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Stevia (*Stevia rebaudiana*) a bio-sweetener: a review

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Abstract
Studies revealed that Stevia has been used throughout the world since ancient times for various purposes; for example, as a sweetener and a medicine. We conducted a systematic literature review to summarize and quantify the past and current evidence for Stevia. We searched relevant papers up to 2007 in various databases. As we know that the leaves of Stevia plants have functional and sensory properties superior to those of many other high-potency sweeteners, Stevia is likely to become a major source of high-potency sweetener for the growing natural food market in the future. Although Stevia can be helpful to anyone, there are certain groups who are more likely to benefit from its remarkable sweetening potential. These include diabetic patients, those interested in decreasing caloric intake, and children. Stevia is a small perennial shrub that has been used for centuries as a bio-sweetener and for other medicinal uses such as to lower blood sugar. Its white crystalline compound (stevioside) is the natural herbal sweetener with no calories and is over 100–300 times sweeter than table sugar.

Keywords: *Stevia leaves, rebaudioside, stevioside, extract, powder, medicinal use*

Introduction

Stevia rebaudiana is a small perennial growing up to 65–80 cm tall, with sessile, oppositely arranged leaves. Different species of Stevia contain several potential sweetening compounds, with *S. rebaudiana* being the sweetest of all. Stevia is a semi-humid subtropical plant that can be grown easily like any other vegetable crop even in the kitchen garden. The soil should be in the pH range 6.5–7.5; well-drained red soil and sandy loam soil. Saline soils should be avoided to cultivate this plant. Stevia has been successfully cultivated in recent years in many areas of Indian states: Rajasthan, Maharashtra, Kerela and Orissa. The increasing demands for natural sweeteners have driven the farmers in India toward large-scale Stevia cultivation. Diterpene glycosides are the group of natural sweeteners that have been extracted from Stevia. The leaves of wild Stevia plants contain 0.3% dulcoside, 0.6% rebaudioside C, 3.8% rebaudioside A and 9.1% stevioside.

Stevia (Asteraceae) is a woody shrub that can reach 80 cm in height when it is fully matured. The Stevia genus comprises at least 110 species (Rajbhandari and Roberts 1983) but there may be as many as 300. Its habitat extends from the southwestern United States to the Brazilian highlands (Soejarto et al. 1982). Different species of

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Stevia contain several potential sweetening compounds, with *S. rebaudiana* Bertoni being the sweetest of all (Soejarto et al. 1982; Kinghorn et al. 1984) The use of *S. rebaudiana* as a sweetener can be found in many parts of Central and South America, where this species is indigenous (Melis 1992), as well as in Japan (Kinghorn et al. 1984). People in Japan have been using Stevia as a sweetener in products such as seafood, soft drinks, and candies (Soejarto et al. 1982). This plant has been used in several areas of the world, such as in Brazil and Paraguay, as a natural control for diabetes (Jeppesen et al. 2000). Stevia also has been used to help control weight in obese persons (Suttajit et al. 1993).

Chemical constituents

The complete chemical composition of Stevia species is not yet available. However, a variety of Stevia species has been tested for their chemical compositions. The useful part of this shrub is the leaves. Out of 110 species tested for sweetness, only 18 were found to possess this characteristic (Soejarto et al. 1982). Eight ent-kaurene glycosides—namely dulcoside A, rebaudiosides A–E, steviolbioside, and stevioside—produce the sweet taste sensation (Kinghorn et al. 1984). These glycosides are mainly compounds of the diterpene derivative steviol (Shibata et al. 1995). *S. rebaudiana* Bertoni, the sweetest species, contains in its leaves all of the eight ent-kaurene glycosides (Kinghorn et al. 1984), with stevioside being the major constituent (3–8% by weight of the dried leaves) (Melis 1992). In addition, *S. rebaudiana* Bertoni contains stigmasterol, β-sitosterol, and campesterol (D'Agostino et al. 1984). The same species also contains steviol, a product formed by enzymatic hydroxylation within the plant (Kim et al. 1996). Other chemicals with no sweet taste are also found in Stevia species and some may even be bitter in taste. Stevisalioside A (from the roots of *Stevia salicifolia*) (Mata et al. 1992), longipinane derivatives in the roots of *Stevia connata* (Sanchez-Arreola et al. 2000), epoxylabdane diterpenes and a clerodane derivative in the leaves of *Stevia subpubescens* (Roman et al. 2000), flavonoids from the leaves of *S. rebaudiana* (Soejarto et al. 1982), *Stevia nepetifolia* (Rajbhandari and Roberts 1983), *Stevia microchaeta*, *Stevia monardifolia*, *Stevia origanoides* (Rajbhandari and Roberts 1985) and *Stevia procumbens* (aerial parts) (Sosa et al. 1985), and sesquiterpene lactones from the aerial parts of *S. procumbens* and the leaves of *S. origanoides* (Calderon et al. 1987) are in this group.

Proximate composition of Stevia

Six sweet-tasting compounds have been reported in the leaves of *S. rebaudiana* Bertoni—stevioside, rebaudiosides A, D and E, dulcosides A and B (Kohda et al. 1976; Kobayashi et al. 1977). Stevioside is a glycoside with a glucosyl and sophorosyl residue attached to the aglycon steviol; the latter has a cyclo-pentanoperhydrophenanthrene skeleton. The C4 and C13 of steviol are connected to the β-glucosyl and β-sophorosyl group, respectively. The structure of rebaudioside A is the same as that of stevioside except that the sophorosyl residue is replaced by a glucosyl-(1–3)-sophorosyl residue. The Stevia sweeteners are similar in structure, in that a steviol aglycon is connected at C4 and C13 to trisaccharides consisting of glucose and/or rhamnose residues (Kobayashi et al. 1977). Stevioside is a natural sweetener extracted from leaves of Stevia (Genus Jan 2003).

Soejarto et al. (1983) believed that the sesquiterpene lactones are responsible for the bitter aftertaste. Phillips (1987) described a European patent held by the Stevia

Company, which attributes the bitter aftertaste to the presence of essential oils, tannins, and flavonoids. Nevertheless, as pointed out, stevioside and rebaudioside A are partially responsible for the aftertaste, even though the contribution of rebaudioside A is significantly less than that of stevioside. The *S. rebaudiana* Bertoni contains a complex mixture of labdane diterpenes, triterpenes, stigmasterol, tannins, volatile oils, and eight diterpenenic glycosides: stevioside, steviobioside, dulcoside, and rebaudiosides A, B, C, D, and E. The most abundant substances are stevioside and rebaudioside A. Of the Stevia glycosides, rebaudioside A is the sweetest and the most stable, and it is less bitter than stevioside. Rebaudioside E is as sweet as stevioside, and rebaudioside D is as sweet as rebaudioside A, while the other glycosides are less sweet than stevioside (Cramer and Ikan 1987). According to Pederson (1987), stevioside is a white, crystalline powder extracted from the leaves of the Stevia plant. Its chemical identification and quantitative compositions are listed for those with a more scientific interest in the product. It is 100% natural, having no (zero) calories, is 200–300 times sweeter than sugar, heat stable to 198°C, non-fermentable, a flavour enhancer, and is anti-plaque and anti-caries. He reported the proximate composition of *S. rebaudiana* Bertoni that is presented in Table I, and compared Stevia leaf powder and Stevia white extract with granulated sugar (Table II).

Ngowatana (1997) purified the Stevia extract and obtained stevioside and its products that were a white fine powder and highly hygroscopic. It must be kept in an air-tight package to prevent moisture absorption. In large-scale production the same methods are used, except for the final step that produced dry products by using a spray dryer. Researchers reported that 3,000 g Stevia could produce 101.56 g light-yellow fine powder of stevioside and its products (Table III). Product compositions were stevioside. The amounts of iron and calcium were 0.97 and 1.47 mg/g product, respectively. The moisture content of the product was 9.31%.

Table I. Proximate composition of *S. rebaudiana* Bertoni.

Sample number	Constituent	Value (%)
1	Aluminium	0.0072
2	Manganese	0.0147
3	Ash	6.3000
4	Phosphorus	0.3180
5	β-Carotene	0.0075
6	Potassium	1.7800
7	Calcium	0.5440
8	Protein	11.200
9	Chromium	0.0039
10	Selenium	0.0025
11	Cobalt	0.0025
12	Silicon	0.0132
13	Fat	1.9000
14	Sodium	0.0892
15	Fibre	15.200
16	Tin	0.0015
17	Iron	0.0039
18	Vitamin	0.0110
19	Magnesium	0.3490
20	Water	82.300

Table II. Comparison of Stevia leaf powder and Stevia white extract with granulated sugar.

Granulated sugar	Stevia leaf powder	Stevia white extract
1 teaspoon	1/8 teaspoon	Dust on spoon
1 tablespoon	3/8 teaspoon	1/2 pinch
1/4 cup	1/2 teaspoon	Pinch
1/2 cup	1 tablespoon	1/8 teaspoon
1 cup	2 tablespoons	1/4 teaspoon
3.75 pounds	7.2 ounces	0.3 ounces
10 pounds	19.2 ounces	0.8 ounces

According to Sharma et al. (2006), the fresh Stevia leaves contain a large amount of water between 80 and 85%. The main constituents present were glycosides such as stevioside, steviol and rebaudioside A and B. The other constituents present in Stevia were ascorbic acid, β-carotene, chromium, cobalt, magnesium, iron, potassium, phosphorous, riboflavin, thiamin, tin, zinc, and so forth. The other chemicals found in Stevia include apigenin, austroinulin, avicularin, β-sitosterol, caffeic acid, compesterol, caryophyllene, centaureidin, chorogenic acid, chlorophyll, cynaroside, daucosterol, di-terpene glycoside, dulcosides A and B, foeniculin, formic acid, gibberellic acid, gibberellin, indole-3-acetonitrile, isoquercitrin, isosteviol, kaempferol, kaurene, lupeol, luteolin, polysatachoside, quercetin, quercitrin, scooletin, stigmasterol, umbelliferone and xanthophyllus.

Physiological and pharmacological actions

Stevia is used in many parts of the world as a non-caloric sweetener (Matsui et al. 1996). Along with sweetness, a bitter taste is also felt in humans (Jakinovich and Moon 1990). As an extract, this herb was found to have similar potency with regard to sweetness as a 10% sucrose solution at either pH 3.0 or 7.0. The same study also showed that the herbal extract had similar potency to that of aspartame and a cyclamate/saccharin mixture (Cardello et al. 1999). The potency of Stevia extracts was found to be higher than other herbal sweet extracts such as those of *Thladiantha grosvernorii* (Cucurbitaceae) or *Abrus precatorius* (Fabaceae). The sweetness of stevioside, the major sweet component in Stevia species, was detected in a concentration as low as 24 mg/ml (Jakinovich and Moon 1990).

Table III. Some commercial available Stevia products in the USA.

Product	Manufacturer	Type
Stevia	At Stevia LLC (Valley Forge, PA, USA)	Crystals
Stevia extract	Life Extension Foundation (Fort Lauderdale, FL, USA)	Powder
JAJ Stevioside	JAJ Group, Inc. (Jacksonville, FL, USA)	Powder
Stevia Liquid Extract	Baar Products, Inc. (Downingtown, PA, USA)	Liquid
Stevia Dark Liquid Concentrate	Stevia NOW (Shrub Oak, NY, USA)	Liquid concentrate
Stevia Pure Powder Extract	Stevia NOW	Powder extract
Stevia Tablet	Stevia NOW	Tablets (100–400 mg)

Human studies

Despite centuries of use, there is still a lack of comprehensive clinical studies on Stevia as a supplement. In normal human volunteers, the effect of administering extracts of *S. rebaudiana* on glucose tolerance tests was investigated. Subjects were given aqueous extracts from 5 g leaves every 6 h for 3 days. A glucose tolerance test was performed before and after administration of the extracts. The results showed that treatment with Stevia resulted in an increase in glucose tolerance and a decrease in plasma glucose concentrations (Curi et al. 1986). Moreover, it was shown recently that both steviol and stevioside can produce a direct effect on beta cells in the pancreas to release insulin. The authors concluded that this plant may have a potential use in the management of type 2 diabetes (Jeppesen et al. 2000).

Cariogenic and mutagenic effects

Since Stevia products are used as sugar substitutes by many populations, a study was conducted to test whether stevioside and rebaudioside A may have the potential of causing dental caries from prolonged use. Rats were fed a diet containing 0.5% stevioside or 0.5% rebaudioside A for 5 weeks. Neither compound showed a potential of increasing the risk of developing dental caries (Das et al. 1992). Several researchers investigated the risk of mutagenicity. In two studies (Matsui et al. 1986; Pezzuto et al. 1996), steviol produced a dose-related positive mutagenic effect in some tests. In the same studies, stevioside was found to be devoid of this effect. Other reports indicated lack of mutagenicity of both compounds (Suttajit et al. 1993; Klongpanichpak et al. 1997). Because of these contradictory reports, the Food and Drug Administration is still cautious in introducing this herb as a sugar substitute until its safety is completely established (FDA 1999).

Stevia products

Some examples of Stevia products available on the market in the USA are presented in Table III. Products of Stevia can be purchased directly from various companies or from local pharmacies. Many companies sell Stevia products via the Internet.

Medicinal values

Studies on food safety, including an extensive review of the literature, undertaken prior to 1982 (Lee 1979; Kinghorn 1982) concluded that Stevia leaves and extracts are safe; studies since then confirm this. Possible medicinal uses have been investigated often by using Stevia extracts as intravenous infusions in rats; possible effects on glucose metabolism, diuresis, organ weights, endocrine function, and so on, have been studied in this way (Kinghorn 1987; Nunes and Pereira 1988; Oliveira Filho 1988; Suanarunsawat and Chaiyabut 1996, 1997). Stevia extract infusions have also shown some anti-androgenic activity in rats (Sincholle and Marcorelles 1989). Likely beneficial effects of Stevia extracts, as antioxidants and to relieve blood pressure and hypertension, have also been shown (Chan et al. 1998; Xi 1998; Xi et al. 1998). Steviol (a precursor in the biosynthesis of steviosides) can be produced from steviosides experimentally using specific bacteria but not *in situ* in the human body. Steviol can exhibit some toxic and mutagenic activity (Tateo 1990).

Investigations of the effect of aqueous extract of *S. rebaudiana* leaves on glucose tolerance have been carried out by Curi et al. (1986) on volunteers. Aqueous extract of 5 g leaves were administered to volunteers at regular 6-hourly intervals for 3 days, with glucose tolerance tests performed before and after extract administration. The extract increased glucose tolerance; it significantly decreased plasma glucose levels during the test and after overnight fasting in all volunteers. In Japan, where artificial chemical sweeteners are not approved, many toxicology safety studies have been conducted (Elton Johnson 1990). Among studies carried out are some to investigate carcinogenicity and mutagenicity (if any) in animal testing (Oliveira Filho 1988; Toruan-Mathius et al. 1995; Toyoda 1997), to show dental benefits in the form of plaque inhibition and cavity reduction (Elton-Johnson 1990), to confirm the safety of Stevia for diabetic use (Polyanskii et al. 1997; Thamolwan and Narongsak 1997). The safety of feeding to animals, chickens and humans has also been confirmed by a wide range of studies (Sincholle and Marcorelles 1989; Smolyar 1993; White et al. 1994; Melis 1995, 1997; Suanarunsawat and Chaiyabut 1996, 1997; Wood 1996; Polyanskii et al. 1997).

The traditional method of use by the Paraguayan Guarani Indians was to dry the leaves and to use them to sweeten tea and medicines or to chew the leaves as a 'sweet treat'. Stevia was regularly used in drinks many times a day, not just occasionally, with no side effects. The use of dried leaves (pieces or powdered) is unacceptable in domestic cooking and does leave a sediment in clear drinks, and so forth, and can also leave a green colour. There may also be an unpleasant aroma associated with the dried leaves. Appropriate processing of the dry herbage may remove this aroma, which is due to specific leaf compounds (not steviosides) (Tsanava et al. 1991). Although Stevia has been used without any problems for many years in its native Paraguay and in other countries for lesser periods, health and safety issues have been receiving considerable attention in the past 20 years. There has been considerable media attention in the USA, including claims and counterclaims before the US FDA. Many of these claims relate to its potential competitive position in relation to aspartame. Stevia products have been approved for use in the USA as nutrition supplements although many protagonists claim it should be granted Generally Regarded As Safe status in the same manner as tea, coffee, sugar and fruit and vegetables, and so on. The general safety of steviosides could be largely due to the fact that they are not broken down nor are absorbed in the digestive tract (Hutapea 1997). Bacteriological studies on hot water extract from *S. rebaudiana* have been carried out by Tomita (1997). Lactobacilli were not killed on exposure to the fermented extract; however, under acidic conditions, the extract was found to be bactericidal.

In Japan, artificial sweeteners were banned some 40 years ago so Stevia has been their chosen alternative to sweeten their food and beverages. The Japanese have performed over 40,000 clinical studies and found Stevia to be safe. Stevia in its raw form, although incredibly sweet, has a very subtle liquorice essence to it. A sign of an excellent Stevia product is one that is free of this liquorice essence and still not bitter (Tateo et al. 1998). Genus Jan (2002) concluded that Stevia and stevioside are safe when used as a sweetener. Stevia is suited for both diabetics and Phenylketonuria (PKU) patients, as well as for basepersons intending to lose weight by avoiding sugar supplements in the diet. No allergic reactions to it seem to exist. Midmore and Rank (2002) found that the aqueous extracts of the leaves—boiled in water, cooled, then

strained (filtered)—are preferred in many situations and are better suited for controlled levels of sweetening. Crystalline powders and extracts are preferred in commercial situations as they have a fixed known sweetening value. Fixed concentration liquids are also acceptable. Kumar et al. (2007) reported that the Stevia is sweetest plant in the world because leaves contain diterpene glycoside that has a sweet taste but it is not metabolized and contains no calories. It is native to a relatively small area of eastern Paraguay (on the Brazilian border) where its leaves have been used by the local Guarani Indians as a sweetener for many hundreds of years. They specially used it in the local green tea (Mate tea-Hex sp.), as well as with other unpalatable medicinal and other drinks. The leaves are 30 times sweeter than cane sugar and can be safely used by diabetic patients. Sharma and Mogre (2007) observed the effect of consumption of Stevia extract on 20 selected hypercholestronic women: 20 ml extract was used to intervene in one subject in a glass of water (200 ml). They found the consumption of Stevia extract reduces the levels of cholesterol, triglyceride and low-density lipoprotein-cholesterol significantly while an increase in high-density lipoprotein-cholesterol was noted, which is desirable. They concluded that Stevia extract had a hypolipidaemic effect used to reduce the resistance of cardiovascular disease. The documented properties of Stevia are anti-bacterial, anti-fungal, anti-inflammatory, anti-microbial, anti-viral, anti-yeast, cardio-tonic, diuretic, hypoglycaemic, hypotensive and as a vasodilator. Stevia has an advantage over artificial sweeteners because it is stable at high temperatures and has a pH range 3–9. Stevia extract is used as a sweetener or flavour enhancer in many countries such as China, Japan, Korea, Israel, Brazil and Paraguay. It is also used in soft drinks, ice creams, cookies, pickles, chewing gum, tea and skincare products (Lee 1979; Kinghorn 1982, 1987; Elton Johnson 1990; Tateo 1990). Stevia plant and its extract both are used in weight-loss programmes because of their ability to reduce the craving for sweet and fatty foods (Jain et al. 2007).

Uses of Stevia

- Stevia is safe for diabetics, as it does not affect blood sugar levels.
- Stevia does not have the neurological or renal side effects as other artificial sweeteners.
- Stevia possess anti-fungal and anti-bacterial properties in addition to its other versatile uses. It can be safely used in herbal medicines, tonics for diabetic patients and also in daily usage products such as mouthwashes and toothpastes.
- Mild Stevia leaf tea offers excellent relief for an upset stomach.

Conclusion

Stevia is a herb that is used extensively in various areas of the world (without documentation of long-term use and effects) as a non-caloric sugar substitute. Various reports in animals and humans indicate that the safety of this herb is not yet completely determined. The current status of using this herb in the USA is as a ‘dietary supplement’. Until further information is available, pharmacists should be advised to conform to the FDA recommendation when counselling patients about this herb. Specifically, mild to moderate use as a supplement should be safe, but increased use for other pharmacological effects may not be warranted.

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