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Review

# Health benefits of *Stevia rebaudiana* Bertoni as zero calorie natural sweetener: a review

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**Abstract**

*Stevia rebaudiana* Bertoni is a perennial herbal species with a number of therapeutic properties. The leaves of *S. rebaudiana* are the most important part of the plant as they contain high level of sweetener compounds known as steviol glycosides; which are known to possess antioxidant, antimicrobial, and antifungal activities. Among the steviol glycosides, stevioside and rebaudioside A are the most abundant sweetening compounds of interest, documented to be 30 - 250 folds sweeter than sucrose or refined sugar. The therapeutic properties of the species make it more interesting as they play important roles as anti-hyperglycaemic agent to lower glucose levels in the blood, thus commonly used in the treatment of diabetes mellitus and obesity. Known to have sweet tasting leaves, its extract which contains antioxidant compounds have been used to treat cancer, reduce inflammatory, and hypertension. *S. rebaudiana* has drawn the attention of health-conscious fitness lovers all over the world as non-caloric sweetener, and has been widely cultivated for being the most suitable sweetening substitution.



## Introduction

*Stevia rebaudiana* has been documented to originate from Rio Monday valley in Paraguay, and grows well on any soil type with adequate moisture and drainage (Katayama *et al.,* 1976). The species has attracted an overwhelming attention among Europeans when in 1899, a South American naturalist and scientist named Moises Santiago Bertoni discovered the unique sweetening compounds of the leaves from natives of Mestizos and Paraguayan Indians. The sweet taste of the phytochemical compounds was later successfully isolated in 1900 by a Paraguayan chemist named Ovidio Rebaudi. In 1905, the original name of the species, *Eupatorium rebaudianum*, was changed to *S. rebaudiana* as an honour to Ovidio Rebaudi, and has since remained the same (Lewis, 1992).

Among the local Guarani Indians, which is a group of culturally related indigenous peoples of South America, *S. rebaudiana* was known as "kaa he-he" which means "sweet herb" (Lewis, 1992). The leaves of the plant were used to enhance culinary flavours and as sweetener for their herbal green teas. The first attempt on the establishment of *S. rebaudiana* seeds outside Paraguay was conducted in 1942, in England. However, the attempt was unsuccessful as seeds failed to establish. Later, seeds were exported to Japan and consequently, great effort was put in the establishment of the species. Successful cultivation of *S. rebaudiana* in Japan was due to the initiative undertaken by Sumida in 1968 (Lewis, 1992). Presently, the species is extensively cultivated in a number of countries including Brazil, Uruguay, Thailand, Australia, Japan, Korea, and China, all of which are currently the world's leading countries in cultivation and exporting of *S. rebaudiana;* with Japan as the highest consumer and biggest market.

Steviol glycosides are the main compounds that give the sweet taste of *S. rebaudiana*. Compounds such as stevioside and rebaudioside A are actively being extracted to be used as substitute for refined sugar or saccharose (Gupta *et al.,* 2013). These compounds are widely used in pharmaceutical industries as they contain therapeutic benefits such as anti-hyperglycaemic, anti-tumour, anti-hypertensive, and anti-cancer properties (Chatsudthipong and Muanprasat, 2009).

This review article brings together numerous scientific researches from several sources on pharmacological properties of *S. rebaudiana*. The importance of the species as a sweetener in place of refined sugar has attracted much attention, resulting in the plant-based products being widely available in markets worldwide. As *S. rebaudiana* plant is zero-calories with low glycaemic index, it helps pharmaceutical industries especially in the treatment of diabetes mellitus, a condition in which the body's ability to produce or respond to the hormone insulin is impaired and resulting in abnormal metabolism of carbohydrates and elevated levels of glucose in the blood. This review article may provide

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a better understanding of the benefits of *S. rebaudiana* as a natural sweetener.

*Botanical description of S. rebaudiana*

*Stevia rebaudiana* belongs to the Asteraceae family, a compositae or sunflower family, which is the biggest family of flowering plants consisting of more than 1,600 genera, 13 subfamilies, and over 30,000 plant species. A member of the genus *Stevia*, it has 154 species, among which only two species, *S. rebaudiana* and *S. phlebophylla*, produce the sweet compounds of steviol glycosides (Brandle and Telmer, 2007). The taxonomy of *S. rebaudiana* is shown in Table 1.

Table 1: The taxonomy of *Stevia rebaudiana.*

| Taxonomic Rank | Taxonomic Name |
|---|---|
| Kingdom | Plantae |
| Subkingdom | Tracheobionta (vascular plants) |
| Superdivision | Spermatophyta (seed plants) |
| Division | Magnoliophyta |
| Class | Magnoliopsida |
| Subclass | Asteridae |
| Group | Monochlamydae |
| Order | Asterales |
| Family | Asteraceae |
| Subfamily | Asteroideae |
| Tribe | Eupatorieae |
| Genus | *Stevia* |
| Species | *S. rebaudiana* |

*Stevia rebaudiana* is a perennial herb that grows up to 1 m tall. The root system is extensively spreading horizontally in the soil (Shock, 1982). The leaf is 3 - 4 cm long, borne in an alternate arrangement. The leaf is lanceolate or oblanceolate in shape with serrated margin from the middle of the leaf blade. The leaf surface is covered with trichomes with an average length of 2.5 - 5 mm (Singh and Rao, 2005). The leaf is the most important part of the plant, whose quality is mostly influenced by environmental factors such as soil conditions, amount of sunlight received, and postharvest handling processes including the age of leaves at harvest, processing, and storage methods (Maiti and Purohit, 2008). The flowers of *S. rebaudiana* generally are white and purple corollas, small (15 - 17 mm), covered by involucres of epicalyx, and borne in composite arrangement. The species produces flowers as early as when four true leaves are formed (Marsolais *et al.,* 1998; Dwivedi, 1999).

*Phytochemical constituents of S. rebaudiana*

Sugar is the sweet crystalline substance obtained from sugar cane or sugar beet, consisting essentially of sucrose, and used as sweetener. It is a major component in diet and consumed daily either in food or drink. Excessive intake of refined sugar in the daily diet is worrisome as it leads to obesity and diabetes. Ashcroft and Rorsman (2012) cited that there are two types of diabetes which is Type 1 diabetes (insulin-dependent) and Type 2 diabetes (non-insulin-dependent). According to the National Diabetes Statistics Report in 2017, majority of the diabetes patients worldwide are Type 2 diabetes mellitus. In the United States alone, 30.3 million peoples in a ratio of 1:10 of the population are diabetes patients (CDC, 2017). Chronic diseases such as obesity and diabetes are becoming more of concern, and people begin to find natural sweetener in order to stay healthy.

In recent years, *S. rebaudiana* has gained global attention due to its natural sweet compounds that can be an alternative to refined sugar. More than 100 compounds have been discovered with the most abundant compounds being terpenes and flavonoids (Singh and Rao, 2005).

Diterpene glycosides are sweetening compounds that can be found only in several species of plants including *S. rebaudiana* and *Rubus suavissimis* (sweet tea) (Singh and Rao, 2005; Uhler and Yang, 2018). The natural sweetener, steviol glycosides, have been isolated and classified into steviosides, steviolbioside, rebaudioside A, B, C, D, E, F, M, and dulcoside A (Shibata *et al.,* 1995; Geuns, 2003; Chatsudthipong and Muanprasat, 2009). Among these, steviosides have been found to be the most abundant (4 - 13% of leaf extract) (Geuns, 2003; Prakash *et al.,* 2014). Pure steviosides at the concentration of 0.4% was found to be 210 times sweeter than sucrose, and stable at various processing and storage conditions. However, steviosides has bitter after-taste that makes it less appealing (Kroyer, 2010; Prakash *et al.,* 2014).

Besides steviosides, rebaudioside A has also been found to be 200 times sweeter than sucrose. It has been reported that rebaudioside A also has bitter after-taste but is more stable than steviosides (Yang *et al.,* 2019). Other sweetening compounds sweeter than sucrose in *S. rebaudiana* leaves include rebaudioside B (150 times), rebaudioside C (30 times), rebaudioside D (220 times), rebaudioside E (170 times), rebaudioside F (200 times), rebaudioside M (250 times), and dulcoside A (30 times) (Prakash *et al.,* 2014). The average sweetness level of *S. rebaudiana* leaves are 250 - 300 times greater than sucrose with zero caloric level (Gardana *et al*., 2003; Chatsudthipong and Muanprasat, 2009; Marcinek and Krejpcio, 2015).

*Therapeutic constituents of S. rebaudiana*

*Antimicrobial activity*

Herbal plants have gained much attention as an alternative source of medicines due to their therapeutic properties to fight against a wide range of infectious diseases caused by bacteria, fungi, and viruses (Tan *et al.,* 2015). In plants, tannins, flavonoids, essential oils, and other aromatic compounds are continuously synthesised to protect themselves from infections caused by microorganisms (Jayaraman *et al.,* 2008). In turn, these compounds are extracted for the production of antimicrobial medicines, for example, antibiotics for use against bacteria and antifungal for use against infectious fungi in human.

*Stevia rebaudiana* has been tested in its ability to inhibit growth of bacteria, fungi, and viruses. In several studies, various extraction solvents such as water, ethanol, methanol, ethyl acetate, and hexane have been used to study their effects on the inhibition of various strains of bacteria, fungi, and viruses. Leaf extracts of *S. rebaudiana* have been tested to inhibit the growth of a number of bacteria including *Aeromonas hydrophila, Bacillus cereus, B. megaterium, B. subtilis, Enterococcus faecalis, Escherichia coli, Lactobacillus acidophilus, L. brevis, L. casei, L. plantarum, Proteus mirabilis, Pseudomonas aeruginosa, Salmonella paratyphi A, S. typhii, S. typhimurium, Sarcina lutea, Shigella boydii, S. dysenteriae, Staphylococcus aureus, Streptococcus cricetus, S. mitis, S. mutans* Ingbritt*, S. rattus, S. salivarius, S. sobrinus, Vibrio cholera, V. mimicus, V. parahemolyticus* (Tadhani and Subhash, 2006; Debnath, 2008; Jayaraman *et al.,* 2008; Ghosh *et al.,* 2008; Gamboa and Chaves, 2012; Siddique *et al.,* 2014).

Besides functioning as an antibacterial, *S. rebaudiana* leaves extract also were able to function as an antifungal to inhibit *Alternaria solani, Aspergillus niger, Candida albicans, Cryptococcus neoformans, Epidermophyton* spp., *Helminthosporium solani, Penicillium chrysogenum, Saccharomyces cerevisiae,* and *Trichophyton mentagrophytes* (Ghosh *et al.,* 2008; Jayaraman *et al.,* 2008; Siddique *et al.,* 2014).

*Stevia rebaudiana* extracts have also been investigated on infections against human rotaviruses (HRV) that attack children worldwide, causing severe dehydrating gastroenteritis (Kapikian, 1996). The anti-HRV inhibitory effect of *S. rebaudiana* extract was conducted on MA104 cells (African Rhesus monkey kidney cells), and examined by using MTT assay. The results showed that *S. rebaudiana* extract had the ability to inhibit HRV (Takahashi *et al.,* 2001).

*Anti-hyperglycaemic activity*

Jeppesen *et al.* (2003) reported that *S. rebaudiana* extract had the ability to rejuvenate beta cells of the pancreas. Sensitivity of insulin was documented to have increased and promoted the production of additional insulin. Chen *et al.* (2005) cited that stevioside was able to regulate glucose levels in the blood by enhancing insulin secretion and utilisation in the insulin-deficit experimental rats. Glucogenesis was slowed down because stevioside acted by lowering phosphophenol pyruvate carboxykinase gene expression in the experimental rat's liver. Another experiment on normal and healthy humans showed that glucose tolerance was increased following consumption of leaf extracts of *S. rebaudiana*. The stevioside compound was said to be responsible for reducing post-prandial blood glucose levels. Hence, *S. rebaudiana* leaf extract can be an alternative medicine in Type 2 diabetes treatment (Jeppesen *et al.,* 2003; Gregersen *et al.,* 2004; Chen *et al.,* 2005; Barriocanal *et al.,* 2008; Anton *et al.,* 2010).

*Antioxidative activity*

Chronic diseases such as cancers, inflammations, cardiovascular diseases, stroke, as well as Alzheimer's and Parkinson's are caused by reactions of free radicals in the human body. In order to prevent oxidative damages, antioxidants play an important role in neutralising free radicals, hence, their reactions are interfered (Büyükokuroğlu *et al.,* 2001; Devasagayam *et al.,* 2004). Antioxidative compounds including phenolic compounds, vitamins, and essential oils are naturally present in fruits, vegetables, and medicinal plants. However, their compositions differ from one plant to another (Han *et al.*, 2004; Shukla *et al.,* 2012). Nevertheless, natural antioxidants received worldwide attention due to their lower or no side effects to users. Synthetic antioxidants such as butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA) are readily available commercially. However, their toxicity and side effects are still unclear and have become one of major concerns to users (Shukla *et al.,* 2012).

Studies on antioxidative properties of a number of plant species were undertaken by Phansawan and Poungbangpho (2007) on *S. rebaudiana, Pueraria mirifica, Cassia alata, Andrographis paniculata,* and *Curcuma longa* using the 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) assay. Extracts of *S. rebaudiana* was found to exhibit the highest inhibition followed by *C. alata, C. longa, A. paniculata,* and *P. mirifica*. Other studies also found that leaf, callus, and stem extracts of *S. rebaudiana* exhibited high total phenolic and total flavonoid contents, and antioxidant activities by using the ferric reducing antioxidant power (FRAP) and

2,2-diphenyl-1-picrylhydrazyl (DPPH) assays (Tadhani and Subhash, 2006; Shukla *et al.,* 2009; Abou-Arab *et al.,* 2010; Ahmad *et al.,* 2010; Tavarini and Angelini, 2013; Zeng *et al.,* 2013). Further, *S. rebaudiana* extracts have also been reported to contain high total phenolic and total flavonoid contents, and exhibited high antioxidant potential using the FRAP assay (Jahan *et al.,* 2010).

*In vitro* enzymatic and non-enzymatic antioxidant properties of different parts of *S. rebaudiana* were investigated by Singh *et al.* (2012). The plant was divided into roots, leaves, stems, and flowers, and extraction was performed by using methanol as the extraction solvent. Enzymatic antioxidants were determined using the superoxide dismutase, catalase, and peroxidase assays. Based on the results, roots of *S. rebaudiana* exhibited the highest phenolic content followed by stems, flowers, and leaves. Leaves exhibited the highest content for tannins and flavonoids.

In a study by Shukla *et al.* (2012), aqueous leaf extracts of *S. rebaudiana* were found to inhibit DPPH radical scavenging activity, hydroxyl radical, nitric oxide, and superoxide anions scavenging activity. The total phenolic content of aqueous extract of *S. rebaudiana* was also found to be significantly higher in gallic acid which served as reference standard.

Antioxidant activities of *S. rebaudiana* Bertoni varieties Morita II and Criolla were conducted by Ruiz Ruiz *et al.* (2015). Total phenolic and flavonoid compounds exhibited were found to be higher in Criolla variety. Antioxidant activities of FRAP, copper chelating capacity, and iron chelating activity were slightly higher in Morita II as compared to Criolla variety.

*Antihypertensive activity*

Antihypertensive properties of *S. rebaudiana* were found to play crucial roles in controlling hypertension. Based on studies by Ferri *et al.* (2006) and Maki *et al.* (2008), the intake of 750 – 1,500 mg/day of stevioside helps to reduce 10 - 11 mmHg of systolic blood pressure and 6 - 14 mmHg of diastolic blood pressure within 7 d of consumption. In addition, stevioside was also found to inhibit $Ca^{2+}$ influx into blood vessels through vasorelaxation (Lee *et al.,* 2001; Liu *et al.,* 2003). Further, stevioside compounds found in *S. rebaudiana* plant have been demonstrated to possess antihypertensive activity in human.

*Anti-cancer activity*

Studies on anti-cancer properties of *S. rebaudiana* were conducted by Yasukawa *et al.* (2002) on animal cells. Four steviol glycosides (stevioside, dulcoside A, and rebaudioside A and C) were isolated from leaves of *S. rebaudiana*. The compounds were tested and showed significant inhibition effects on 12-O-tetradecanoylphorbol-13-acetate (TPA) induced tumour promotion of mice skin carcinogenesis.

*Anti-inflammatory and immunomodulatory activity*

Medicines having the properties of reducing swelling and inflammation are known as anti-inflammatory. Bookaewan *et al.* (2006) published that stevioside compounds found in *S. rebaudiana* have been established to have anti-inflammatory substances by reducing synthesis of inflammatory mediators in LPS stimulated THP-1 cells and interfering with signalling pathways of l Kappa B kinases (IKKBeta) and Kappa B, hence a beneficial substance as anti-inflammatory and immunomodulatory.

*Hypoglycaemic activity*

Hypoglycaemia occurs when blood glucose level is less than normal. In diabetes treatment, hypoglycaemia frequently occurs which leads to neurogenic and neuroglycopenic symptoms, and can be fatal (Cryer *et al.,* 2003; Briscoe and Davis, 2006). The common symptoms of hypoglycaemia include shakiness, anxiety, sweating, hunger, pale, fatigue, and irregular heart rate. If the hypoglycaemia is not treated immediately, complications such as confusion, seizures, blurred or reduced vision, and fainting can occur (Cryer *et al.,* 2003). Stevioside compounds found in *S. rebaudiana* have been reported effective in curing hypoglycaemic by restoring pancreatic functions into normal state. After 6 - 8 h intake of Stevia extract, blood glucose level was able to increase to a normal level (Schrier, 2007).

*Toxicity of S. rebaudiana*

The toxicological researches on *S. rebaudiana* have shown that active compounds such as steviosides do not have teratogenic, carcinogenic, or mutagenic effects on human. In addition, the consumption of stevioside as a sweetener has not shown any known allergic reaction (Pól *et al.,* 2007). A study by Carakostas *et al.* (2008) reported that high dietary intake levels of rebaudioside A is safe and does not produce toxicity to human.

## Conclusion

*Stevia rebaudiana* is an ancient plant species with great beneficial properties to human. The species has a promising future in the agricultural sector and high potential to be commercialised. Based on the phytochemical constituents in *S. rebaudiana*, it is suitable for the production of functional food ingredients.

The sweetening properties in *S. rebaudiana* due to compounds such as stevioside and rebaudioside A can be a potential substitution for refined sugar. Apart from being used as a sweetener, *S. rebaudiana* has been proven to be non-toxic. Besides being used in the treatment of diabetes mellitus, obesity, cancer, inflammatory, and many more, the use of *S. rebaudiana* can also be maximised in other pharmaceutical industries.

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