Stevia (*Stevia rebaudiana*): A Natural Healer for Diabetes, Heart Diseases & Other Metabolic Disorders

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Abstract

Stevia rebaudiana is a calorie-free natural sweetener and 300 times sweeter than sugar-cane. It's near like sugar taste and minimum calorie contribution to food makes it ideal replacement of sugar. Stevia for last few years has been seen as healthy replacement of sugar; especially for those people who are suffering from metabolic disorders or want to maintain healthy and balanced-calorie diet, as sugar is major calorie contributor in human diet. Stevia is a small perennial shrub that has been used for centuries as bio-sweetener and many other medicinal uses such as diabetes, heart diseases & other metabolic disorders. Stevia & its extract are also known to have good and positive effect on human health as well.

Key words: *Stevia rebaudiana*, *extract, medicine,* diabetes, phytochemicals

Introduction

Stevia rebaudiana (Bertoni) is a small perennial herb, with an extensive root system and brittle stems with small, elliptic leaves belonging to family *Compositae* (Mishra *et al*., 2010). It is frequently called by different names as, honey, candy and sweet leaf. In India, it is known by local names like "Metthi Patti" & "Cheeni-Tulsi" (Kumar *et al.,* 2008). Around 150 species known of *Stevia* family, most common are *Stevia rebaudiana, S. dianthoidea*, *S.Phlebophylla, S. bertholdii, S. micrantha*, *S. ovata*, *S. plummerae*, *S.salicifolia*, *S. serrata* and *S. viscid.* The plant is indigenous to the northern regions of South America but *different* varieties of Stevia are cultivated in many countries including Japan, Malaysia, Taiwan, Philippines, Hawaii etc. It is successively cultivated in warmer regions of India majorly in Orissa, Rajasthan, Kerala and Maharashtra. Leaves of stevia plant are known to be used as natural sweetener for centuries; it possesses various medicinal applications. Two French chemists isolated the glycosides in early nineteenth century which is secondary metabolites responsible for its sweet taste (Bridel *et al*., 1931). Glycosides are white-crystalline compounds around 300 times sweeter than sugar. Wide numbers of crude and pure Stevia products are used with beverages like tea, coffee, juices, and sherbets. Stevia in other forms like cooked, baked products & other preparations are also used as food in some parts of country. Stevia can attain height of 80 cm when it is mature, the soil pH should be of 6.5 to 7.5. *Stevia leaves are* rich in complex mixture of eight sweet diterpene glycosides or simply steviosides. These steviosides can improve and increase sweetness of several foods and drinks without adding or increasing the calorie consumption. Due to this reason stevia products are gaining popularity as a healthy alternate of sugar around the world.

Apart from their low or nil calorie reputation; steviosides are scientifically proven to have direct beneficial effects on human health. Steviosides are reported to enhance skeletal muscle glucose transportation as the action of insulin on glucose transport might be improved due to the low concentration of stevioside. These steviosides have commercial value so they are producing by many industries in huge quantity (Silva *et al.,* 2008).

Apart from that its known to possess various therapeutic activities like anti-tumour, anti-bacterial (Kumar *et al.,* 2008), anti-inflammatory, anti-diarrheal, diuretic, anti-human rota-virus activities (Takahashi *et al.,*2001), anti-viral (Kedik *et al.,* 2009), antifungal (Silva *et al.,*2008), anti-hypertensive (Lee *et al.,*2001; Hsieh *et al.,*2003), anti-hyperglycaemic (Jeppesen *et al.,*2002), anti-HIV (Takahashi *et al.,*1998), hepatoprotective (Mohan and Robert, 2009) and immune modulatory effects (Jaroslav *et al.,* 2006). It is regarded as safe for consumption for everyone as it does not have any adverse effect on human body as studies confirm that it is non-terato genic, non-mutagenic/non-carcinogenic (Pol *et al.,* 2007). Stevia extract may stimulate beta cells of pancreas to secrete insulin (Esmat and Ferial, 2009).

History

Indigenous population of South America was using stevia leaves as sweetener since recorded history (Soejarto, 2002). In 1887 Moises Santiago Bertonia European botanist was the first person to work on Stevia, later on in 1931 the French chemist extracted stevioside, white crystal compound. After wards Stevia was widely utilized as sweetener. During the World War II, British army used stevia as a sweetener after experiencing food shortage. In Japan, Stevia is replaced by saccharin after long term ban in 1970s, now majority of its population is using Stevia instead of sugar. Since it possesses therapeutic value & has significant lower-calorie contribution to diet, it is widely used and easily available in markets of North America and Europe. In 1954 the first time in the world started growing stevia. In year 1995, Food & Drug Administration, USA, approved Stevia safe for human consumption. In year 2004, WHO approved Stevia and its product as safe natural sweetener and food additive based on previous studies. In year 2000, study reported overall good effect of stevia extract on pancreatic cells.

Chemical Composition

Most of the Stevia species were tested for their chemical ingredients & stevioside composition. The leaves are valuable part of the Stevia, around 110 of its species are tested for sweetness and only 18 species were found to have natural sweetness (Soejarto *et al*., 1982). Glycosides (Dulcoside-A, rebaudiosides A & E, steviolbioside and stevioside makes its leaves sweeter than sugar (Kinghorn *et al.,* 1984). Stevia rebaudiana is the sweetest amongst all known species of family *Asteraceae* it contains all ent-kaurene glycosides in good quantities (3-8% by weight of the dried leaves) (Kinghorn et al. 1984, Melis 1992). Stevia leaves are also enriched in nutrients & phytochemicals like protein, fiber, amino acids, free sugars, iminosugar steviamine, lipids, essential oils, sterebins, thiamine, niacin, beta carotene, ascorbic acid, riboflavin, austroinulin, rebaudi oxides, quercetin, isoquercitrin, xanthophyllus and trace elements (Jayaraman *et al.,*2008; Esmat and Ferial, 2009; Hu *et al.,*2010). The chemical structure of stevioside and its derivatives are presented in the Fig. 1 (Crammer and Ikan, 1987). The nutritional profiles of the leaves of *S. rebaudiana* are shown in Tables 1 to 3

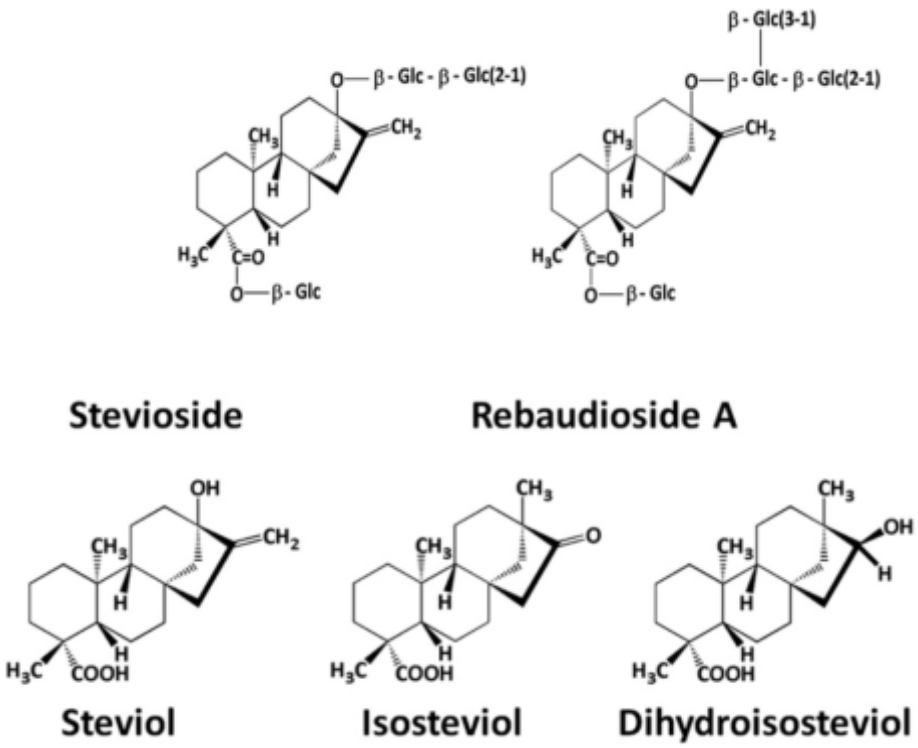

Figure 1*: Chemical structure of stevioside and other interrelated compounds found in the leaf of Stevia* (Crammer and Ikan, 1987)

Table 1: Amount of sweet glycosides in *Stevia rebaudiana* leaves (% of the leaves dry weight).

References							
Glycoside	**Kinghorn & Soejarto (1985)**	**Crammer and Ikan (1987)**	**Kolb et al. (2001)**	**Gardana et al. (2010)**	**Goyal et al. (2010)**	**Atteh et et al. (2011)**	**Jaworska al.(2012)**
Stevioside	5-10	3-10	3.78-9.75	5.8	9.1	6.5	2.5
Steviol	ND	ND	ND	ND	ND	ND	0.7
Steviolbioside	ND	ND	ND	ND	ND	ND	1.2
Rebaudioside A	2-4	1.0	1.65-7.27	1.8	3.8	2.3	5.0
Rebaudioside B	ND	ND	ND	ND	ND	ND	0.50
Rebaudioside C	1-2	ND	ND	1.3	0.6	ND	2.0
Rebaudioside D	ND	ND	ND	ND	ND	ND	3.3
Dulcoside A	0.4-0.7	0.2	ND	ND	0.3	ND	1.0

Table 2: Analysis of dried *Stevia rebaudiana* leaves (dry weight basis).

References							
Component	**Tadhani & Subhash (2006)**	**Goyal et al. (2010)**	**Kaushik et al. (2010)**	**Mishra et al. (2010)**	**Serio (2010)**	**Abou-Arab et al. (2010)**	**Atteh et al. (2011)**
Moisture	ND	4.65	7.7	7	ND	5.37	ND
Protein	20.4	11.2	12	10	11.2	11.40	16
Fat	4.34	1.0	2.7	3	5.6	3.73	2.6
Ash	13.1	6.3	6.4	11	ND	7.41	15.5
Carbohydrate	35.2	ND	ND	52	53	61.9	ND
Crude fiber	ND	15.2	ND	18	15	15.5	6.8

Table 3: Fatty acid composition of Stevia *rebaudiana* leaf extract (g 100 g_1).

References		
Fatty acids	**Tadhani and Subhash (2006)**	**Atteh et al. (2011)**
Palmitic acid (C16)	27.51	29.5
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: Concentration of water-soluble vitamins of Stevia rebaudiana leaves (mg/100 g dry base of extract).

References	
Vitamin	**Kim et al. (2011)**
Vitamin C	14.97
Vitamin B2	0.43
Vitamin B6	0.00
Folic acid	52.18
Niacin	0.00
Thiamin	0.00

Metabolism

Stevia extract (steviosides) are zero-caloric sweetner does not cause any adverse effect on the metabolism of human and animal body (Soejarto *et al.,* 1982; Geuns *et al.,* 2007). Human intestinal microbes are reported to metabolise stevioside into glucose and steviol. These bacteria consume glucose and it is not absorbed and excreted without any accumulation into body. A report suggests that steviol is not altered as observed in human waste, suggesting that steviol is the end product of *Stevioside metabolism*. A similar study also reported absorption followed by glucuronidation of steviol glycosides in the liver (Koyama *et al.,* 2003).

Therapeutic aspect of Stevia

Stevia recommended as safe for the treatment or prevention of various chronic and non-chronic diseases. Various chemical components of Stevia are responsible for treatment or prevention of various diseases like diabetes (glucoregulation), cardiovascular diseases, cancer, blood pressure, kidney diseases, obesity, inflammatory bowel diseases (IBD) and dental caries. A number of biological activities of stevia phytochemicals have been studied against various diseases which are listed in table 5.

Table 5: Activities of Stevia *rebaudiana* phytochemicals (Ahmed *et al.,* 2011)

Compounds	Activity tested	Mode of test	Dosage	conclusion
Steviol	Genotoxicity	Oral Mice	250 mg/kg 500 mg/kg 1000 mg/kg 2000 mg/kg	Negative
Stevioside	Mutagenic effect	Cell Culture	50 mg	Negative
Steviol	Mutagenic effect	Cell Culture	2 mg	Negative
Stevioside	Antireproductive Activity	Oral Hamster Femal	0.5 g/kg 1 g/kg 2.5 g/kg	Negative
Stevioside	Antireproductive Activity	Oral (rat)	0.025 g/kg	Negative
Stevioside	Insulin Enhancement	Rat	0,025 g/kg	Positive
Stevioside	Insulintropic Activity	In vitro- Mouse islent cell	1nmol/L	Positive
Stevioside	Pancreatic beta-cell stimulate	Cell Culture	1-100 micromole/L	Positive

Stevia and glucose tolerance in Diabetic patients

Diabetes has become a major disorder around the world caused due to the Insulin intolerance, pancreatic alpha cell dysfunction and comparative glucose excess (Unger, 1997). India is the country with one of the largest burdens of

Diabetic patients around 177 million peoples are suffering from Diabetes in our country. (Kolterman *et al.,* 1980). A number of studies reports improvement in condition of patient suffering from Diabetes.

Stevia containing Rebaudiana-A is safe as medicine alternative of diabetic patients. One report suggested that human insulin secretion is increased by Stevia glycosides by acting directly on β-cells without altering the K^+ - ATP channel function and cAMP level in the islets, this suggest that stevioside and steviol may act as potent antihyperglycemic agents (Jeppesen *et al.,* 2000). These claims are further consolidated by another study reported increased glucose intolerance and decreased plasma glucose level in animal and human subject after consumption of aqueous Stevia extract (Curi *et al.,* 1986). Moreover, stevioside are known to regulate blood level of glucose enhancing insulin secretion and utilization in insulin-deficient animal suggested by Chen *et al.* (2005).

A study conducted on patients suffering from Diabetes, reported where a single acute dose of stevioside (1,000 mg) was able to induce a significant reduction in the glucose level by (18%) as compared to control (Gregersen *et al.,* 2004). *S. rebaudiana leaf extract* (200 and 400 mg/kg) induced a significant ($P < 0.01$) fall in the glucose level in rats, without making them hypoglycemic (Misra *et al.,* 2011). Research provide evidence that Stevioside significantly enhances glucose-related insulin secretion, does not alter the fasting insulinemia (Chen *et al.,* 2006). In a 42 days long study, stevioside- fed diabetic rats on stevioside containing diet displayed statistically significantly improved insulin responses with suppression of glucagon secretion and attenuation of blood glucose concentration. Overall, *Stevia* possess the ability to increase the insulin effect on cell membranes, increase insulin production, stabilize glucagon secretion and sugar levels and better glucose tolerance to consumed carbohydrates and decreased post-prandial glucose in both animal models and humans (Jeppesen *et al.,*2003).

Heart disease and Stevia

Stevia sweeteners consumption is overall beneficial for human health. Its extract controls blood pressure by relaxing the muscles of the heart (Gardana *et al.,* 2010). Regular Stevia consumption has been suggested to decreases cholesterol levels (Atteh *et al.,* 2008). In circulatory system it is known to improve cell regeneration, promote blood co-agulation, suppresses neoplastic growth and strengthening of blood vessels. Rebaudiana-A from Stevia leaves also reported to prevent of Cardiovascular diseases and improvement of deranged blood pressure level. Stevia aqueous extract is suggested to decrease systolic and diastolic blood pressure. They *are reported to* act at on the plasma membrane in same way as a type of some medication known to block calcium channel in heart. (Jeppesen *et al.,* 2003; Maki *et al.,* 2008).

A clinical study on hypercholesterolemic women have reported reduction in bad cholesterol (triglycerides & LDL) & increase in level of good cholesterol (HDL), after long term stevia use it was demonstrated that Stevia had an overall good hypolipidaemic effect (Sharma and Mogre, 2007).

Other disorders and Stevia

Along with various effects of Stevia on Diabetes and heart disease, its compounds have potential anti-inflammatory properties and known to prevent inflammation and related disorders for example Inflammatory Bowel Disease (Bamias and Cominelli, 2007), Autoimmune Diseases (Atassi and Casali, 2008) Atherosclerosis, (Niessner *et al.,*2007) and Diarrhea (Kelly, 1999). An animal's-based study suggested that steviosides may inhibit contraction of intestinal smooth muscle cells which is related to Diarrhea (Shiozaki *et al.,* 2006).

Non- stevioside components of Stevia like labdane and sclareol, has strong anti-tumorous activity. The products yielded after hydrolysis of stevioside, isosteviol are known to potently inhibits DNA replication and cell growth of cancer cell lines in vitro (with LD50 values of 84 to 167 μMol) (Mizushina *et al.,*2005).

Studies also suggest that various other metabolites like stevioside, aglycones, steviol and isosteviol have been reported to inhibit Lymphoma by inhibiting Epstein-Barr virus early antigen (EBV-EA) induction (Akihisa *et al.,* 2004).

Stevia compounds are also found to be useful against kidney diseases and disorders. Melis (1992) worked on effects of steviosides on kidney function of normal and hypertensive rats. It was found that it acted as systemic vasodilator which lead to hypotension, diuresis and natriuretic in both the normal and hypertensive rats. Frequent feeding of stevioside in these rat improved the renal plasma flow (RPF) and glomerular filtration rate (GFR) caused by Stevia induced vasodilation of arterioles.

Obesity, caused by high calorie diet, a major cause of wide number of health problems including hypertension, diabetes, pulmonary malfunctions, renal problems, hyperlipidemia, pregnancy disorders and some cancers. Stevia sweeteners in beverages and foods offer low calorie alternative substitute of sugar which assist both weight control and loss by limiting or controlling calorie intake.

Dental cariesis, a common chronic disease worldwide. Stevia, as a non-nutritive sweetener can give good oral health benefits and protection against dental cariesis (Wu *et al.,* 1998)

Liquid extract of Stevia has the ability to help remove skin problems. Some unconfirmed studies also suggest effectiveness of Stevia extract against common skin ailments like acne, dermatitis, seborrhea eczema, etc. Good healing properties are evident when Stevia is placed on injury cuts and wounds. Recent observations also indicated that Stevia prepration is believed to smoothen skin, improve shining & reduces wrinkles (Shiozaki *et al.,* 2006).

Globally uses of Stevia

Stevia is quickly becoming popular in Asia, South America, Europe and USA. It gained permission for use as foods and beverages in a number of countries including Australia, Brazil, China, India, Japan, Korea, Malaysia, Mexico, Uruguay, NewZealand, Switzerland, Taiwan, Russia Ukraine and Several new Stevia containing products from consumables to beverages are launched every year. Plenty of research work proves that stevia consumption has no bad effects on human health (Esmat and Ferial, 2009).

Table 6: Uses of stevia. (Taylor, 2005)

Country	**Uses of Stevia**
Brazil	Dental Cavities, diabetes, hypertension, depression, fatigue, hyperglycemia, infections, obesity, sweet cravings, tonic, urinary infections, wounds
Paraguay	Diabetes
South America	Diabetes, infections, hypertension and obesity
United States	Diabetes, hypertension, hyperglycemia, infections, vasodilator

Uses in India

In last few decades India has seen rapid modernization. Income of people has increased significantly. This rapid growth is parallel with change in lifestyle and habits. Currently, India is only next to China in incidence and mortality related of Diabetes. The food regulatory authority of Indian - Food Safety and Standards Authority of India (FSSAI) had recently cleared the consumption of Stevia in India. It can become a safe alternate of sugar without affecting the health of individuals using it.

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