



Unveiling *Stevia rebaudiana*: origins, composition, and health implications

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Abstract: *Stevia rebaudiana* is an important plant known for its high-quality, non-caloric sugar substitute properties, making it a beneficial option for metabolic disorders. Diabetes and obesity are interlinked and are a surging health issue around the globe. This review article aims to synthesize existing literature to offer a comprehensive understanding of stevia, its origin, nutritional composition, and health implications, contributing to the body of knowledge in this area. Research methods employed for this review included a systematic literature search in reputable databases such as PubMed and Web of Science to gather and synthesize relevant findings. This review focuses on the composition of stevia, including nutritional profiling) and phytochemical profiling, its metabolic absorption and health implications, emphasizing its role in weight management and glucose regulation. The stevia leaf drying technique for extending the shelf life of the leaves and the extraction of steviol glycosides has been thoroughly discussed. This review primarily envisages the mechanisms involved in the therapeutic effects of *Stevia rebaudiana* components and their contribution toward reducing metabolic diseases.

Keywords: diabetes, health benefits, phytochemicals, stevia

1. Introduction

Stevia rebaudiana (Bertoni) is a member of the Asteraceae family, which encompasses around 950 genera. Centuries ago, the indigenous people of Paraguay used the leaves of this small, herbaceous, semi-bushy, perennial shrub to sweeten their bitter beverages ([Rashid et al., 2021](#)). The Guarani Indians utilized this plant for over 1500 years. Dr. Moises Santiago Bertoni first identified the plant in Paraguay in 1888. In 1905, the scientific name *Stevia rebaudiana* was given in honor of Dr. Rebaudi, a Paraguayan chemist. It is noted that there are approximately 150 species within the *Stevia* genus, including *Stevia dianthoidea*, *Stevia phlebophylla*, *Stevia anisostemma*, *Stevia bertholdii*, *Stevia crenata*, *Stevia enigmatica*, *Stevia eupatoria*, *Stevia lemmonii*, *Stevia micrantha*, *Stevia ovata*, *Stevia plummerae*, *Stevia rebaudiana*, *Stevia salicifolia*, *Stevia serrata*, and *Stevia viscida*. *Stevia rebaudiana* is known for being the best sweetener ([Gupta et al., 2013](#)).

Stevia rebaudiana has been utilized globally for various applications. The Guarani tribes traditionally used *Stevia rebaudiana* as a sweetener in their herbal infusions. Japan pioneered in Asia to introduce steviol glycosides into the food and pharmaceutical industries. This led to the spread of its cultivation to countries such as China, Malaysia, Singapore, South Korea, Taiwan, and Thailand ([Lemus-Mondaca et al., 2012](#)). Steviol glycosides have been employed as a substitute for sucrose and in the treatment of conditions like diabetes mellitus, obesity, hypertension, and dental caries ([Pól et al., 2007](#)). Research indicates that steviol glycosides offer therapeutic benefits, including antihyperglycemic, antihypertensive, anti-inflammatory, antitumor, antidiarrheal, diuretic, and immunomodulatory effects ([Chatsudhipong & Muanprasat, 2009](#)). Additionally, stevia leaves possess functional and sensory attributes that surpass those of many other sweeteners ([Pól et al., 2007](#)).

Sweetness is one of the basic taste sensations that significantly influences human food preferences and dietary habits ([Li et al., 2020](#)). Sugars, straightforward carbohydrates such as sucrose (table sugar), supply immediate

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energy and enhance the taste of food. However, high consumption of sugar is associated with numerous health issues, including obesity, type 2 diabetes, and cardiovascular diseases (Nguyen et al., 2023). This concern has driven the quest for alternative sweeteners that can provide sweetness without the adverse health effects linked to sugar. The search for sugar substitutes has driven the investigation into various natural sources of sweetness. Over the past few decades, artificial sweeteners like aspartame and sucralose have been commonly used. However, safety concerns and potential long-term health effects have reignited interest in plant-derived natural sweeteners (Soares et al., 2021).

Diabetes and obesity are both major concerns for global health, and they are closely related. Obesity increases the risk of having diabetes, and it can also contribute to the progression of the disease, as well as cardiovascular issues (Verma & Hussain, 2017). While weight loss is widely recognized as a beneficial means of preventing and managing diabetes, it is challenging for those with type 2 diabetes due to various metabolic and psychological factors (Ibrahim et al., 2018). For some individuals, lifestyle changes alone may not be sufficient for weight loss, and other options like pharmacotherapy must be considered. Nonetheless, many conventional glucose-lowering medications can cause weight gain (Van Gaal & Scheen, 2015). Diabetes is a non-communicable and metabolic disorder characterized by hyperglycemia, a condition in which either the pancreas is unable to produce insulin, or the body is unable to utilize the produced insulin, which, as a result, increases the blood glucose level (Shahid et al., 2021). Insulin, a hormone produced by β -cells of the pancreas, plays a key role in the metabolism of carbohydrates and fats. It allows glucose to enter the cells from the bloodstream (Qaid & Abdelrahman, 2016). The insulin resistance or inability of the cells to respond to insulin can lead to a rise in blood glucose levels. This condition is known as hyperglycemia, which indicates diabetes. The signs and symptoms of diabetes occur gradually, including polyuria (excess urination), polydipsia (excess thirst), polyphagia (excess hunger), lethargy, blurry vision, irritability, mood swings, and unexpected weight loss (Roglic, 2016).

Type 2 Diabetes or Non-Insulin Diabetes Mellitus is the most prevalent type of diabetes, accounting for more than 90.0% of the people suffering, and is also ranked as the sixth leading cause of disability (Chatterjee et al., 2017). It is a metabolic condition characterized by increased levels of blood glucose resulting from defective secretion of insulin or ineffective insulin action. It is considered adult-onset diabetes or insulin-independent diabetes mellitus. In type 2 diabetes, insulin resistance occurs, and cells of the body do not respond properly to the insulin produced (Shawahna et al., 2021). The primary causes of Type 2 diabetes include genetics and overweight or obesity. In Type 2 diabetes, insulin is present inside the blood, but insulin receptors lose their sensitivity and cannot sense available insulin, due to which glucose channels remain closed, and glucose cannot penetrate the cells (Davies et al., 2018).

Globally, 422 million people are diabetic. More than 95.0% of diabetic individuals are type 2 diabetic, and Type 1 diabetes in children and adolescents is above 1.1 million (Manjunatha & Jayashree, 2019). Diabetes is considered the ninth leading cause of mortality, with a death count of 1.5 million deaths per year. The total number of people with diabetes will increase to 578 million by the end of 2030, and may increase to 700 million by the end of 2045 (Lemieux, 2020). The International Diabetes Federation (IDF) in its ninth report stated that the prevalence of diabetes in Pakistan has reached 17.1% in the adult population, which is 148.0% higher than previous reports, and it is estimated that by the end of 2019, the diabetic adult population will increase to over 19 million (Saeedi et al., 2019).

The diagnostic criteria for pre-diabetes and diabetes are recommended by the American Diabetes Association (Schwartz et al., 2017). It includes a non-fasting blood glucose test (HbA1c), a random blood glucose test, a fasting blood glucose test, and a glucose tolerance test (GTT) (Olson et al., 2010). HbA1c (glycated hemoglobin) is the test that measures average blood glucose levels over the past 3 months. The normal results for the HbA1c test are between 4.6 and 5.6%. 5.7-6.4%, in terms of millimole/mole (mmol/mol) (between 39 and 47 mmol/mol) indicates pre-diabetes, and $\geq 6.5\%$ (≥ 47 mmol/mol) indicates diabetes (Li et al., 2018).

Numerous pharmaceutical drugs have been developed for managing and treating type 2 diabetes mellitus, with metformin being the primary choice. Metformin functions by enhancing insulin sensitivity, thereby facilitating increased glucose uptake in the liver (Overbeek et al., 2017). Glitazones were utilized in the past to improve insulin sensitivity in muscles, but their withdrawal from the market was necessitated due to severe side effects



([Rubenstrunk et al., 2007](#)). Antidiabetic agents such as Sodium-glucose cotransporters (SGLT-2) inhibitors and Dipeptidyl Peptidase IV (DPP-4) inhibitors have been introduced to manage hyperglycemia. SGLT-2 inhibitors exert their antidiabetic effects by blocking SGLT-2, which enhances glucose excretion in urine, consequently reducing blood glucose levels. On the other hand, DPP-4 inhibitors promote insulin secretion and inhibit the breakdown of Glucagon-like peptide 1 (GLP-1), an insulinotropic hormone, resulting in decreased blood glucose levels ([Scheen, 2015](#)). Certain medications demonstrate insulin-resistance-reducing properties and may decrease the reliance on insulin secretagogues like meglitinides and sulfonylureas. However, it is important to note that none of the current drugs offer a complete cure for diabetes, and most of them are associated with potential side effects and high costs ([Anker et al., 2019](#)).

Obesity is a metabolic disturbance where there is an excess accumulation of body fat, which is affected by both genetic and environmental factors that are challenging to manage with dietary interventions alone ([Schwartz et al., 2017](#)). Adipose tissue is an endocrine organ where fat cells within it are endocrine cells. They secrete various products, including cytokines, lipids, metabolites, and coagulation factors ([McGown et al., 2014](#)). Excessive adiposity or obesity leads to increased levels of circulating fatty acids and inflammation, which results in insulin resistance and, ultimately, type 2 diabetes ([Siddiqui et al., 2018](#)). The 2nd National Diabetes Survey conducted in Pakistan during 2016-2017 concluded that the overall prevalence of generalized obesity in Pakistan was 57.9%. The occurrence of generalized obesity was recorded at 42.0% among males and 58% among females, using the cutoffs established by the World Health Organization (WHO) ([Qazi et al., 2023](#)). Meanwhile, the rate of central obesity was 73.1%, with 37.3% among males and 62.7% among females, respectively. The province of Punjab had the highest prevalence of generalized obesity at 60%, followed by Khyber Pakhtunkhwa at 59.2%. In terms of abdominal obesity, Baluchistan had the highest prevalence at 82.1%, followed by Punjab at 73.3%. It was noted that there was a high association between obesity (generalized and abdominal), diabetes, hypertension, and dyslipidemia ([Basit et al., 2021](#)).

Being overweight is a major risk factor for type 2 diabetes, but not all obese populations develop this condition ([Wilding, 2014](#)). Latest research has revealed the existence of a connection between obesity and type 2 diabetes, which involves various factors, including pro-inflammatory cytokines like tumor necrosis factor, interleukin-6, insulin resistance, disordered fatty acid metabolism, and cellular biochemical reactions such as dysfunction of mitochondria and stress in the endoplasmic reticulum ([McCracken et al., 2018](#)). The interactions between these factors are complex, and the significance of each is not entirely clear. Further genetic studies could help identify more ways for obesity and diabetes and identify new treatments. Doctors commonly prescribe glucose-reducing medications that can lead to weight gain, so it is essential to consider the compromise between glycemic control and body weight ([Lipska et al., 2016](#)). This is particularly important because there is growing evidence that even modest weight loss can improve glycemic control and lower the chances of diabetes through behavioral interventions, obesity medications, and bariatric surgery ([Eckel et al., 2011](#)).

Diet is considered a key factor in numerous chronic diseases. A poor-quality diet and food choices increase the risk of type 2 diabetes ([Organization, 2003](#)). Abnormal dietary patterns are associated with the onset and progression of cardiovascular diseases, hypertension, cancers, and type 2 diabetes. Once established, food selection and diet play an important role in the management of Type 2 diabetes ([Conklin et al., 2016](#)). Dietary management and physical activity are key elements in preventing and managing Type 2 diabetes and obesity. Emphasizing the acceptance and maintenance of physical activity is required for managing blood glucose levels and health in individuals with type 2 diabetes ([Sami et al., 2017](#)).

Recommendations and precautions should be tailored/ to individual characteristics and good health status. Physical activity has been shown to improve blood glucose control in Type 2 diabetes ([Lamberta & Bullb, 2014](#)). A study has found that structured lifestyle interventions, consisting of at least 150 min per week of physical activity in addition to dietary changes and modest weight loss, are effective in managing Type 2 diabetes. This approach was found to overcome the risk of type 2 diabetes up to 58% in high-risk populations ([Colberg et al., 2016](#)).

Stevia leaves possess superior sensory and functional properties compared to many other high-potency sweeteners, making them a promising natural sweetener for the expanding food market ([Goyal et al., 2010](#)). Known for their beneficial effects on human health, Stevia leaves have garnered significant research interest.

The leaves of *S. rebaudiana* offer various medicinal applications, including antimicrobial ([Jayaraman et al., 2008](#)), antiviral ([Kedik et al., 2009](#)), antifungal ([Silva et al., 2006a](#)), antihypertensive ([Chan et al., 2000a](#); [Hsieh et al., 2003](#); [Lee et al., 2001](#)), antihyperglycemic ([Benford et al., 2009](#); [P. B. Jeppesen et al., 2003](#)), antitumor ([Jayaraman et al., 2008](#)), anti-inflammatory, antidiarrheal, diuretic, anti-human rotavirus ([Das et al., 1992](#); [Takahashi et al., 2001](#)), anti-HIV, hepatoprotective ([Mohan & Robert, 2009](#)), and immunomodulatory effects ([Chatsudthipong & Muanprasat, 2009](#); [Pól et al., 2007](#)).

Excessive sugar consumption has raised significant health concerns, increasing the risk of chronic diseases for future generations. A large portion of an individual's caloric intake often comes from sugar, with many unaware of its detrimental effects. Recent studies have introduced better alternatives, and Stevia has emerged as a highly researched substitute worldwide. Although some benefits of Stevia have been identified, many more remain to be discovered. As people learn about its functionality, they gradually incorporate Stevia into their diets ([Khan et al., 2019](#)). Many countries now recognize the harmful effects of sugar on health and are increasingly turning to Stevia as a natural, safe alternative. Stevia serves as a versatile sweetener, used in a wide range of consumer products, including soft drinks, toothpaste, ice creams, confectionery, and ointments. Its numerous benefits extend beyond sweetening foods, as it can also be used to manufacture medicines ([Yadav & Guleria, 2012](#)). Stevia outperforms sugar in various aspects: it is cheaper, more efficient, and offers numerous health benefits. It tastes sweeter than sugar and can be easily integrated into daily routines. Stevia finds applications in skin care products, dental products like toothpaste and mouthwashes, edible products, sanitary products, flavoring products, and sweetening products. Although current use is limited, ongoing and future research will likely encourage a significant shift from sugar to Stevia. Known as herbal sugar and a magical sweetener, *Stevia rebaudiana* promises a valuable future with countless health benefits. According to the WHO, Stevia is expected to gain a larger share of the sweetener market, positioning it as the future of sugar ([Wang et al., 2014](#)).

The existing research on Stevia and diabetes or obesity is limited and inconclusive, highlighting the need for more rigorous investigation. Therefore, this review article aims to investigate the potential health benefits of Stevia in type 2 diabetic patients and other metabolic disorders by exploring Stevia's nutritional profile, potential benefits, and limitations. This study can provide insights into its role as an alternative therapy for individuals with diabetes who face challenges in achieving weight loss.

2. Materials And Methods

The methodology used in this study included a comprehensive literature review. The search was conducted by searching articles from Google Scholar (<http://www.GoogleScholar.com>), ScienceDirect (<https://www.sciencedirect.com/>), Scopus (<http://www.scopus.com>), and PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>) by searching keywords such as "*Stevia rebaudiana*", "Effect of stevia", "Mechanism of stevia". The search was conducted in English. Findings from relevant contexts and research journals are presented in an instructive manner. Articles published between 2003 and 2023 were included in the analysis.

3. *Stevia rebaudiana* Bertoni

Stevia rebaudiana Bertoni is an Asteraceae family plant with branches and a bushy appearance. The tree or shrub is indigenous to northeastern Paraguay ([Lemus-Mondaca et al., 2012](#)). China and Southeast Asia have also raised the plant. For several decades, Japan, Korea, and Brazil have utilized stevia sweeteners, which are unprocessed extracts from their leaves, to sweeten beverages and dishes ([Madan et al., 2010](#)).

Products made from *Stevia rebaudiana* are utilized as dietary supplements in the United States of America. Stevioside (triglucosylated steviol) and rebaudioside A (tetraglucosylated steviol), along with the additional ingredients rebaudioside C and glucoside A, are the two primary components of stevia, the sweetener, which is a diterpene derivative of steviol (ent-13-hydroxykaur-16-en-19-oic acid) glycosides ([De et al., 2013](#)). Both stevioside and rebaudioside A are glycosides found in stevia that provide no calories ([Mathur et al., 2017](#)). Along with glycosides, stevia also includes a variety of volatile oils, tannins, stigmaterol, labdane diterpenes, and triterpenes. Together, these compounds make up around 5.0–10.0% of the dry leaf weight. Dulcoside A, as well as rebaudioside C, lack 200–300 times the sweetening capacity of table sugar, sucrose, which only stevioside and rebaudioside A possess ([Chaturvedula & Prakash, 2011](#)).



4. Composition

4.1. Nutritional profiling of stevia

Nutritional profiling of stevia has been estimated in several studies. The proximate analysis of stevia was estimated per 100 grams (g) of dried sample, including the moisture content 5.5 g, proteins 16.2 g, fats 3.8 g, ash 8.2 g, fiber 7.9 g, and carbohydrates 58.8 g (Befa et al., 2020).

The mineral analysis of dried stevia leaves was estimated through an Atomic Absorption Spectrophotometer. The results expressed in milligrams (mg) per 100 grams showed that stevia contains calcium 470.3 mg, phosphorus 27.0 mg/100 g (Gupta et al., 2015), sodium 102.9 mg, magnesium 347.4 mg, iron 297.9 mg, zinc 3.7 mg, copper 1.1 mg, and manganese 9.4 mg/100 g (Befa et al., 2020).

4.2. Phytochemical Profiling of Stevia

The estimation of phytochemical profiling, including Total Phenolic content (TPC), Total Flavonoids content (TFC), and Ferric reducing Antioxidant Power (FRAP) assay of stevia, involved the preliminary steps, including preparation of the sample extract through maceration of 1 gram of dried stevia leaves in 25 ml methanol for 24 hours (Mandal & Madan, 2013).

The prepared dried stevia extract was then used for the estimation of phytochemical profiling. Stevia contains the TPC 18.6 mg of gallic acid equivalent per gram, TFC 3.91 mg quercetin equivalent/gram of dry weight, and FRAP 56.6 mmol of Fe²⁺ per gram of dry weight (Shahu et al., 2022). The procedure of phytochemical profiling is shown in Figure 1.

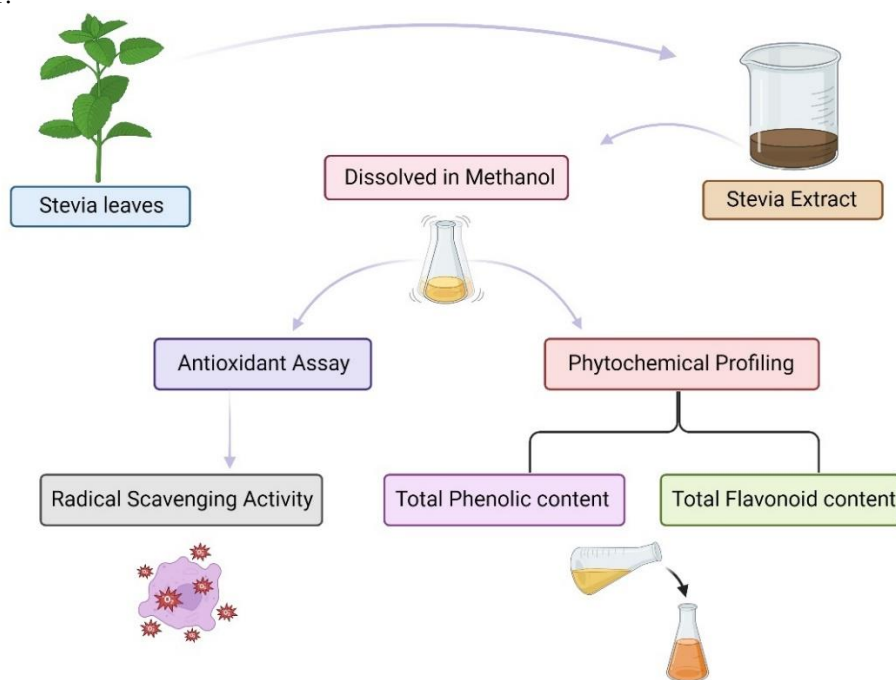


Figure 1. Phytochemical Profiling of *Stevia Rebaudiana*

4.3. Extraction of Stevia glycosides

Stevia leaf drying is a useful technique for extending the shelf life of the leaves. But drying alters the product, mostly in ways that affect the fragrance (Babu et al., 2018). It is unclear what chemicals exactly cause these alterations. Depending on the volatile molecule and the product being dried, a certain drying method's impact on the release or retention of volatile compounds is unpredictable. The most common treatment, by far, is drying, but it must be done properly to retain as much of the raw materials' flavor and color as possible (Ibrahim et al., 2007).

Ashwell mentioned in his study about the extraction of steviol glycosides from stevia. Stevia is purified into stevia leaf extract through a series of stages that start with the harvested, raw plant material and conclude with

the finished product ([Ashwell, 2015](#)). The leaves must first be dried before being steeped in boiling water. The liquid extract is filtered and purified using either water or food-grade alcohol, depending on the situation ([Samsudin & Aziz, 2013](#)). In cases where alcohol is used, it is later evaporated, leaving no detectable levels of it in the finished material. In some situations, several techniques could be applied ([Wang et al., 2020](#)). The procedure of extraction of steviol glycosides is explained in Figure 2.

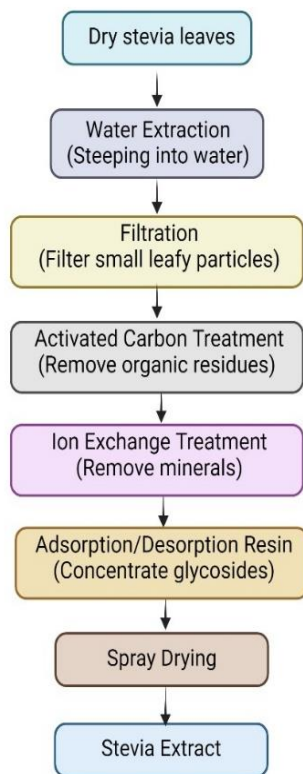


Figure 2. Processing steps to obtain stevia glycosides leaf extract from the stevia plant

Carakostas and colleagues reported the early formulations of stevia extract, which is known as a licorice flavor with a sweet and bitter aftertaste, which hindered its extensive growth in the United States in the 1990s ([Carakostas et al., 2008](#); [Prakash et al., 2008](#)). Some off-tastes were caused by essential oils, tannins, and flavonoids present in the crude extracts; efforts were made to purify extracts and characterize steviol glycosides chemically ([Samuel et al., 2018](#)).

Sweetness in stevia is derived from steviol glycosides, which are composed of steviol as their central component. These glycosides contain various groups of glycosides attached to the steviol core to create a range of sweet compounds ([Gerwig et al., 2016](#)). Steviol glycosides do not degrade in the upper gastrointestinal tract. However, when they reach the colon, gut bacteria remove the glucose units from the glycosides, converting them into steviol ([Prakash & Chaturvedula, 2018](#)). The liver is primarily responsible for metabolizing steviol, which results in the formation of steviol glucuronide, which is eliminated in the urine, and steviol is subsequently absorbed by the body through the portal vein ([Meesschaert et al., 2021](#)). Research suggests that the body does not accumulate stevia; instead, it is metabolized as it moves through the body. Since fermentation in the glucose unit produces 2 calories per gram of energy, stevia is considered to have no caloric value ([Gardana et al., 2003](#)).

4.4. Safety of steviol glycosides

The safety of steviol glycosides has been assessed by the Joint Food and Agriculture Organization/World Health Organization (FAO/WHO) Expert Committee on Food Additives (JECFA) in 2000, 2004, 2005, 2007, and 2009 ([Additives et al., 2020](#)). Stevia has also been Generally Recognized as Safe (GRAS) by regulatory agencies, including the United States Food and Drug Administration (FDA) and the European Food Safety Authority (EFSA). During these reviews, an Acceptable Daily Intake for steviol glycosides was established, with a



maximum limit of 4 mg per kilogram (kg) of body weight per day, expressed as steviol equivalents ([Magnuson et al., 2016](#)).

Research conducted on human subjects has revealed that the consumption of steviol glycosides up to 1000 mg per day for a person is safe and does not cause any adverse health effects ([Additives et al., 2020](#)). The amount mentioned is equivalent to 16.6 mg per kg body weight per day for a person weighing 60 kg. Therefore, it is equivalent to roughly 330 mg or 5.5 mg steviol equivalent/kg body weight/day ([Blaauboer et al., 2016](#)). These findings are consistent for individuals with normal glucose metabolism as well as those with type 2 diabetes ([Samuel et al., 2018](#)). Many South American and Asian countries already use stevioside as a food sweetener. Stevioside and Stevia extracts have been shown in several trials to have hypoglycemic and hypotensive effects, especially in those with type 2 diabetes and hypertension ([Chen et al., 2005](#); [P. B. Jeppesen et al., 2003](#)).

4.5. Metabolic absorption of steviol glycosides

Absorption, metabolism, and excretion of steviol glycosides have undergone extensive examination by numerous scientific authorities and experts, such as EFSA ([Additives et al., 2020](#)). Steviol glycosides are resistant to digestion in the upper gastrointestinal tract but can be broken down by colonic microbiota through the enzymatic cleavage of glycosidic linkages ([Pang et al., 2021](#)). This enzymatic process removes the sugar components, resulting in the absorption of the steviol backbone into the systemic circulation. Subsequently, the steviol undergoes glucuronidation in the liver and is excreted through urine by humans and through feces by rats ([Magnuson et al., 2016](#)).

An early in-vitro study has demonstrated that human saliva, salivary amylase, pepsin, pancreatin, pancreatic amylase, and jejunal brush border enzymes of mice, rats, and hamsters cannot break the glycosidic bonds within stevioside ([Samuel et al., 2018](#)). The gut microbiota of humans, hamsters, and rodents is capable of degrading stevioside into steviol. Emerging of stevioside and Rebaudioside A (Reb. A) along human fecal microbiota has revealed complete hydrolysis to steviol within 10 and 24 hours, respectively ([Purkayastha et al., 2015](#)). The released sugar components are not absorbed and are likely utilized as an energy source by the gut microbes, ultimately contributing to the zero-calorie nature of steviol as a sweetener ([Wang et al., 2023](#)). The mechanism of absorption of steviol glycosides is explained in Figure 3.

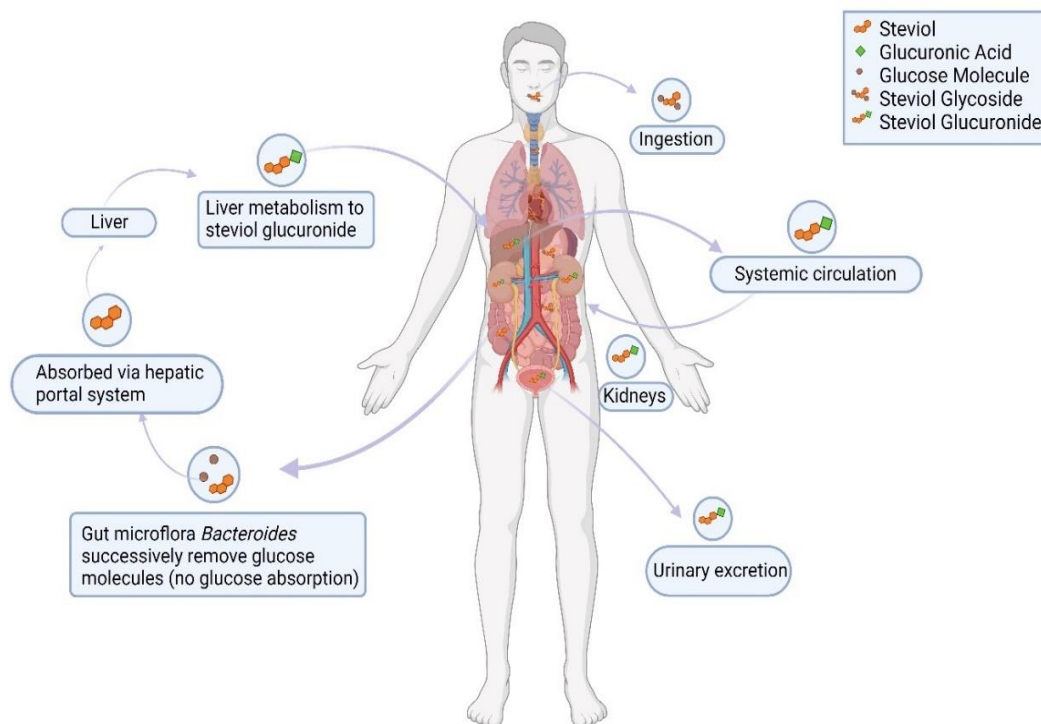


Figure 3. Mechanism of absorption of steviol glycosides in the human body

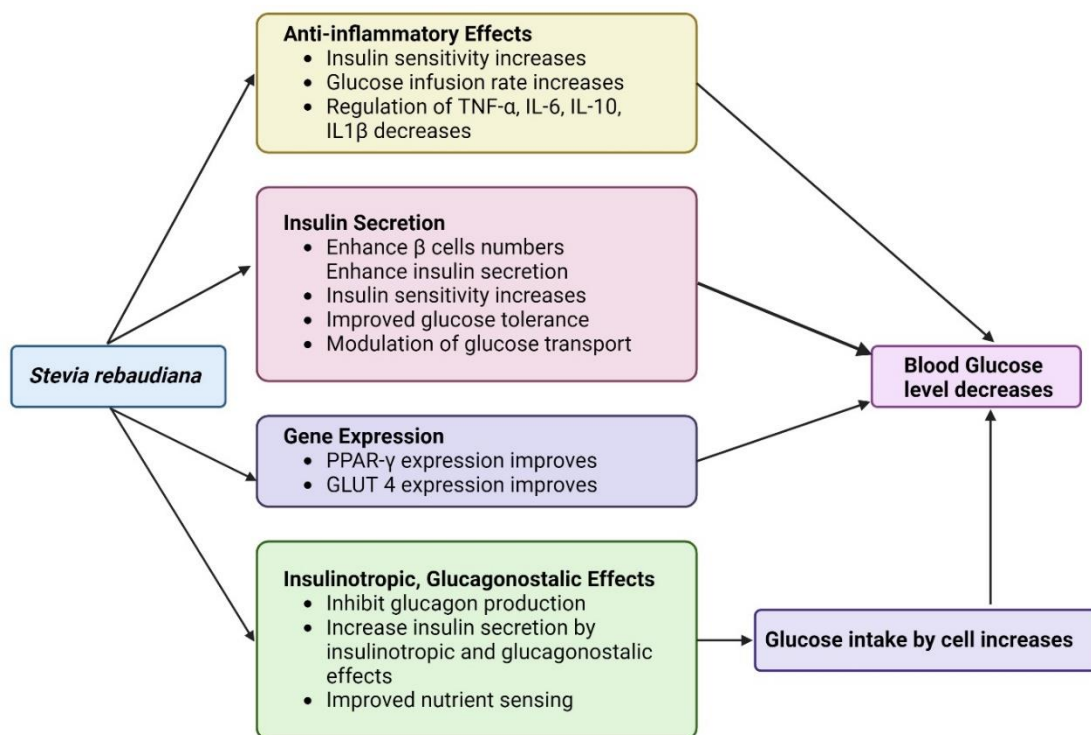
5. Health Implications

5.1. Antihyperglycemic effects of stevia extract

The active ingredients in stevia have been shown to lower blood glucose levels. Stevioside, the main compound in stevia, lowers blood glucose levels through several mechanisms, including increased insulin secretion and sensitivity, as well as decreased glucagon metabolism ([Carrera-Lanestosa et al., 2017](#)).

Ritu and Nandini proved in their study that stevia has several positive benefits, including the ability to reduce blood sugar levels, manage diabetes, prevent dental cavities, control weight, heal wounds and blemishes, lower blood pressure, and modulate the immune system ([Mathur Ritu & Johri Nandini, 2016](#)). It also has anti-fungal and antibacterial characteristics. It is non-toxic and harmless for diabetics, and long-term usage of it may help individuals with long-term diabetes prevent cardiovascular illnesses ([Singh & Rao, 2005](#)).

The direct effect of stevioside on pancreatic beta cells to increase insulin secretion and enhance their function in glucotoxicity may be the cause of the potential glucose-lowering effect ([Jehan & Ashoush, 2008](#)). As it improves the initial insulin response and concurrently suppresses the levels of glucagon, it can also have a hypoglycemic effect. It is highly advised for use by diabetics ([Talevi, 2022](#)). It causes hypoglycemia in diabetics by decreasing glycogenolysis and gluconeogenesis processes by absorbing glucose in the duodenum. It may also be used effectively and safely to replace sweeteners ([Assaei et al., 2016](#)). The actions of *Stevia rebaudiana* on the blood glucose levels are shown in Figure 4.



In a study with 16 participants, the impact of *Stevia rebaudiana* leaf extracts on glucose tolerance was investigated over 3 days. Aqueous extracts were administered at 6-hour intervals. Glucose tolerance tests were conducted at the initial and final administration. A second group ingested an aqueous arabinose solution. Results showed a positive influence on glucose tolerance, with a significant reduction in plasma glucose levels during the test and after overnight fasting in all participants, suggesting a potential benefit for glucose metabolism ([Curi et al., 1986](#)).

An insignificant decline was observed in both HbA1c and fasting glucose levels among the individuals with type 2 diabetes following a 16-week treatment with Reb. About 1000 mg/day. A marginal increase in HbA1c levels was observed in both the intervention and placebo groups, with no discernible change in HbA1c noted between the Reb. The A and placebo groups. Additionally, there was a significant increase in fasting insulin within the Reb. A group, when compared to the placebo group. Alterations from the baseline to the treatment



did not exhibit a significant distinction between the two groups ([Maki et al., 2009b](#)). The research concluded that a water extract derived from stevia leaves at doses of 3.125 mg/kg BW, 6.25 mg/kg BW, and 12.5 mg/kg BW exhibited significant reductions in blood glucose levels ([Lestari et al., 2019](#)). Refer to Table 1 for the reference studies performed to evaluate the beneficial effects of stevioside.

Table 1: Health Benefits of Stevioside in Humans

| Subjects | Trials duration | Treatment/Dosage | Results | References |
|---|-----------------|--|--|---|
| Diabetic and obese males and females | 4 hours | 1000 mg/day stevioside | Decline in random blood glucose levels | (Gregersen et al., 2004) |
| Type 2 diabetic males and females | 3 months | 1500 mg/day stevioside | No effects on blood glucose, HbA1c, and triglycerides levels | (P. Jeppesen et al., 2003) |
| Males and females with or without type 1 or type 2 diabetes | 3 months | 750 mg/ day stevioside | No effects on blood glucose, body mass index, HbA1c, and cholesterol levels | (Barriocanal et al., 2008b) |
| Males and females with hypertension | 1 year | 750 mg stevioside | Lowered blood pressure but shown no effects on blood glucose and lipid profile | (Chan et al., 2000b) |
| Type 2 diabetic males and females | 16 weeks | 1000 mg rebaudioside | No changes in blood pressure and blood glucose levels | (Maki et al., 2009a) |
| Obese and healthy males and females | 3 days | 400 g stevia incorporated in tea and crackered with cream cheese | Improved appetite, normal blood glucose levels, and insulin levels | (Anton et al., 2010) |
| University students | 1 week | Stevia incorporated as a sweetener in beverages and foods | Improved normal weight and nutritional status | (Durán Agüero et al., 2015) |
| Males and females with hyperlipidemia | 90 days | 200 mg stevioside | No improvement in blood lipid levels | (Silva et al., 2006b) |
| Males and females with or without type 1 or type 2 diabetes | 3 months | 750 mg/ day stevioside | No beneficial effects on blood cholesterol levels | (Barriocanal et al., 2008b) |

| | | | | |
|--|--------|---------------|---------------------------------|---|
| Type 2 diabetic males and females | 3 days | 1 gram stevia | Decrease in blood lipid profile | (Mathur Ritu & Johri Nandini, 2016) |
|--|--------|---------------|---------------------------------|---|

(mg= milligrams, HbA1c= glycated hemoglobin)

5.2. Weight management effects of stevia

Anton and colleagues conducted a randomized clinical study to evaluate the impact of two preloads on food consumption and levels of satiety in both lean and obese individuals over three days. The preloads contained Stevia 580 kcal, aspartame 580 kcal, or sucrose 986 kcal, and were taken for 20 minutes before the ad libitum meals twice daily ([Anton et al., 2010](#)). The study found that the stevia group showed a significant decrease in overall food intake as contrasted to the sucrose-taking group, including the preloads ([Farhat et al., 2019](#)). Preload calories were excluded from analysis; there was no difference in food consumed between the groups. The researchers could not observe any changes in satiety levels between the groups at the time, suggesting participants had not compensated for consuming more during lunch or dinner ([Anker et al., 2019](#)).

A cohort trial encompassing 1454 participants who reported regular intake of artificial sweeteners over a long time revealed a noteworthy increase in BMI among users compared to nonusers. The study showed an independent relation between low-calorie sweetener use and a heightened incidence of obesity in the abdominal area, broad waist, and increased body weight. Baseline characteristics indicated that artificial sweetener consumers exhibited larger BMI values and larger waist circumference than non-users. This observation may reflect weight management efforts in this group through the utilization of artificial sweeteners. Conversely, several studies exploring the connections between artificial sweeteners and obesity, diabetes, and cardiovascular disease couldn't be solely related to elevated baseline waist circumference or BMI ([Rojas et al., 2018](#)).

The study on the impact of stevia extracts on diet-induced obesity and associated lipid abnormalities while contrasting with the adverse effects of a sucrose diet, concluded that stevia extract supplementation contributes to reducing weight gain, as well as decreased levels of serum and liver triglycerides. The study hinted at a potential upregulation of genes responsible for encoding enzymes used for the oxidation of fatty acids in the liver. Effectiveness of stevia extract in preventing obesity and related symptoms, such as hyperlipidemia and cardiovascular diseases ([Khiraoui & Guedira, 2018](#)).

The randomized control trial among 20 healthy subjects who consumed the cookies enriched with stevia leaf powder proved a significant decline in hunger in contrast to the control group. Importantly, all cookie variants were palatable, and no adverse effects on gastrointestinal well-being were reported, affirming their acceptability for consumption ([Ahmad et al., 2018](#)).

5.3. Effect of stevia on blood pressure

Maki and colleagues conducted a trial to investigate the effects of a steviol glycoside preparation on glucose levels and blood pressure responses during a meal tolerance test. The study involved 93 participants with normal glucose tolerance or type 2 diabetes, who consumed a steviol glycoside preparation at three different dose levels (500 mg, 750 mg, and 1000 mg) ([Maki et al., 2009b](#)). The results revealed no positive differences in the Incremental Areas Under the concentration Curves (IAUC) for glucose levels, insulin, C-peptide, and glucagon levels between the steviol glycoside preparation and placebo groups, or between any of the dose levels ([Additives et al., 2020](#)). Additionally, there were no significant differences in postprandial systolic or diastolic blood pressure between the steviol glycoside preparation and placebo groups ([Ray et al., 2020](#)). The authors concluded that a dose of up to 1000 mg of the prepared steviol glycoside (equivalent to 319 mg steviol) did not affect glucose homeostasis or blood pressure in people with normal glucose tolerance or type 2 diabetes mellitus ([Benford et al., 2009](#)).

Barriocanal and colleagues conducted a study to investigate the outcome of steviol glycosides on blood glucose and blood pressure among three groups of individuals through a study ([Barriocanal et al., 2008a](#)). Participants in the groups were randomly assigned to either treatment (250 mg steviol glycoside) or placebo and were



followed up for three months ([Ulbricht et al., 2010](#)). Results showed no significant differences in after-treatment systolic Blood Pressure (BP), diastolic BP, glucose, and HbA1c from baseline measurements, except for the placebo type 1 diabetic group, where a significant difference was observed for systolic BP and glucose. It was concluded that oral steviol glycosides taken as sweeteners are highly tolerated and do not show any pharmacological effect ([Carakostas et al., 2008](#)).

Wang and colleagues conducted a study to compare the Angiotensin-Converting Enzyme inhibitory activity of ethanol extracts, steviol glycosides, and protein hydrolysates with captopril. The order of ACE inhibitory activity from highest to lowest was captopril > protein hydrolysate > steviol glycosides > ethanol extract from stevia. Despite lower ACE 2 inhibitory protein hydrolysate and steviol glycoside compared with captopril, their toxicity results were good ([Wang & Wu, 2019](#)).

5.4. Effects of stevia on cancer

Khare and colleagues investigated the potential anti-cancer attributes of purified stevioside isolated from *Stevia rebaudiana* leaves in human breast cancer cells. The findings indicated that *Stevia rebaudiana* exhibits the ability to impede the growth of cancerous cell lines, specifically MDA-MB-231 and SKBR3, by inducing apoptosis and inhibiting cell proliferation. Moreover, the study revealed that purified stevioside plays a significant role by enhancing chemosensitivity in breast cancer cells to Fluorouracil (5-FU) treatment in vitro ([Khare & Chandra, 2019](#)). In HT29 colon cancer cells, stevioside was shown to be active in promoting apoptosis by increasing the expression of MAPK (mitogen-activated protein kinase) as well as ERK and p38, which play a role in ROS-mediated apoptosis ([Ren et al., 2017](#)).

The anticancer mechanism of stevia involves the regulation of cyclin-dependent kinases (CDK), which are proteins important in cell cycle regulation and proliferation. Ethanol extract of stevia exhibited anticancer activity in HeLa, HCT116, and MiaPaCa-2 cells by inhibiting CDK4 ([López et al., 2016](#)). Previous studies showed that steviol exerted an inhibitory effect on six types of human esophageal cancer cells Yati, comparable to 5-FU. Steviol pathway inhibition includes upregulation of Bax/Bcl-2 levels, activation of p21 and p53, and caspase 3-independent activation ([Chen et al., 2018](#)).

5.5. Effects of stevia on lipid profile

The research was conducted on 20 hypercholesterolemic women to investigate the impact of stevia extract consumption administered as 20 ml in 200 ml of water. The findings demonstrated a reduction in blood cholesterol, triglyceride, and LDL levels, accompanied by a desirable increase in HDL. The observed hypolipidemic effect suggests that stevia extract could play a role in lowering the risk of cardiovascular disease ([Sharma et al., 2009](#)).

In the diabetic cohort, the administration of stevioside over 24 weeks demonstrated improvement in both lipid profile and glycemic control as evident across various parameters, including plasma glucose in the fasting state, 2-hour plasma glucose, fasting serum insulin, and hemoglobin A1c (HbA1c). Additionally, stevioside exerted positive effects on serum total cholesterol, triglycerides, low-density lipoprotein, and high-density lipoprotein across all intervention groups studied ([Rashad et al., 2019](#)).

The decrease in LDL levels caused by stevioside is due to its mechanism of upregulating LDL receptors and modulating cholesterol transport. This upregulation of LDL receptors increases the absorption of LDL cholesterol from the blood. Furthermore, studies have shown that stevioside, as well as methanol and water extracts from stevia leaves, lower VLDL levels ([Sunanda Singhand & Veena Garg, 2014](#)). The daily consumption of 1 gram of stevia over 60 days among diabetic patients demonstrated a significant reduction in blood cholesterol, triglyceride, and LDL-cholesterol levels ([Mathur Ritu & Johri Nandini, 2016](#)).

6. Conclusion

Stevia, a natural sweetener obtained from the plant *Stevia rebaudiana*, has gained considerable attention as a potential alternative to sugar for people with diabetes. It contains several significant phytochemicals such as Steviol, Stevioside, and Rebaudioside. These compounds have beneficial effects on pancreatic tissue by increasing insulin levels and enhancing its anti-diabetic properties. It also possesses hypolipidemic, cancer-

protective, and blood pressure-lowering effects. Extensive research has been conducted on the plant, but further investigation is required on the pharmacological properties of rebaudioside, as well as the adverse effects and ADME (absorption, distribution, metabolism, and excretion) profiles of stevioside in humans. The safety of whole-leaf or crude Stevia extracts for human consumption is still debated, highlighting the necessity for additional studies to understand the metabolic pathways of steviol glycosides and to assess their potential genotoxic risks.

CRedit authorship contribution statement

Samra Munir conceptualized and wrote the manuscript, and other authors drafted and revised the manuscript.

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Declaration of Competing Interest

The authors declared no conflict of interest.

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