Review Paper

The anti-diabetic activities of natural sweetener plant Stevia: an updated review

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Abstract
Diabetes mellitus is one of the key metabolic diseases cause due to defects in the secretion of insulin, insulin resistance in peripheral tissues, or both. Plants remained an important source of nutrition as well as medicine. *Stevia rebaudiana* Bertoni is one of the important high qualities non-caloric sugar substitute sweetener plants against diabetes disease. The compounds like steviol, rebaudioside A, stevioside, etc. can lower the sugar level many fold. In addition, it decreases oxidative stress, hence reduces the risk of diabetes. Its leaves have been used for the control and treatment of diabetes and many other metabolic diseases. In animal model experiments it reduces blood sugar level and promotes liver and kidney functions. In this review, we highlighted the most recent literature on the safe use of Stevia for the treatment of diabetes, its use as a functional food, and its mode of therapeutic action in different animal model experiments. However, keeping Stevia as a model plant; detailed investigations are needed for the identification of new metabolites and its use against diabetes and related diseases.

Keywords Anti-diabetic · Animal model · Diabetes · Stevia · Oxidative stress

1 Introduction

Stevia (*Stevia rebaudiana* Bertoni) is a branched bushy shrub and belongs to the family Asteraceae. It is considered native to the northeastern regions of Paraguay [27, 28]. It is also found in Brazil and Argentina. In addition, its cultivation is directly spread all over the world including Canada and some Asian and European regions [28]. It is known as "calorie free bio-sweetener of high quality" [34]. It shows resistance to high temperatures and used in many food products including beverages, jams, sauces, confections, and other dental products. The 50 g Stevia leaf can replace 1 kg of sugar and the stevioside does not indicate any brown appearance in cooking [32].

Diabetes mellitus is the most common metabolic disease characterized by an increase in glucose levels due to defects in the secretion of insulin, insulin resistance in peripheral tissues, or both [3]. According to World Health Organization (WHO), worldwide it will be the seventh leading cause of death by 2030 [30]. Proper diet, exercise, and medicine can overcome this lethal disease [29]. The pharmacological drugs and combinations have several side effects and are too costly. Therefore, use of traditional medicinal plants is a best option to treat diseases [23, 37, 43]. Stevia is one of the miracle medicinal plants against many diseases. Limited review articles are available on the applications of Stevia in medical field. No single comprehensive review is available that explain its role against diabetes diseases in different animal model of diseases and other human cell lines, and to discuss it functional food values for a healthy life. The present review highlighted the new up to date literature related to the anti-diabetic

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properties of Stevia plants and also emphasized its role against diabetes in the different animal models. The detailed functional food products of Stevia for the diabetic patients were also discussed.

2 Bioactive compounds of Stevia

More than 1200 medicinal plants mimic anti-diabetic activities have been identified so far. These phyto-therapies are considered safe and cost effective methods as compared to synthetic treatment options [41]. Stevia is full of many important phytochemicals/compounds that have properties to reduce blood cholesterol and sugar levels, as well as blood pressure. In addition, it can to enhance taste and flavor; and also have reported antibacterial properties [32]. The leaves contain eight important diterpene glycosides *i.e.* rebaudiosides A-E, dulcoside A, stevioside and steviolbioside [1]. Among 230 species of Stevia, the two species namely *rebaudiana* and *phlebophylla* produce important steviol glycosides [11]. The stevioside and rebaudioside A are the two important sweetening thermostable compounds used as a source of cooked foods [28]. Stevioside, is found in the leaves of *S. rebaudiana* Bertoni and is 300 times sweeter than sucrose [21]. The rebaudioside A is considering 250 to 400 times sweeter than sucrose and used for food/sweetener purposes [20]. The leaves are also full of carbohydrates [21].

3 Use of Stevia as functional food against diabetes

The functional food is useful to provide nutrient requirements to the body and helps against other degenerative diseases related to today's changing lifestyles [25]. The modified coconut jelly was prepared by replacing 50% sugar with Stevia. This jelly decreases the postprandial Blood Glucose Level (BGL) without any release of insulin. Hence are recommended as a safe food product for the diabetic patient [15]. Ruiz-Ruiz et al. [36] designed an efficient functional wheat bread by replacing the sugars with the aqueous extract of *S. rebaudiana* Bertoni. The 50% sugars replaced with aqueous extract showed maximum anti-oxidant activities and lower level of sugar by inhibition of alpha amylase (IC50 = 198.40 µg/mL) and glucosidase (596.77 µg/mL). While the IC50 value (335.94 mg/mL) was noted with radical scavenging activity. They also found lower microbial growth during the shelf-life of soft Stevia extract. All the quality characteristics were more acceptable at 50% substitution through the sensory test. All the biological properties of retained after bread making process and they recommend it as optimum nutrient and quality of bread for human nutrition. Mayasari et al. [31] also reported that consumption of Rosella-Stevia Tea can decrease fasting BGL with no changes in 2-h postprandial BGL in pre-diabetic women. The application of Stevia as functional food is given in Table 1.

4 Anti-diabetic activities of Stevia

Various extracts of Stevia have been used for many years by South Americans a therapy for diabetes [16, 39]. Regular use of Stevia glycosides decreases sugar, cholesterol, and radionuclides level in the blood [7]. It possesses high anti-hyperglycemic activity [14, 24, 40], and serves as a substituent for saccharose in diabetes patients [14, 24, 35]. In vivo experiments show that *S. rebaudiana* increases glucose tolerance in diabetic rats by maintaining the blood glucose level [16]. In diabetic patients, it also leads hypoglycemia via lowering both the glycogenolysis and gluconeogenesis processes, and by absorbing the glucose in the duodenum part. In diabetic patients, Stevia and its glycosides have been found associated with antioxidant and anti-hyperglycemic activities in several body parts like the pancreas, liver, and kidney [5, 22, 38]. It has beneficial activities in pancreatic tissue by increasing the insulin level and enhances anti-diabetic properties in PPARγ-dependent manner, and through its anti-oxidant activities [5]. Moreover, the stevioside of Stevia has been reported to lower the inflammation by lowering the level of pro-inflammatory cytokines [44]. According to Jeppesen et al. [24] the stevioside increases the insulin level by affecting

Table 1 The uses of Stevia as functional food for the treatment of diabetes disease

Name of functional food with Stevia	Mode of action	References
Modified coconut jelly	It lowers postprandial Blood Glucose Level without any release of insulin	Chupeerach et al. [15]
Rosella-Stevia Tea	In prediabetic women, It lowers fasting BGL without any changes in 2-h postprandial BGL	Mayasari et al. [31]
Wheat bread with Stevia	It decreases the sugar level via inhibition of alpha amylase (and glucosidase activities. In addition, it also shows strong antioxidant activity	Ruiz-Ruiz et al. [36]
Mango nectar based Chocolates supplement with Stevia	It shows sensory, anti-oxidant, and polyphenolic properties	Cadena et al. [12]

the *β*-cells of the pancreas and lowers the blood sugar levels. Ahmad and Ahmad [2] noted that extracts of Stevia lower random BGL, decreased fasting blood glucose level and glycosylated (HbA1c) hemoglobin (5.32%) amount in streptozotocin-induced diabetic albino rats. In addition, they recorded an improved level of insulin and liver glycogen in diabetic samples after eight weeks of treatments.

According to Chen et al. [13], stevioside not only increases insulin levels but also lowers the gluconeogenesis process by decreasing the expression of phosphoenolpyruvate carboxykinase gene in rats'liver; hence maintain optimum blood glucose levels. The stevioside and steviol are the two bioactive compounds that decrease inflammation by activation and increasing the expression *IκBα* gene (NF-κB localization inhibitor) [10]. Similar findings were also recorded by Bayat et al. [8] by using Stevia aquatic extracts against the interleukin-6 (IL-6) amounts in serum by using Streptozotocin-Nicotinamide based induced diabetic rats. They found that Stevia and metformin could lower fasting blood sugars and IL-6 amounts in the diabetic group and thus could help in lowering insulin resistance in diabetic patients. Fengyang et al. [19] reported that in RAW2647 cells, the stevioside inhibits the NF-κB and IκB amounts by lowering the important inflammatory factors *i.e.* IL-1*β,* IL-6, and TNF-*α*. Boonkaewwan et al. [10] found no cytotoxicity on human colon carcinoma cell line (Caco-2). But, stevioside and steviol lower LPS-induced pro-inflammatory cytokine productions by affecting cytokine gene expression via IκBα/NF-κB signaling pathway.

The steviol glycosides have been reported to increase uptake of glucose in neonatal rat fibroblast by activation of PI3K/Akt pathway; hence induces translocation of Glut4 to plasma membrane. It also acts as a strong antioxidant compound by lowering the concentration of glutathione and by increasing the expression of two important antioxidant enzymes *i.e.* superoxide dismutase and catalase (Fig. 1) [33]. The similar insulinomimetic activity of two bioactive compounds (steviol and stevioside) of Stevia was recorded by Bhasker et al. [9] in diabetes induced L6 and 3T3L1 cells. In STZ-diabetic rat model of experiment, Shivanna et al. [38] also found anti-diabetic activities with stevia leaves. In addition they also reported that it protect both liver and kidney by lowering the oxidative stress. The *S. rebaudiana* extracts could lower BGL in diabetic rats at time dependent manner [26]. It also protects rats from intreptozotocin-induced diabetes by lowering oxidative stress [38]. Das et al. [17] envisaged the anti-diabetic properties of the leaves based crystals of *S. rebaudiana* inalloxan induced type-1 diabetic mice. Their findings showed that crystal concentration (500 mg/kg) significantly improved the body weight loss and lower the BGL in the diabetic animal. The detailed applications of Stevia glycosides against diabetes disease are given in Table 2. However some previous studies showed some negative effect of Stevia glycosides in animal model experiments. For example, According to Dyrskog et al. [18] the oral use of rebaudioside A (0.025 g/kg BW/day) for eight weeks does not improve glycemic control in the Goto-Kakizaki rat. According to Toskulkao et al. [42] the steviol decrease the intestinal glucose absorption up to 43% at 1 mM concentration and also altered the morphology of the intestinal absorptive cells in hamster. Similarly, according to Aranda-Gonzalez et al. [4], the acute intraperitoneal or chronic oral administration of 20 mg/kg of minor steviol glycosides of *S. rebaudiana* had no antihyperglycemic effect in normoglycemic or induced-diabetic Wistar rats.

5 Conclusion

Stevia is full of many important phytochemicals (Steviol, Steviosides, rebaudiosides, etc.) that have properties to reduce blood sugar levels. It possesses high anti-hyperglycemic activity and serves as a substituent for saccharose in diabetes patients. It has beneficial activities in pancreatic tissue by increasing the insulin level and enhances antidiabetic properties. It also helps in maintaining normal blood sugar level by lowering inflammation and oxidative response. It is a major source of high potency sweetener for the growing natural food market. The efficient functional Stevia breeds, tea, jelly, etc. can provide optimum nutrients to the body but also help in controlling of diabetes. Further research is needed to determine if its regular consumption brings sustained benefits for human.

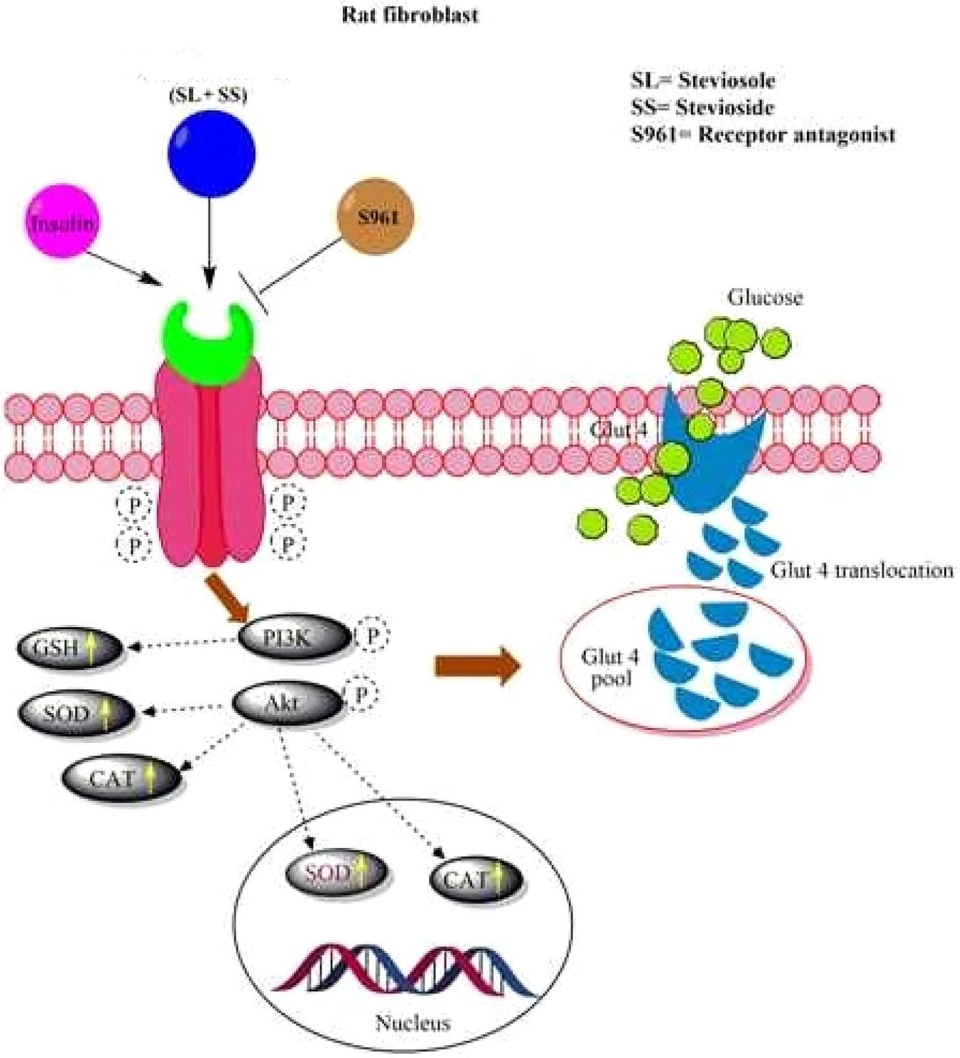

Fig. 1 Role of stevia glycosides as insulin-mimetic and antioxidant activities in neonatal rat fibroblast; S961; the insulin receptor antagonist; blocks the insulin and glycosides induced signals. Signals from the steviol glycoside lead to translocation of Glut4 from intracellular pool to plasma membrane, thus allowing glucose which mimics the insulin activity. The expression and activity of both the antioxidant enzymes SOD and CAT is also enhanced due to the activation of the same pathway (dashed arrows). Furthermore, GSH levels are also increased with steviol glycosides

Table 2 The Potential bioactive metabolites of Stevia and their mode of actions against diabetic disease

Potential agents	Mode of action	References
Stevia extracts	Stevia extract at a dose of (300 mg/kg) has a significant anti-hyperglycemic action in diabetic rats. In addition, the combined dose of stevia extract (300 mg/kg) and glimepiride (1 mg/kg) showed a more reduction in the BGL	Assi et al. [6]
Stevioside	It lower random BGL and fasting blood glucose level and glycosylated (HbA1c) hemoglobin amount in streptozotocin induced based diabetic albino rats	Ahmad and Ahmad [2]
Steviol	Act as a strong antioxidant compound by lowering the concentration of glutathione and by increasing the expression of two important antioxidant enzymes i.e. superoxide dismutase and catalase	Prata et al. [33]
Glycosides	Stevia crystal reduces body weight loss and BGL	Das et al. [17]
Glycosides	It leads hypoglycemia by lowering the glycogenolysis and gluconeogenesis processes and by absorbing the glucose into the duodenum	Assaei et al. [5], Gregersen et al. [22] and Shivanna et al. [38]
Glycosides	Enhance the anti-diabetic activity of pancreatic tissue by increasing the insulin level by increasing anti-oxidant activity and PPARγ-dependent mechanism	Assaei et al. [5]
Stevioside and steviol	It promote Glut4 protein and glucose transport, together with an enhanced transcription of Glut4 mRNA	Bhasker et al. [9]
Stevioside	It can lower the inflammation by lowering the level of pro-inflammatory cytokines	Wang et al. [44]
Stevioside and steviol	Lowe inflammation by activation and increasing the expression *IκBα* gene (NF-κB localization inhibitor)	Boonkaewwan et al. [10]
Stevioside and steviol	It lowers gene expression of IL-1*β,* IL-6, and IL-10. In addition, it enhances glucose uptake and shows string anti-oxidant activity in neonatal rat fibroblast	Boonkaewwan et al. [10]
Stevioside	Inhibits the f NF-κB and IκB levels by lowering the amounts of IL-1*β,* IL-6, and TNF-*α*	Fengyang et al. [19]
Stevioside	Raise insulin level and lower the gluconeogenesis by decreasing the expression of phosphoenolpyruvate carboxykinase gene in rats' liver	Chen et al. [13]

Declaration

Conflict of Interest The authors declare that they have no conflict of interest.

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