The Journal of Phytopharmacology 2024; 13(1):64-69
Online at: www.phytopharmajournal.com

The Journal of Phytopharmacology
(Pharmacognosy and phytomedicine Research)

Review Article

ISSN 2320-480X
JPHYTO 2024; 13(1): 64-69
January- February
Received: 23-12-2023
Accepted: 26-02-2024

doi: 10.31254/phyto.2024.13109

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Functional aspects of stevia: A review

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ABSTRACT

Stevia, the natural sweetener obtained from the leaves of *Stevia rebaudiana* plant has found commercial application as a sugar substitute in foods, beverages, or medicines all over the world. The leaves of this plant naturally contain diterpene glycosides stevioside, rebaudiosides A-F, steviolbioside, and dulcoside, which are responsible for its sweet taste. As the human body does not metabolize the glycosides in stevia, it contributes to zero calories. Many preclinical and clinical studies have revealed the pharmacological and therapeutic applications of stevia. It is reported to possess antioxidant, antimicrobial, antifungal, prebiotic, antidiabetic, anti-inflammatory, antiobesity, and anticarcinogenic activity. This review focus on the functional aspects related to this natural sweetener and the plant.

Keywords: Stevioside, *Stevia rebaudiana* Bertoni, Natural Sweetener, Antidiabetic, Meethi tulsi, Compositional.

INTRODUCTION

Stevia is derived from the leaves of the plant *Stevia rebaudiana* which is originated from Brazil and Paraguay. Stevia being a natural sweetener can be used as a sugar substitute. Stevia leaves are also referred to as *Meethi Tulsi* in India. The active compounds in stevia such as di-terpene glycosides stevioside, rebaudiosides A-F, steviolbioside, and dulcoside, have 30 to 150 times the sweetness of sugar [1] and these components were found to be pH stable, heat stable and remain unfermented [2]. In 1931, Stevia glycosides were isolated and are reported to as the sweetness imparting factor in stevia [3]. Stevia contributes zero calorific value as the human body does not metabolize the glycosides present in it. Compared to sugar, stevia has a longer-lasting and slower-onset flavor. At higher concentrations, certain of its extracts may also have a bitter or licorice-like aftertaste.

S. rebaudiana Bertoni was botanically classified in 1899 by Moises Santiago Bertoni. Its original name was *Eupatorium rebaudianum*, but in 1905 it was renamed [4]. Native to the northeastern Paraguay area, *Stevia rebaudiana* Bertoni is a bushy shrub with branches that belongs to the *Asteraceae* family. It may also be found in Argentina's and Brazil's surrounding regions [5]. Other places of the world, such as Canada and a few areas of Asia and Europe, have also adopted its cultivation [6]. There are now 230 known species of stevia, and only steviol glycosides are produced by the species *rebaudiana* and *phlebophylla* [7]. It has been shown in commercial studies to improve human health. Many medicinal applications attributed to the leaves of *S. rebaudiana* have been shown in Figure 1 [8-18]. No studies have reported any mutagenic, teratogenic or carcinogenic effect after the consumption of stevia as a sweetener [17]. This article encompasses the nutritional, pharmacological, and therapeutic applications of *S. rebaudiana*.

COMPOSITIONAL ASPECTS

A nutrient-rich herb, stevia contains between 80 and 85 percent water, protein, fiber, amino acids, free sugars, iminosugarsteviamine and its enantiomer, lipids, essential oils, ascorbic acid, beta carotene, riboflavin, thiamine, austroinulin, sterebins A–H, nilacin, rebaudi oxides, gibberellic acid, indole-3-acetonitrile, apigenin, quercetin, isoquercitrin, luteolin, miocene, kaempferol, stigmasterol, xanthophyllus, umbeliferone, chlorogenic acid, caffeic acid, dicaffeoylquinic acid, chromium, cobalt, magnesium, iron, potassium, phosphorus, and trace elements [8, 19, 20]. From *S. rebaudiana*Bertoni, more than 100 compounds have been discovered. Of them, steviol and its glycosides stevioside, rebaudioside AF, steviolbioside, dihydroisosteviol, rubusoside, and dulcoside are the most well-known. According to scientific reports, *S. rebaudiana* leaves have an energy content of 2.7 kcal g^{-1} on a dry weight basis [21]. Nutritional profiles of the leaves of *S. rebaudiana* are shown in Tables 1 to 5.

FUNCTIONAL ASPECTS OF STEVIA

Antidiabetic effect

The leaf extract of Stevia has been traditionally used for the treatment of diabetes [33]. In normal adult humans, ingestion of this leaf extract caused a significantly increased glucose tolerance and a slight suppression in the plasma glucose levels [34]. Administration of a single acute dose of stevioside (1,000 mg) was able to benefit the insulin-glucose ratio in serum by 40% in diabetic humans [35]. Stevioside has been shown to improve glucose-stimulated insulin production, but it has no effect on insulinemia during fasting [36, 37]. Stevioside treatment had a dose-dependent effect on the glucose levels lowering of type-1 and type-2 diabetic rat models as compared to the controls. A decrease in the gene expression of Phosphoenolpyruvate carboxykinase, a rate-limiting enzyme for gluconeogenesis primarily expressed in the liver, and an increase in insulin secretion in a dose-dependent manner are two other ways that stevioside is reported to regulate blood glucose levels [38]. Similar findings were observed in another study [39], wherein rats pre-fed with powdered stevia leaves prior to receiving a streptozotocin injection displayed less severe signs of diabetes, such as polyphagia and weight loss, and their hyperglycemia was elevated to a lesser degree than in the untreated diabetic rats. The results of the study showed that the polyphenol extract and powdered stevia leaves raised the amount of insulin secreted by the pancreatic islet β-cells in rats with type-1 diabetes and improved glucose tolerance and cellular insulin sensitivity in rats with type-2 diabetes. By inhibiting the activity of α-amylase and α-glucosidase, two enzymes crucial for the digestion of dietary carbohydrates, stevia may also have anti-diabetic properties. Studies demonstrated that stevia leaf extract decreased the *in vitro* activity of the enzymes α-amylase and α-glucosidase [40, 41]. Stevia leaf crystals have anti-diabetic qualities [42]. The administration of 500 mg/kg of the crystals to diabetic rats led to a reduction in both body weight and blood glucose levels. Furthermore, the histological investigation showed that the crystals had a protective impact on the pancreas by partially repairing its structural damage. In a study, rats with STZ-induced diabetes treated with an aqueous stevia leaf extract demonstrated a considerable reduction in random and fasting blood glucose levels as well as in glycosylated hemoglobin (HbA1c), while liver glycogen and insulin levels increased dramatically [43]. Steviol glucuronide, a metabolite of steviol glycosides, stimulated insulin secretion from isolated pancreatic islets in a dose- and glucose-dependent manner [44]. Based on these findings, the authors hypothesized that steviol glucuronide may be the main metabolite following oral ingestion of stevia glycosides. Consumption of stevia leaf powder by the diabetic patients for 60 days resulted in a significant reduction in blood glucose level before and after fasting [45].

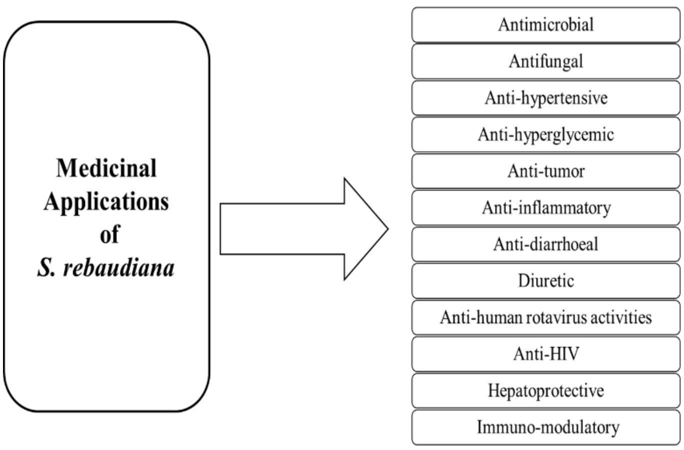

Figure 1: Medicinal applications of leaves of *S. rebaudiana*

Table 1: Number of sweet glycosides in *Stevia rebaudiana* leaves [22-28]

Glycoside	Composition (% of the leaves dry weight)
Stevioside	2.0-10
Steviol	ND-0.70
Steviolbioside	ND-1.2
Rebaudioside A	1.0-7.3
RebaudiosideB	ND-0.5
Rebaudioside C	ND-2
Rebaudioside D	ND-3.3
Dulcoside A	ND-1.0
ND: Not Detected	

Table 2: Proximate analysis of dried *Stevia rebaudiana* leaves [19, 22, 25]

Constituent	Composition (g 100 g^{-1} dry weight basis)
Moisture	ND-7.7
Protein	10-20.4
Fat	1.9-5.6
Ash	ND-15.5
Carbohydrate	ND-61.9
Crude fibre	ND-18
ND: Not Detected	

Table 3: Fatty acid composition of *Stevia rebaudiana* leaf oil [19, 22, 25, 29-32]

Fatty acids	Composition (g 100 g^{-1})
Palmitic acid (C16)	27.5-30
Palmitoleic acid (C16-1)	1.27-3.0
Stearic acid (C18)	1.18-4.0
Oleic acid (C18-1)	4.36-9.9
Linoleic acid (C18-2)	12.40-16.8
Linolenic acid (C18-3)	21.59-36.2

Table 4: Mineral content of dried *Stevia rebaudiana* leaves [19, 22, 25, 29-32]

Minerals	Composition (mg 100 g^{-1})
Calcium	8.2-1550
Phosphorus	ND-350
Sodium	ND-160
Potassium	17.3-2510
Iron	3.9-55.3
Magnesium	ND-500
Zinc	ND-6.39
ND: Not Detected	

Table 5: Water-soluble vitamins of *Stevia rebaudiana* leaves [30-32]

Vitamins	Quantity (mg/100 g dry base of extract)
Vitamin C	14.97
Vitamin B_2	0.43
Vitamin B_6	Absent
Folic acid	52.18
Niacin	Absent
Thiamine	Absent

Antimicrobial effect

Stevia has been traditionally used for treating wounds, sores, and gum disease as it is thought to possess antimicrobial action towards the growth of certain pathogens and other infectious organisms [46]. It has also been advocated for people who are susceptible to yeast infections or reoccurring streptococcal infections. A study revealed that, the crude leaf extract of stevia in methanol and chloroform had antimicrobial action against *Escherichia coli*, *Streptococcus mutans*, *Bacillus subtilis*, and *Staphylococcus aureus*. The chloroform extract was tested on six different fungi, including *Aspergillus niger*, *Curvularia lunata*, *Sclerotonia minor*, *Rhizopus spp*, *Alternaria alternate*, and *Microsporium gypseum*. However, it was discovered that the extract's anti-fungal properties were more limited, and it was only found to be effective against *Sclerotonia minor*. Likewise, of the six fungi that were assessed, only two (*Curvularia lunata* and *Sclerotomy minor*) were shown to be susceptible to the methanol extract's activity [46]. Aqueous stevia leaf extract was also shown to have anti-fungal and anti-yeast activities. The growth of various organisms like *Aeromonas hydrophila*, *Candida albicans*, *Salmonella typhii*, *Vibrio cholera*, *Cryptococcus neoformans*, *Trichophyton mentagrophytes*, *Epidermophyton*, *E. coli*, *B. subtilis*, and *S. aureus* were restricted in the presence of extracts (acetone, chloroform and ethyl acetate) of stevia, owing to its antimicrobial properties [8]. Wild stevia extracts when in comparison with commercial antibiotic chloramphenicol demonstrated a potential antimicrobial action towards pathogenic organism namely; *Enterococcus faecium*, *Pseudomonas aeruginosa*, *Bacillus cereus*, and *Klebsiella pneumoniae* [47]. The antimicrobial action of stevia extracts was found to be dose-dependent [19, 48]. Using stevia extracts as a preservative for salmon paste and other seafood items is one potential use for the plant's antibacterial and antioxidant qualities [49].

Antiobesity effect

Increased sugar intake causes a number of health and nutritional issues, including obesity. Therefore, replacing sugar with low-calorie sweeteners can be successful in weight-loss [50]. Stevia leaves and extract have been shown to be beneficial in weight loss programs because they decrease the desire for sweet and fatty foods [51]. Stevioside and Rebaudiosides, two zero-calorie di-terpene glycosides found in stevia leaves, are not metabolized to produce energy [33, 52]. Stevia sweeteners in food and drink provide a low-calorie alternative to sugar and aid in weight control and reduction. High dosages of steviol has resulted in the decrease in body weight of the experimented rats [53].

Since stevia produces fewer calories per gram than sugar, which is not fully absorbed by the digestive system, it is frequently used as sugar replacer. When rats fed stevia instead of sucrose in their food, the rats' body weight, total cholesterol, triglycerides, and low-density lipoproteins significantly decreased while their high-density lipoprotein increased [54]. Diabetic rats when given an aqueous stevia leaf extract for eight weeks demonstrated better calorie control by consuming less feed and water than the controls, which resulted a drop in body weight [43]. However, the findings of the human study were not so encouraging, since other randomized controlled studies have not been able to identify a difference in body weight between the stevia-treated group and the control group. Those who took a stevia-containing preload before a meal ingested 300 lesser calories than those who took a preload containing sucrose [55]. Furthermore, despite the fact that the stevia-preloaded group had ingested less calories, there was no difference in the self-reported feelings of hunger and fullness between them [50]. In healthy adults' self-reported hunger and desire to eat were reduced when they were preloaded with stevia [29]. The appetite of the individuals was reduced after the intake of stevia leaf containing cookies in comparison with cookies having no stevia [3].

Antioxidant activity

The higher level of bioactive components like tannins, flavonoids, phenolic compounds and vitamin C in stevia plant are attributed towards its antioxidant activities [2, 56, 57]. Stevia extracts, primarily leaf extracts and, to a lesser degree, callus extracts as well, exhibit a dose-dependent antioxidant property [2,56]. The ethanolic and glycol-aqueous extracts exhibited the most antioxidant activity against the DPPH and $ABTS^+$ radicals and had the largest concentration of phenols and flavonoids [58]. In D-galactose-induced aged mice, the polyphenol-rich extract made from byproducts of steviol glycoside synthesis demonstrated protective effects against oxidative stress by raising the activities of superoxide dismutase, catalase, glutathione peroxidase, and total antioxidant capacity and lowering the levels of malondialdehyde and acetylcholinesterase in the blood, brain, or liver. It indicates stevia residue extract may be a useful dietary strategy for reducing or avoiding oxidative stress and age-related disorders since it has protective properties against oxidative stress [59]. When stevia leaf extract and powder were administered to diabetic animals, lipid peroxidation decreased and anti-oxidation markers increased [39,60]. Drinks containing stevia as sweetening agent have demonstrated enhanced antioxidant properties. This is a positive step toward the use of stevia as a possible sweetener in fruit juices, since it may offer superior nutritional and physicochemical qualities and enhance the benefits of the existing fruit drinks [61]. Yoghurts incorporated with 0.25 and 0.5% of stevia extract exhibited higher level of phenolic content and antioxidant activity during the initial and final day of storage (30 days) as well as in the simulated gastrointestinal conditions [25].

Prebiotic effect

S. rebaudiana roots contains fructans and inulin. Both inulin and fructans were reported to have prebiotic effect [62]. *S. rebaudiana* produced fructans with less degree of polymerization (DP<6), which enhanced the growth and development of beneficial microorganisms like *Lactobacilli* and *Bifidobacteria* [63]. The best group of bacteria for hydrolyzing stevioside and rebaudioside A to steviol was discovered to be *Bacteroides* [64]. The fermentation of prebiotic substance has a number of positive effects, including enhanced intestinal absorption of minerals, the synthesis of short-chain fatty acids [65] (SCAs), a decrease in cholesterol and triglyceride levels, the control of hyperglycemia [66], and enhanced immune system efficiency [67]. In addition to their health benefits, fructans possesses technological properties as a fat and sugar replacer in low calorie foods and as a texturizing agent [68].

REGULATORY ASPECTS

Regulatory aspects regarding use of stevia vary from country to country. The Joint FAO/WHO Expert Committee on Food Additives currently set requirements for steviol glycosides, including a minimum purity of 95% of seven identified steviol glycosides, and a safe daily consumption limit for humans (up to 4 mg/kg of body weight). An FDA import notice for leaves and crude extracts was issued in 2019 because to concerns over their safety when used in meals or supplements and the possibility of toxicity. Authors [69] have summarized the GRAS notices for the use of steviol glycosides. The level of stevia permitted by Food Safety and Standard Authority of India (FSSAI, 2015) [70] for use in different foods is given in Table 6.

Table 6: Levels of steviol glycosides permitted by FSSAI in various food items

Articles of food	Maximum level (mg/kg of food) (Steviol equivalent)
Dairy based drink flavored	200
Dairy based desserts (Ice-cream, Frozen desserts, Cream toppings)	330
Yoghurt	200
Fruit Nectars	200
Non-carbonated water-based beverages	200
Ice Lollies or Edible Ice	270
Jams, Jellies, Marmalades	360
Ready to eat cereals	350
Carbonated water	200
Soft drink concentrate	200
Chewing gum	3500

CONCLUSION

Owing to its low-calorie sweetness and health benefitting aspects, the sweet herb *S. rebaudiana* (Bertoni) and its metabolites are increasingly finding commercial value as sugar substitutes in foods, beverages, and in medicine as therapeutic ingredients for curing and managing chronic diseases. But to widen its commercial applications and to comply with the legal standards, a deeper understanding of the functional constituents of this sweet herb is essential and hence further studies are warranted.

Conflicts of Interest

The authors declare no conflict of interest.

Funding

None declared.

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HOW TO CITE THIS ARTICLE

Chaudhary S, Kiran S, Sreeja V. Functional aspects of stevia: A review. J Phytopharmacol 2024; 13(1):64-69. doi: 10.31254/phyto.2024.13109