

Anti-diabetic properties of *Stevia rebaudiana Bertoni* as sugar substitute: a mini-review



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ABSTRACT

The incidence of obesity, type II diabetes mellitus, and metabolic syndrome in children and adults show an alarming increase worldwide. This increase was supported by one factor: the increasing availability of high-calorie foods and beverages, thus increasing the need for sweeteners. Researchers are driven to find a sweetener that can replace sugar. One of the natural sweeteners that can be used is the Stevia plant. Stevia contains stevioside, which is a natural sweetener with 300 times sweetness compared to sucrose. Besides, stevioside can reduce blood sugar levels and show benefits for people with diabetes.

Keywords: *Stevia rebaudiana Bertoni*, steviol, stevioside, sweetener.

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INTRODUCTION

Changes in diet today have had a significant effect on the incidence of disease in recent years. The disease is triggered by an unhealthy diet such as obesity, diabetes mellitus, cardiovascular disease, cancer, and several dental problems. These diseases occur due to improper eating patterns, insufficient food intake, and less physical activity. Changes in food intake can be seen with the high intake of sugar, especially sucrose in food. This changing trend has also triggered food processing manufacturers to use the use of synthetic sweeteners widely.¹ The increase in the intake of energy-dense and high-calorie foods, particularly an increase in sugar intake and various fructose-sweetened products, triggered concerns about the increasing prevalence of metabolic diseases as obesity, diabetes mellitus type II, and metabolic syndrome.²

One way to reduce the use of artificial sweeteners is to use natural sweeteners obtained from nature. *Stevia rebaudiana* is a plant that has been used both medicinally and commercially throughout the world which comes from the Asteraceae family and is native to Paraguay. In Stevia leaves, some compounds have 300 times sweetness than cane sugar, namely

stevioside.^{3,4} Apart from stevioside, Stevia leaves have other compounds that are sweetener components such as dulcoside A, steviolbioside, and rebaudioside A. Stevioside content can be found around 4-20% in dry weight, followed by rebaudioside A (3% dry weight), dulcoside A (0.5% dry weight), and steviolbioside.⁵ Stevioside compounds are the most studied compounds.⁶ Stevioside compounds have also been used as sweetening agents, flavor modifiers, and sugar substitutes in several countries' food industries. The stevioside compound from *Stevia rebaudiana* leaf extract has been accepted as the third glycogen worldwide. There have been no reports regarding side effects caused by the use of stevioside in humans.^{5,7} This review aims to discuss the history, chemical composition and potential as an anti-diabetic.

***Stevia rebaudiana Bertoni* HISTORY**

Stevia rebaudiana Bertoni is a shrub native to South America (Paraguay, Brazil and Argentina), which belongs to the Asteraceae family. The Stevia plant is known by another name, which is often referred to as the "sweet herb from Paraguay."⁸ Since pre-Colombus times, the Stevia plant has been used as a sweetening agent, especially in Indian

tribes, namely the Guarani tribe. The tribe calls the Stevia plant the name Ka'a He'e. The Guarani often use the Stevia plant as a sweetener in their green tea drink known as mate. Since the arrival of a European scientist, Moisés Santiago Bertoni, in 1887, where he introduced the Stevia plant as the plant for the "new world."^{9,10} After being introduced, then in 1931, several experts had successfully extracted stevioside compounds by French chemists. Stevioside compound was found as the main compound, which acts as a sweet component that is crystalline and white.¹⁰ Then Mosettig et al. continue research to get the final structure of the stevioside compound.¹¹

CHEMICAL COMPOSITION AND NUTRITIONAL VALUE OF STEVIA LEAVES

Analysis of Stevia leaves' nutrient composition, based on dry weight, produces total energy of 2.7 kcal per gram. Stevia leaves can be classified as a low-calorie sweetener with a high sweetness intensity compared to other low-calorie sweeteners. There are also other sweeteners classified as intense sweeteners, namely acesulfame potassium (free of calories), saccharin (free of calories), sucralose (free

Table 1. Nutrient composition of Stevia per 100 gram in dry weight basis.¹²

Nutrient Composition	Per 100 gram
Proximate	
Moisture (g)	7
Energy (kcal)	270
Protein (g)	10
Fat (g)	3
Total Carbohydrate (g)	52
Ash (g)	11
Crude Fiber (g)	18
Minerals	
Calcium (mg)	464.4
Phosphorus (mg)	11.4
Iron (mg)	55.3
Sodium (mg)	190.0
Potassium (mg)	1800.0
Anti-Nutritional Factors	
Oxalic acid (mg)	2295.0
Tannins (mg)	0.010

of calories), and aspartame (4kcal/gram). Sucrose used for diet has a high-calorie contribution because its utilization is more completely in the body, so there is a risk of triggering an overweight condition. With this low-calorie total energy, the use of Stevia leaves can greatly help limit food calorie intake and assist in prescribing a diet with limited calories (Table 1).¹²

Apart from the calorie side, Stevia leaves contain significant protein content. The Stevia leaves' protein content can be obtained around 10 - 20.4 grams/100 grams of products. The study of Mohammad et al. in 2007 has identified the amino acid content in Stevia leaves. The study found nine amino acids, namely, lysine, glutamic acid, serine, aspartic acid, alanine, tyrosine, L-isoleucine, proline, and methionine.¹³ A follow-up study by Abou-Arab et al. found additional amino acids in Stevia leaves to be seventeen amino acids and almost all exogenous amino acids except the amino acid tryptophan. The content of these amino acids makes Stevia leaves a source of nutrition. Based on fat content, Stevia leaves have a low-fat content in dry mass. The fat content ranges from 1.9 - 5.6 grams/100 grams of products.¹⁴ Apart from macronutrients, Stevia leaves also contain micronutrients such as calcium, sodium, potassium, magnesium, iron, and zinc. The study of Kim et al. found the presence of vitamins in Stevia leaves. The vitamin content found was vitamin C,

with levels ranging around 14.98 mg/100 grams of Stevia leaf water extract. The folic acid content was also 52.18 mg/100 grams of water extract of Stevia leaves.¹⁵

UPTAKE AND METABOLISM OF STEVIOSIDE

The low-calorie sweetener (steviol glycosides) in *Stevia rebaudiana* leaves, when used, will have a good effect on human health.¹⁶ The biological properties of Stevia glycosides are very valuable. Regular consumption of glycosides can reduce glucose and cholesterol.¹⁷ There are at least eight steviol glycosides (SGs) contained in Stevia leaves. However, the concentration of steviol glycosides will differ in Stevia plants depending on the environment and genetics. Steviol glycosides are tetracyclic diterpenes derived from a kaurenoid precursor similar to gibberellic acid so that it has a high sweet taste. The process of stevioside metabolism leads to the synthesis of steviol.¹⁸

Studies show that the metabolic and elimination processes of steviol glycosides (SGs) in humans and animals have the same pathway.¹⁹ Microbes in the large intestine metabolize the compound Rebaudioside A to stevioside for the first time. Then the stevioside compound will be metabolized into glucose and steviol. Glucose compounds will be utilized by intestinal microbes and do not undergo

absorption into the bloodstream. Steviol compounds that intestinal microbes have metabolized will leave the body and not accumulate. That has been proven in studies that, through human feces' observation, found that high and low concentrations of steviol do not undergo metabolism in the digestive tract. Thus result indicating that steviol is the final metabolic product of stevioside.²⁰ Besides, in studies evaluating stevioside in vitro digestion, it has also been found that no digestive enzymes metabolize stevioside, and intestinal microbes hydrolyze stevioside to steviol and steviol-16,17-alphaepoxide. Steviol-16,17-alphaepoxide will undergo further metabolism into steviol, which will then be excreted in the urine in the form of steviol glucuronide.²¹

A small portion of stevioside can undergo hydrolysis to become steviol before being absorbed in the small intestine. The absorption of stevioside and rebaudioside A's permeability coefficient is very low at 0.16×10^{-6} and 0.11×10^{-6} cm/sec, respectively. While steviol has a higher permeability coefficient, around 44.5×10^{-6} cm/sec at a concentration of 100 mmol/l and a secretory rate of 7.93×10^{-6} cm/sec.²² The absorption of steviol aglycone in the single form (steviol) is better than Stevia's mixed form (rebaudioside A, rebaudioside C, stevioside, and dulcoside A). Steviol is absorbed 76% in the duodenum-jejunum and ileum, while the remaining mixed form in the mucosal fluid is more than 93%. However, steviol levels were low in plasma at 8 hours after oral administration with a dose of 0.5 g/kg of stevioside (95% purity).²³

GLUCOREGULATION OF STEVIA

Traditional diabetes treatment has used Stevia leaf extract as medicine.²⁴ Consumption of Stevia leaf extract in normal adults can suppress plasma glucose levels and increase glucose tolerance.²⁵ Steviol glycosides can act directly on β cells to increase insulin secretion without affect cAMP levels and $K^+ -ATP$ channel activity.²⁶ Apart from increasing insulin secretion, stevioside regulates blood glucose levels through increased insulin utilization in insulin-deficient rats. Stevioside decreased the expression of the phosphoenolpyruvate carboxykinase

(PEPCK) gene in rat liver, thereby slowing gluconeogenesis. In vivo testing on alloxan-induced diabetic rats using medium-polar dissolved Stevia leaf extract (benzene:acetone, 1:1 v/v) significantly reduced blood glucose levels. The doses administered did not cause hypoglycemia and lower post-treatment weight loss than positive controls (glibenclamide).²⁷ Testing in diabetic patients showed a reduction in the area under the curve (AUC) of postprandial glucose levels by 18% and reduced by 40% the serum insulin: glucose ratio with an acute dose of stevioside (1,000 mg).²⁸

STEVIA AS AN ANTIDIABETIC AGENT

Maintenance of blood glucose levels

Stevia leaves have been used because of their antioxidant properties and proven through phenol analysis extracted from the Stevia plant, namely the proportion of total phenol of 91 mg/g. Studies show that Stevia leaf extracts compared to controls such as tertiary butyl hydroxyquinone, butylated hydroxyanisole, and butylated hydroxytoluene, can scavenge free radicals and prevent lipid peroxidation.²⁹ Type II diabetes patients tested with stevioside-added foods experienced decreased postprandial glucose levels significantly by an average of 18%. Studies comparing Stevia with aspartame and sucrose have shown that giving Stevia reduced significantly postprandial glucose levels and did not find after-effects, such as compensating more in subjects given Stevia.¹

Anti-inflammatory response

Administration of stevioside in insulin-resistant model C57BL6J mice showed decreased regulation of the NF- κ B pathway, increased insulin sensitivity, the degree of the glucose-lowering effect of insulin, and the rate of glucose infusion. Besides, there was a significant down-regulation of the expression of TNF α (proinflammatory cytokines that contribute to decreased insulin sensitivity) and the expression of IL-6, IL-10, and IL-1 β expression. It can reduce inflammation through downregulation of TNF α in adipose tissue by stevioside to reduce insulin resistance.³⁰

Influence on insulin secretion

Jeppesen et al. reported the first time that stevioside and steviol directly influence insulin release. That is due to the increase in insulin secretion in both pathways, namely the INS-1 pancreatic β cell line and normal mice's islet. Besides, this study failed to find a glucose depletion effect in non-hyperglycemic conditions and thus hypothesized that stevioside's glucose depletion effect occurs in certain high blood glucose conditions (such as diabetes).²⁶

Insulinotropic, Glucagonostatic, and Nutrient-Sensing Effects

In type II diabetes, insulin depletion occurs and is followed by an increase in glucagon levels. That is closely related to the dysfunction of α -pancreatic cells, thus contributing to the disease's development. Anti-hyperglycemic properties with increased insulin secretion by Stevioside can also occur through insulinotropic and glucagonostatic effects so that glucagon suppression occurs in test animals Goto-Kakizaki rats (non-obese Type II diabetic animal models).³¹

CLINICAL STUDIES ON STEVIA

Stevioside is clinically proven to provide therapeutic benefits, so it is recommended for people with diabetes. The therapeutic benefits are in the form of anti-hyperglycemic, anti-inflammatory, anti-hypertensive, diuretic, anti-diarrhea, immuno-modulatory. Another benefit is that there is no limit to the consumption of steviol glycosides, so it is relatively safe for human health, especially for people with diabetes. The therapeutic value in stevioside shows that in its role as a sugar substitute, stevioside can stimulate insulin secretion in the pancreas during the treatment of diabetic patients and reduce other carbohydrate metabolism disorders.^{22,32}

Various studies have been conducted regarding the Stevia feasibility and safety of both humans and animals. Studies show that oral administration of stevioside in type II diabetes mellitus patients has lower blood glucose levels when compared to controls using cornstarch.²⁸ The study of tolerance test of 5 grams of *Stevia rebaudiana* leaf

extracts given every 6 hours for three days to 16 volunteers significantly improved glucose tolerance, reduced plasma sugar levels during testing and after overnight fasting in all volunteers.²⁵ Research on the supplementation of 1 gram of stevioside in food in 12 patients with type 2 diabetes classified as acute showed a decrease in blood glucose levels after meals. Stevioside increased the insulin index by about 40% compared to controls ($P = 0.01$). Stevioside reduces blood sugar levels after meals.³³

CONCLUSION

Stevia is good for use in humans, especially in patients with diabetes mellitus, considering the sweetness level that reaches 300 times the sweetness of sucrose and contains various substances with nutritional effects. Consumption of Stevia in diabetics and obesity is very safe considering the low-calorie levels. There are therapeutic benefits such as maintaining blood glucose levels, affecting insulin secretion, and as an anti-inflammatory response so that other patients can use the glycosides from Stevia.

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Conflict of Interest

The authors declared no conflict of interest regarding publishing this review.

Author Contribution

All authors involved in concepting, designing, and preparing the manuscript and agree for this final version of manuscript to be submitted to this journal.

Ethical Statement

Not applicable in this review.

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