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Review Article

UNDERSTANDING THE BENEFITS OF *STEVIA REBAUDIANA BERTONI* FOR DIABETES: A COMPREHENSIVE REVIEW

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ABSTRACT

Diabetes Mellitus (DM) is a complicated metabolic condition defined by long-term elevated blood glucose levels. This chronic hyperglycemia induces metabolic dysfunctions that cause structural and functional disruptions in the vasculature, leading to macrovascular and microvascular complications. *Stevia rebaudiana Bertoni*, commonly known as *Stevia*, is a perennial shrub that contains various bioactive constituents responsible for its sweetness and several other activities. Many studies on *Stevia* have shown that it possesses various beneficial effects on health, including being zero-calorie, anti-obesity, anti-diabetic, anti-hypertensive, antioxidant, antimicrobial and anti-tumor. Several studies have found that neither gastric juice nor digestive enzymes decompose stevioside. The presence of bioactive phenolic and flavonoid compounds supports *Stevia's* medicinal properties and its potential use in both the food/nutraceutical and pharmaceutical industries. A significant antioxidant capacity of *Stevia* has been identified recently. It can also help limit essential nutrient supply to tumor cells. Research on *Stevia's* effects on the human body has largely found no negative side effects. The growing body of evidence underscores *Stevia's* potential role in managing various health conditions, particularly for diabetic patients, due to its minimal impact on blood sugar levels. However, to fully harness its benefits and meet the increasing global demand, further scientific research is essential to optimize its cultivation, enhance its chemical constituents and ensure its safety. Overall, *Stevia* stands out as a promising natural sweetener with significant health benefits for diabetic patients. In this review article, we explore different aspects of *Stevia* and its beneficial effects on diabetic patients.

Keywords: Stevia rebaudiana bertoni, Stevia, Natural sweetener, Zero-calorie sweetener, Stevioside, Rebaudioside a, Diabetes

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INTRODUCTION

Diabetes Mellitus (DM) is an endocrine disease diagnosed by high levels of blood glucose. DM is known as one of the fastest-growing and most common diseases worldwide [1]. It was projected to affect around 693 million adults by 2045 [2]. The leading cause of mortality and morbidity in diabetes is its vascular complications. These include both macrovascular and microvascular complications [3]. It poses a significant financial burden in both developing and developed countries [4].

Hyperglycemia in diabetes results from a defect in insulin secretion or insulin action, which causes chronic carbohydrate, protein and fat metabolic dysfunctions [5, 6]. These metabolic dysfunctions disrupt normal functioning and affect the kidneys, heart, eyes and nerves. In Type 1 Diabetes Mellitus (T1DM), insulin production is reduced because the beta cells are destroyed [7]. The destruction of β-cells occurs due to autoimmune reactions [8]. Type 2 Diabetes Mellitus (T2DM) is strongly linked to environmental factors like poor diet, obesity and reduced physical activity. Research has indicated that physical activity can lower HbA1C levels [9]. Symptoms associated with high blood sugar include frequent urination, increased hunger, excessive thirst, extreme fatigue, blurred vision and weight changes [10].

The disease's covert nature often results in many patients not being diagnosed until complications develop [11]. The complications are Diabetic retinopathy, Diabetic nephropathy, Atherosclerotic Cardio Vascular Disease (ASCVD), Diabetic autonomic neuropathy and Diabetic gastroparesis. In elderly patients with diabetic neuropathy, factors such as dyslipidemia, Coronary Artery Disease (CAD), Hypertension (HTN) and high Body Mass Index (BMI) contribute to its progression. Additionally, the duration of diabetes and comorbidities like HTN and dyslipidemia further exacerbate the condition. Metabolic syndrome associated with T2DM often manifests as liver disease [12-14].

Stevia rebaudiana bertoni, is a perennial shrub that belongs to the family Compositae (Asteraceae) [15]. It is commonly known as *Stevia*. It contains various bioactive constituents that are responsible for sweetness and several activities [16]. *Stevia* is frequently referred to as "the sweet herb of Paraguay" since it was indigenous to Paraguay and Brazil [17]. Several centuries ago, the natives of Paraguay used the leaves of this plant to sweeten their bitter drinks. In 1888, this plant was discovered by Dr. Moises Santiago Bertoni. It was scientifically named *Stevia Rebaudiana* after Dr. Rebaudi, a Paraguayan chemist [18].

It has been cultivated in various regions of the world like North America, Asia and Europe [19]. It is a subtropical semi-humid plant that can be grown easily even in the kitchen garden [20]. As the demand for natural sweeteners has increased, *Stevia* has been cultivated on a large scale in India. Currently, China is said to be the world's largest producer of *Stevia,* which is cultivated in 13400 acres of land and around 40 thousand tonnes of *stevia* leaves are produced per day [21]. China is said to be the leading exporter of stevioside.

There are different species of *Stevia,* which contain several sweetening compounds among which *S. rebaudiana* is the sweetest of all. *Stevia* consists of a group of natural sweeteners called Diterpene glycosides. It has eight steviol glycosides (ent-kaurene glycosides) which are rebaudioside A-E, dulcoside A, stevioside and steviolbioside which are naturally occurring in its leaves [22, 23]. The extracts of *Stevia* contain potential sweetening compounds namely rebaudioside and stevioside. These glycosides are 200-300 times sweeter than conventional sucrose.

In the early 1970s, the first commercial products of *Stevia* were launched in the country Japan [24]. Progressively *Stevia* is used as a substitute for sugar in many countries [25]. The World Health Organization (WHO) and the Joint Food and Agriculture Organization (FAO) agreed on an acceptable daily intake (ADI) of steviol glycosides as 2 mg/kg. This, after a few years, was modified by FAO and WHO and increased the ADI to 4 mg/kg [26, 27]. Subsequently, *Stevia* products were approved in major markets such as the US, Europe and Oceania. It was estimated that 500 million US dollars of global market for *Stevia* [28].

The treatment of diabetes requires comprehensive management including a balanced diet, physical activity, proper knowledge of a balanced diet, good quality sleep and proper anti-diabetic medications. *Stevia* is a valuable addition to the diet of individuals with diabetes due to its natural sweetness without affecting blood glucose levels. Many studies on *stevia* have shown that it possesses various beneficial effects on health such as anti-obesity, anti-diabetic, anti-hypertensive, anti-oxidant, anti-microbial and anti-tumor [29].

In this review article, we try to explore different aspects of *Stevia* and its beneficial effects on diabetic patients.

DISCUSSION

Pharmacokinetics of stevia

Several studies have found that neither gastric juice nor digestive enzymes decompose stevioside [30-32]. Fig. 1 illustrates that oral stevioside, due to its high molecular weight, does not get absorbed at the level of the upper small intestine. But it gets degraded by bacterial intestinal flora of the *Bacteroides* genus in the lower gastrointestinal tracts of mice, rats, pigs and humans. This transforms it into free steviol, which is an aglycone of steviol glycosides [33-35].

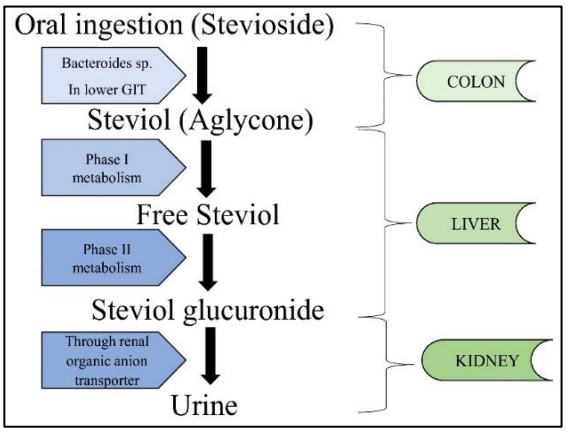

Fig. 1: Metabolism and excretion of stevia

Bioactive compounds in stevia

Stevia, is a rich source of many phytochemicals. *Stevia* leaves are known to contain a diverse mix of sweet diterpene glycosides, such as stevioside, steviolbioside, rebaudioside (A, B, C, D, and E) and dulcoside A. Another study identified several phytochemicals in *Stevia*, including austroinullin, β-carotene, dulcoside, steviol, stevioside, rebaudi oxides, riboflavin and thiamine [36]. Additionally, the extract from *Stevia* leaf residue-obtained from byproducts during the production of steviol glycosides—has been found to contain several significant phenolic compounds. The presence of these bioactive phenolic and flavonoid compounds supports *Stevia's* medicinal properties and its potential use in both the food/nutraceutical and pharmaceutical industries.

Beneficial effects of stevia in diabetes

Zero calorie ingredient

S. rebaudiana, is known by its other names such as sugar leaf, sweet and candy leaf. It is being used as a natural sugar substitute and sweetener [37]. It has been used as a sweetener in chocolates, beverages, canned vegetables, chewing gums, ice cream, tabletop sweeteners, ketchup and yogurts. *Stevia* is rich in metabolites such as thiamine, β-carotene, riboflavin, austroinulin, diverse terpenes and flavonoids [38]. Stevioside and rebaudioside are the two major sweetening compounds present in *Stevia*. Even though it has a sweet taste, it has a zero-calorie property. This could be beneficial for diabetic and obese patients. In contrast to this, sucrose, which is extracted from sugarcane and beetroot can increase the calories and can cause dental caries and stomach infections [39].

Anti-oxidant property

Oxidative stress is a condition in which there is an unbalanced redox status that leads to increased production and accumulation of Reactive Oxygen Species (ROS) and decreased ability of antioxidant systems in cells or tissues [40]. High blood sugar is associated with oxidation and leads to increased formation of free radicals [41]. The vascular endothelial cells in diabetic patients are more commonly damaged due to oxidative stress that destroys endothelial junctions, leading to increased intravascular permeability. This ultimately leads to the development of microvascular and macrovascular complications [42].

A significant anti-oxidant capacity of *Stevia* was found in a study conducted using an aqueous leaf extract of *S. rebaudiana* [43]. Proanthocyanidins and flavonoids in *Stevia* were found to inhibit the production of Nitric oxide in macrophages when stimulated by Lipo-Polysaccharides (LPS)/Interferon-γ (INFγ). The natural diterpenoids like austroinulin and 6-O-acetyl austroinulin in *Stevia* inhibit the formation of Nitric Oxide Synthase (iNOS), Prostaglandin E2 (PGE2) and pro-inflammatory cytokines such as TNF-α, IL-6, IL-1β, and mast protease-1 cells. This is due to inhibition of MAPK phosphorylation and NF-κB activation [44, 45].

Anti-hyperglycemic effect

Diabetes is a metabolic disorder which is characterized by high blood glucose levels in the body [46]. Diabetes is said to be the most common non-communicable disease worldwide. Diabetes occurs due to impaired insulin secretion, insulin resistance or defective insulin action. Its increasing prevalence is attributed to sedentary lifestyle, urbanization and obesity.

Steviosides were shown to have comparable anti-hyperglycaemic effects in human subjects. In a 2004 study by Gregersen *et al.*, participants with T2DM were involved in a paired-crossover study. On two separate occasions, they consumed a standard test meal of 412 kcal (1,725 kJ) along with either 1g of stevioside or 1g of maize (control). Serum glucose, insulin, glucagon, Glucagon-Like Peptide 1 (GLP-1) and Glucose-dependent Insulinotropic Polypeptide (GIP) levels were measured at 30-minute intervals, starting 30 min before the test meal and continuing until 240 min afterward. The study found that 240 min after consuming stevioside, mean postprandial blood glucose levels were significantly lower by 18% compared to controls. Additionally, there was a notable 40% increase in the insulinogenic index, reflecting improved beta cell function with stevioside [47]. Steviosides enhance insulin secretion, leading to reduced long-term serum glucose levels. Beta cells in the islet of the pancreas synthesize and secrete insulin directly into the portal vein which will be delivered to the liver. The liver is known as the major site of insulin clearance [48]. A 2017 study by Philippaert *et al.* explored the specific molecular mechanisms through which *Stevia* extracts enhance insulin secretion. The researchers focused on the effect of stevioside on the transient receptor potential cation channel subfamily melastatin 5 (TRPM5), a monovalent Ca^{2+} activated cation channel present in type II taste receptor cells and pancreatic beta cells. They found that steviosides increase the frequency of glucose-stimulated action potentials and shift the voltage-dependent activation of TRPM5 to more negative membrane potentials, changing from a V1/2 of+145 mV to+42.8 mV. This shift leads to a more negative resting membrane potential, resulting in cell depolarization and enhanced signal potentiation with less electrical input. Overall, these results suggest that stevioside directly affects TRPM5 channels, extends their activation duration and enhances insulin secretion [49].

Anti-obesity property

Obesity is recognized as a state of chronic, low-grade inflammation in adipose tissue, leading to a pro-inflammatory environment in T2DM. Inflammatory cytokines play a significant role in the pathogenesis of T2DM [50]. In a 2012 study, Wang *et al.* investigated the effect of stevioside on inflammatory markers in mice. Over four months, mice were given either a normal or high-fat diet. In the

fourth month, they received either 10 mg/kg/day of stevioside or a control vector. The researchers measured mRNA levels of inflammatory cytokines TNF-α, IL-6, IL-10, IL-1β, MIP-1α, KC, CD11b, and CD14 in adipose tissue using quantitative reverse transcriptase PCR. Results showed that mice on the high-fat diet had significantly higher levels of these inflammatory markers after three months, indicating a pro-inflammatory state typical of obesity. However, the addition of stevioside to the high-fat diet in the fourth month led to a significant reduction in all inflammatory markers compared to the control vector and decreased macrophage infiltration in the adipose tissue of mice fed a high-fat diet [51].

Several studies have explored the impact of *Stevia* consumption on satiety and weight loss. In a 2010 study, Anton *et al.* investigated the impact of *Stevia* consumption on satiety in both lean (BMI = 19.5–24.9 kg/m^2) and obese (BMI = 30–39.9 kg/m^2) human subjects. Participants attended three separate study days. The researchers found that daily calorie intake was significantly lower in the *Stevia* (2257 kcal/day) and *Aspartame* (2248 kcal/day) groups compared to the sucrose group (2557 kcal/day), likely due to the zero-calorie nature of the sweeteners. Since food intake was only assessed over a single study day, the long-term effects of *Stevia* on appetite and weight loss cannot be concluded. A more extended, blinded and interventional study would be needed to better understand *Stevia's* impact on these factors [52].

Anti-hyperlipidemic property

Research has demonstrated that stevioside can significantly lower total cholesterol, triglyceride, LDL and VLDL levels while increasing HDL levels. The reduction in total cholesterol is attributed to the increased excretion of bile acids, achieved by preventing their reabsorption in the small intestine through the disruption of micelle formation. This increased bile acid excretion activates 7α-hydroxylase, which enhances the conversion of liver cholesterol to bile acids, thereby reducing cholesterol levels [53, 54].

Stevioside reduces triglyceride levels by stimulating the activity of the lipase enzyme produced by the liver, which leads to lipid breakdown and increased excretion of triglycerides through faeces [55]. The hypolipidemic effect of *Stevia* is also due to the activation of PPAR receptors. PPAR, a regulating factor in lipogenesis, enhances the expression of Lipoprotein Lipase (LPL) and the C-II apo gene, boosts liver absorption and free fatty acid esterification, and increases the oxidation of mitochondrial free fatty acids. Additionally, *Stevia* decreases the activity of acetyl-coenzyme A carboxylase and fatty acid synthase [56].

Anti-hypertension property

Cardiovascular disease is a common complication of DM and recent research indicates that *Stevia* and its metabolites may support cardiovascular health by reducing HTN. Several clinical trials have investigated the antihypertensive effects of *Stevia* compounds. In a study by Chan *et al.*, 106 healthy adults with mild to moderate HTN (baseline diastolic blood pressures between 95 and 110 mmHg) participated in a multi-center, double-blind, placebo-controlled trial. The participants were instructed to take 250 mg of stevioside or a placebo three times a day and were monitored monthly for a year. Within just three months, the stevioside group showed a significant reduction in mean systolic blood pressure from 166.5 mmHg to 152.6 mmHg and mean diastolic blood pressure from 102.1 mmHg to 90.3 mmHg [57]. A 2008 study by Barriocanal *et al.* supported these findings, showing no significant differences in blood pressure between the groups taking 250 mg of *Stevia* three times daily and those receiving a placebo over a 3-month period. The study included participants with T1DM/T2DM/no diabetes, all of whom had normal or low-normal blood pressure [58]. Stevioside shows promising therapeutic effects in individuals with HTN and does not carry the risk of causing hypotension, highlighting its potential clinical value for treating cardiovascular patients.

Anti-cancer property

It was also found that occupational stress contributes to the development of T2DM, potentially due to negative psychological factors [59, 60]. In recent years, there has been a significant increase in cancer cases seen in diabetic patients, particularly in tumor types linked to lifestyle risk factors and occupational stress. *Stevia* can significantly contribute to cancer prevention by reducing blood glucose levels, thereby mitigating risk factors such as obesity, inflammation and oxidative stress. Additionally, it can help limit an essential nutrient supply for tumor cells [61]. Since only a few studies have examined the effectiveness, future research should thoroughly investigate this crucial parameter before we can confidently label *Stevia* products as "cancer preventive and therapeutic" agents.

Safety profile

Stevia is often compared to table sugar, but it cannot replace it completely. This is because steviol glycosides do not have all the desirable properties of sucrose. For example, *Stevia* does not influence on color of the product and does not form a proper texture [62].

However, its extensive traditional use by Paraguayans for over 1500 years serves as a long-standing testament to its safety [63]. Steviosides have been consumed in substantial quantities in Japan for over 20 y without any reported adverse effects. The safety of *Stevia* can also be attributed to the fact that steviol glycosides are minimally absorbed in both humans and rats in the stomach and upper intestine [64]. The acceptable daily intake of *Stevia* dry extract, as established by the Scientific Committee on Food of the European Food Safety Authority (EFSA) and the Food and Drug Administration (FDA), is 4 mg/kg of body weight [65]. Research on *Stevia's* effects on the human body has largely found no negative side effects [66-68]. The authors concluded that hamsters fed stevioside at a dose as high as 2.5 g/kg body weight per day exhibited no abnormalities in growth or reproductive performance [69]. Usami *et al.* investigated the teratogenic effects of stevioside by giving pregnant rats doses of 0, 250, 500 and 1000 mg/kg/d. The study found that stevioside did not cause any teratogenic effects and no adverse impacts were observed in either the pregnant rats or their foetuses [70]. A thorough weight-of-evidence assessment of the full genotoxicity profile for steviol glycosides has demonstrated that the consumption of stevioside and rebaudioside A does not pose a risk of genetic mutations in humans [71].

CONCLUSION

In conclusion, the comprehensive review of *Stevia* highlights its multifaceted benefits and applications. The growing body of evidence underscores its potential role in managing various health conditions, particularly for diabetic patients, due to its natural sweetness and minimal impact on blood sugar levels. The rich phytochemical profile of *Stevia* contributes to its therapeutic properties, making it a valuable ingredient in both the pharmaceutical and food industries. However, to fully harness its benefits and meet the increasing global demand, further scientific research is essential to optimize its cultivation, enhance its chemical constituents and ensure its safety. Overall, *Stevia* stands out as a promising natural sweetener with significant health benefits for diabetic patients.

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AUTHORS CONTRIBUTIONS

All authors played a role in the study's conception and design. B. Dharani, Suba. A and Stephy Sebastian conducted the data collection and analysis. The initial draft of the manuscript was prepared by B.

Dharani and Suba. A, while Stephy Sebastian assisted with article collection. Each author reviewed earlier drafts, provided feedback and approved the final version.

CONFLICTS OF INTERESTS

The authors declare that they have no conflicts of interest.

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