to be acutely poisonous and neither teratogenic, carcinogenic, nor mutagenic. There is a dearth of contemporary research explicitly addressing stevia's impact on diabetes mellitus, despite the fact that numerous studies have examined the plant's potential to treat a variety of illnesses. Thus, the purpose of this study is to offer a thorough assessment of stevia in connection to diabetes, emphasizing its therapeutic potential and mechanisms of action.

Diabetic Mellitus

Diabetes is a long-term illness marked by anomalies in the action or secretion of insulin, or occasionally both. Diabetes affects the entire body and causes problems in particular organs like the eyes, nerves, and kidneys. Insulin is a hormone released by the pancreas that serves as the main messenger for transferring glucose from consumed meals from the bloodstream into the body's cells where it is used for energy (Sanyaolu et al., 2013). The World Health Organization estimates that 9.0% of adults worldwide suffer from it (WHO, 2021). The rapid increase in obesity and inactivity may be the cause of this emerging epidemic (Herman, 2007). being divided into two categories: adult-onset type 2 (non-insulin-dependent) and type 1 (insulin-dependent) (American Diabetes Association, 2010). Diabetes raises the risk of heart disease and associated complications, which is one of the major health issues it causes worldwide.In low- and middle-income countries, it affects 80% of the population; in wealthier countries, it primarily affects individuals between the ages of 35 and 64 (Whiting et al., 2010).

Types of Diabetes

Insulin is a key component of diabetes, a metabolic disease. The pathophysiology of this condition involves multiple pathogenic mechanisms. They range from a condition that inhibits the action of insulin to the autoimmune destruction of pancreatic beta cells, which leads to chronic insulin insufficiency. An abnormal metabolism of proteins, fats, and carbohydrates brought on by inadequate or even faulty insulin action is the root cause of this illness.A deficit in insulin secretion or effect at one or more sites along its path of action is the primary cause of hyperglycemia (American Diabetes Association, 2010).

Type 1 Diabetes Mellitus

Insulin-producing cells are the focus of an autoimmune reaction that causes type 1 diabetes mellitus (T1DM) (Roep et al., 2021). Patients with type 1 diabetes have varying degrees of beta cell disintegration; in some, it is very slow, while in others, it is quite rapid (Wajchenberg, 2007). For most patients, the most prevalent initial sign of the condition is keto-acidosis. In the setting of environmental factors, others display signs including keto-acidosis and fasting hyperglycemia.Many people eventually become insulin dependant and experience keto-acidosis, even though some may maintain sufficient beta-cell activity to avoid it. Insulin production declines as the illness worsens, and C-peptide levels drop and frequently become undetectable (Eskeziya et al., 2020). The autoimmune destruction of beta cells has been associated with a number of factors, including idiopathic causes, environmental factors, and inheritance (Eringsmark Reg αll & Lernmark, 2013).

Type 2 Diabetes Mellitus

Ninety to ninety-five percent of those with diabetes have type 2 diabetes mellitus (T2DM). Insulin resistance to insulin-stimulated glucose in the blood is the outcome of a complex process in type 2 diabetes that is primarily caused by an imbalance between insulin synthesis by beta cells and insulin action The intermediate stage of the condition that establishes the risk of heart disease is impaired glucose tolerance (Herman, 2007). Obesity may cause some form of insulin resistance, as many people with type 2 diabetes are fat (American Diabetes Association, 2010). In this kind of diabetes, keto-acidosis develops gradually and spontaneously. It is often brought on by the same factors that produce type 1 diabetes, such as illness and stress. T2DM frequently goes untreated due to the lack of obvious symptoms (Elendu et al., 2023).

Medicines for Diabetes

Insulin therapy is one of several therapies for diabetes mellitus. Type 1 and Type 2 diabetes mellitus are treated with additional oral hypoglycemic medications like sulphonylureas, thiazolidinediones, and peptide analogs (Mohajan & Mohajan, 2024). Over-the-counter herbal remedies are widely accessible. Serious illnesses are treated with these natural treatments. When pharmacological therapies for disorders don't work, these medications are also used (Tabish, 2008). These medications are natural, risk-free, and have no unfavorable side effects. Unlike manufactured medications, which do not permanently cure ailments, herbal treatments treat the condition and heal the patient (Karimi et al., 2015). Herbal remedies employ natural fruit, vegetable, and herb extracts to treat a range of illnesses without causing any negative side effects. Chemical medications, on the other hand, are manufactured artificially and have disadvantages. When compared to allopathic medications, herbal remedies are less costly. Natural mixtures are made with herbs. Herbal remedies are made with natural ingredients, whereas allopathic medicines are made with natural ingredients. Prescription-free herbal formulations are accessible such as *S. Rebadiana* (Maqbool et al., 2019).

Origin and Distribution of *S. Rebadiana*

Only one of the 230 species in the Asteraceae family's genus Stevia, *S. rebaudiana* Bertoni, yields sweet steviol glycosides. Previous research disproves the notion that S. phlebophylla possesses this characteristic as well (Ceunen et al., 2013). S. rebaudiana, often known as "Honey Leaf," "Sweet-Leaf," or "Sweet-Herb," is a perennial shrub that grows throughout South America, especially in Brazil and Paraguay. Fresh and dried stevia leaves, stevia leaf powder, extracts, and liquid concentrates are only a few of the various types of stevia preparations. Because stevia extract is 200–300 times sweeter than sugar, it is an excellent substitute for artificial sweeteners (Singh and Rao, 2005).

The highlands of northeastern Paraguay, near the Brazilian border, are where *S.rebaudiana* first appeared (Katayama et al., 1976). It originated in the Rio Monday Valley of the Amambay mountain range and is found throughout the Southwestern United States, Mexico, and Central America. Additionally, it is found from non-Amazonian South America all the way south to Central Argentina. Thirty-six species have been identified in Brazil, most of which are found in the country's southern and central areas. In its natural state, it grows in grasslands with shallow water tables or on the margins of marshes. Semi-humid subtropical climates with temperatures between 6 and 43 °C, with an average of 23 °C, and annual rainfall between 1500 and 1800 mm are ideal for optimal growth (Yadav et al., 2014). *S. rebaudiana* is a herbaceous plant that can reach a height of 30 cm. In tropical and subtropical regions, it is a perennial plant; in colder regions, it is typically planted as an annual. It has lanceolate-shaped, tiny, sessile leaves that are arranged alternately (Singh & Rao, 2005). They have two different-sized trichomes on the leaf surface and are mildly glandular pubescent. The apex of the leaf is blunt, and its edge is serate. Numerous environmental factors, such as soil conditions, irrigation techniques, sunlight, air cleanliness, and farming procedures, cause stevia leaves to differ greatly. The cool, delightfully sweet flavor of leaves can stay in the mouth for hours. In the veins, the bitter components encircle the material's sweet components (Maiti & Purohit, 2008). According to Goettemoeller and Ching (1999), the small white flowers are dioecious. The seeds are tiny, thin achenes that are only 3

mm long. Their hairy pappus disperses them in the wind, and they contain a relatively little endosperm. Infertile seeds are often pale in color, while viable seeds are typically dark in color (Yadav et al., 2011).

Biochemical and Nutritional aspects

Flavonoids, alkaloids, water-soluble chlorophylls and xanthophylls, hydroxycinnamic acids (caffeine, chlorogenic, etc.), neutral water-soluble oligosaccharides, free sugars, amino acids, lipids, essential oils, and trace elements are all present in the dry extract from stevia leaves (Komissarenko et al., 1994). A dry weight analysis of stevia leaves by Savita et al. (2004) yielded an energy value of 2.7 kcal g-1; further analysis by Khiraoui et al. (2017) revealed an energy value of 3.05–3.17 kcal g-1. This implies that stevia could be considered a low-calorie sweetener (Khiraoui and others, 2017).

Steviol (ent-13-hydroxykaur-16-en-19-oic acid and its glycosides) and its glycosides stevioside, rebaudioside AF, steviolbioside, dihydroisosteviol, rubusoside, and dulcoside A are the most well-known of the more than 100 compounds that have been identified from *S. rebaudiana* Bertoni (Blumenthal, 1996). determined the energy value of 2.7 kcal g-1 by analyzing the S. rebaudiana leaves on a dry weight basis. Stevioside (13- [2-O-ß Dglucopyranosyl-X-glucopyran-osyl) oxy] kaur-16-en-19-oic-acid ß-D-gluco-pyranosyl ester) is a glycoside with a glucosyl and a sophorosyl residue linked to the aglycone steviol, which has a cyclopentanon hydrophenanthrene skeleton (Alahmad, 2018).

Since saccharose is fully metabolized by the body, its calorie contribution to the diet is regarded as substantial and has the potential to lead to overweight status. In this situation, using stevia as a low-calorie sweetener could greatly aid in limiting or managing dietary calorie consumption (Lemus-Modaca et al., 2012). Stevia leaf exhibits bulk density of 0.443 g ml-1, water holding capacity of 4.7 ml g-1, fat absorption capacity of 4.5 ml g-1, emulsification value of 5.0 ml g-1, swelling index of 5.01 g g-1, solubility of 0.365 g g-1, and pH of 5.95, according to Mishra et al. (2010). Mishra et al. (2010) found that stevia leaf powder had a higher water-holding capacity, which seems to be beneficial and could be because of its high protein content. Proteins have a crucial role in the creation of viscous meals such soups, gravies, dough, and baked goods by increasing their capacity to hold water. Cake, batters, coffee whiteners, milk, frozen desserts, and many other food applications depend on the protein's capacity to help build and stabilize emulsions. Since fat affects flavor retention and improves food texture, stevia leaf powder appears to have a sufficient capacity to absorb fat, enabling it to play a significant role in food processing (Khiraoui et al.,2017).

Anti-Diabetic Activities of Stevia

For many years, stevia extracts have been used to treat diabetes (Pérez et al., 2016). Frequent usage of stevia glycosides lowers blood levels of radionuclides, sugar, and cholesterol (Ferdous et al., 2025). It has a strong anti-hyperglycemic effect (Patel & Navale, 2024) and can replace saccharose in diabetics (Saharudin et al., 2020). *S.rebaudiana* improves glucose tolerance in diabetic rats, according to in vivo studies (Ahmad & Ahmad, 2018). Additionally, it causes hypoglycemia in diabetic patients by reducing the processes of glycogenolysis and gluconeogenesis and by absorbing glucose in the duodenum. Stevia and its glycosides have been linked to anti-hyperglycemic and antioxidant properties in the pancreas, liver, and kidney in diabetic patients (Shivanna et al., 2013). By raising insulin levels and improving anti-diabetic qualities in a PPARγ-dependent manner, as well as through its antioxidant activities, it has positive effects on pancreatic tissue (Assaei et al., 2016). Additionally, it has been observed that stevia's stevioside reduces inflammation by reducing pro-inflammatory cytokines (Wang et al., 2014). Chen et al. (2004) state that stevioside decreases blood sugar levels and raises insulin levels by influencing the pancreatic β-cells. Ahmad and Ahmad (2018) found that in streptozotocin-induced diabetic albino rats, extracts of stevia reduced random blood glucose levels, fasting blood glucose levels, and the quantity of glycosylated (HbA1c) hemoglobin (5.32%). Additionally, after eight weeks of treatment, they found that the diabetic samples had better levels of insulin and liver glycogen.

Chen et al. (2005) claim that stevioside not only raises insulin levels but also inhibits the process of gluconeogenesis by reducing the expression of the phosphoenolpyruvate carboxykinase gene in the

liver of rats, maintaining ideal blood glucose levels. The two bioactive substances that reduce inflammation are stevioside and steviol, which activate and increase the expression of the IκBα gene (NF-κB localization inhibitor) (Boonkaewwan & Burodom, 2013). Similar results were also reported by Bayat et al. (2017) employing stevia aquatic extracts against serum levels of interleukin-6 (IL-6) in rats with diabetes caused by streptozotocin-nicotinamide. They discovered that metformin and stevia might reduce IL-6 levels and fasting blood sugar levels in the diabetic group, which could aid in reducing insulin resistance in diabetes patients. According to Fengyang et al. (2012), stevioside reduces NF-κB and IκB levels in RAW2647 cells by reducing key inflammatory factors like IL-1β, IL-6, and TNF-α. According to Boonkaewwan et al. (2013), the human colon cancer cell line (Caco-2) did not exhibit any cytotoxicity. However, by influencing cytokine gene expression through the IκBα/NF-κB signaling pathway, stevioside and steviol reduce LPS-induced pro-inflammatory cytokine outputs (Jan et al., 2021).

Conclusion

Stevia is rich in numerous bioactive compounds (phytochemicals) such as steviol, steviosides, and rebaudiosides, which possess significant blood sugar-lowering effects. These compounds exhibit strong anti-hyperglycemic activity, making stevia a safe and effective substitute for sucrose in diabetic patients.Additionally, stevia helps maintain normal blood glucose levels by reducing inflammation and oxidative stress. Thanks to these highly active compounds, stevia serves as a major source of high-potency natural sweeteners, catering to the growing natural food market.

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