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Stevia: Medicinal Miracles and Therapeutic Magic

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ABSTRACT

Stevia (*Stevia rebaudiana* Bert., Asteraceae) has drawn the attention of health conscious fitness lovers all over the planet as a non-caloric sweetener. It was regarded by almost the whole world replacing saccharin. The major sweet compounds that are isolated from the stevia leaves are several glycoside compounds including stevioside, steviolbioside, rebaudiosides and dulcoside. Studies found that kaempferol can reduce risk of pancreatic cancer by 23%. Taking stevioside as a supplement can reduce blood pressure. Stevia has been studied in diabetic patients with impressive results. Stevia has also been shown to have anti-inflammatory, anti-cancer, diuretic and immunomodulatory effects. Being a non-carbohydrate sweetener, stevia would not favor the growth of *Streptococcus mutans* bacteria in the mouth which is attributed to be a causative agent of dental caries and tooth cavities. An extract can be obtained as a tincture of alcohol or glycerin. The concentrated stevia extract tincture can also be dried and purified to produce a fine white powder containing the full spectrum of steviosides. The paper presents a comprehensive review on present status, plant profile, composition, structure of major active compounds, their mode of action and research studies on medicinal benefits and therapeutic implications of *S. rebaudiana* across the globe.

Key words: Stevia, sweetener, stevioside, diabetes, health benefits, therapeutics

INTRODUCTION

Stevia rebaudiana (Bert.) is a herbaceous perennial plant of the Asteraceae family. The crop is native to Paraguay and by mid-1970s, standardized extract and pure stevioside was utilized commercially in Japan for sweetening and flavouring foods and beverage as a substitute for several synthetic sweeteners. Leaves of this plant produce zero-calorie ent-kaurene diterpene glycosides (stevioside and rebaudiosides), a non-nutritive, high-potency sweetener, and substitute to sucrose, being 300 times sweeter than sucrose (Ahmed *et.al*.,2011). It is recommended for diabetes and has been extensively tested on animals and has been used by humans with no side effects.

Stevia, commonly known in Sanskrit as "madhu patra," meaning sweet leaf is a natural and healthy alternative to sugar and artificial sweeteners. It is also known as "honey yerba" and "honeyleaf" and by some other variations of these names. It is a famous perennial shrub, belongs to the family Asteraceae, genus *Stevia* and species *rebaudiana*. It is extensively grown in the subtropical regions, and has been available since decades for its wide use as a

sweetener in beverages and to mask the bitter taste of certain herbal medicinal also been reported that *S. rebaudiana*, as a non-calorie first natural sweetener used in medicinal green teas for treating heart burn and other ailments (Vanek *et.al*., 2001) even though there are more than 200 species of the genus *Stevia*, only *S. rebaudiana* gives the sweetest essence (Savita *et.al.,* 2004). Japanese have been using stevia and its products in cooked or baked goods, processed foods and beverages, fruit juices, tobacco products, pastries, chewing gum and sherbets (Brandle, 1992)As it possesses flavor enhancing property, it is used in food products and soft (Carakostas *et.al.,* 2008). Today it is widely cultivated in countries like China, Korea, Thailand, Brazil, Peru, Paraguay and Israel.

Apart from its sweetness stevioside along with related compounds which include rebaudioside A and steviol offer many therapeutic benefits that include antihypertensive, antidiabetic, anti-inflammatory, anti tumor, antioxidant, antidiarrhoeal, diuretic and immunomodulatory actions. Steviol interacts with the drug transporters and for this property of its, Steviol is proposed as drug modulator (Goyal *et.al*., 2010, Boonkaewwan *et.al*., 2008 and Chatsudthipong, 2009). *S. rebaudiana* is used for the treatment of various conditions such as cancer (Yasukawa et al. 2002), diabetes (Lailerd *et al*. 2004), obesity, cavities, hypertension (Dyrskog *et al*., 2005), fatigue, depression, and yeast infection. It possesses hypoglycemic, hypotensive, vasodilating, taste improving, sweetening, anti-fungal, anti viral, anti inflammatory, anti bacterial properties and increases urination function of the body. It has been found to be non toxic, non addictive, non carcinogenic, non mutagenic, plants in several countries like Brazil, Japan, and Paraguay (Parsons, 2001). It has non teratogenic and is devoid of genotoxic effect. It does not affect blood sugar level hence safe for diabetics (Alan 2002). Keeping in mind the sweetening property and other medicinal uses of *Stevia rebaudiana*, an attempt has been made to explore the use of *Stevia rebaudiana* as a sweetener in comparison with the other sweetener available in the market, so that the diabetic and calorie conscious people can add variety to the diet and relish the food.

The paper presents a comprehensive review on present status, plant profile, composition, structure of major active compounds, their mode of action and research studies on medicinal benefits and therapeutic implications of S. *rebaudiana* across the globe.

PRESENT STATUS

Stevia is native of Paraguay and Brazil. It is cultivated primarily in South America and Asia. Countries growing Stevia include Paraguay, Brazil, Canada, USA, China, Korea, Taiwan, |Japan, and United Kingdom. Worldwide, more than 100000 hectares are reported to be covered under Stevia cultivation of which China has a major chunk. Major food companies used Stevia extracts to sweeten the foods for sale in Japan, Brazil and Paraguay etc (Parsons, 2001). Until recently, stevia products could be marketed in the U.S. only as dietary supplements. However, a new U.S. Food and Drug Administration (FDA) ruling has cleared the way for stevia's expanded use and increased the market potential of this crop. Stevia has huge demand potentials in India, since it is a natural sweetner without

calories, particularly considering the huge diabetic population in this country. Though Stevia is cultivated in India at present, but it is only in a few hundred hectares and the production is very negligible. All India import figure of Stevia extract is around 5 tonnes per annum. Stevia production, particularly considering the fact that it is around 300 times sweeter than sugar, will elegantly meet the requirement of pharmaceutical industries and soft drink industries in India (Ahmed *et. al*., 2011).

PLANT PROFILE

Stevia rebaudiana belongs to the family Asteraceae (Kingdom- Plantae,Order- Asterales, Family- Asterceae, Tribe- Eupatoricae). The genus *Stevia* comprises about 240 species, out of which the important ones are namely *S. anisostemma, S. micrantha, S. bertholdii, S. ovate S.crenata, S. plummerae, S. dianthoidea, S.salicifolia, S. enigmatica, S. serrata, S. eupatoria, S. vircida, S. lemmonii* etc. Stevia, sweet leaf of Paraguay, is also commonly known as sweet-herb, honey yerba, honey leaf, yaa waan and candy leaf. It is a perennial shrub that grows up to one metre and has 2-3 cm long ovate leaves. The colour of leaves are green, having no odour which taste sweet. Moreover the leaves are petiolate, acuminate, faces are glabrous, planted cross wise. Flowers are white, throats funnel form, lobes five.

For hundreds of years, indigenous people in Brazil and Paraguay have used the leaves of Stevia as a sweetener. They have also used Stevia to sweeten other teas and food and have used it medicinally as a cardio tonic, for obesity, hypertension and heartburn and also to help lower uric acid level. In addition to being a sweetener, Stevia is considered to be hypoglycemic, diuretic, cardio tonic and tonic. The leaf is used for diabetics, obesity, hypertension, fatigue, depression, sweet cravings and infection.

Fig a. Stevia Herb

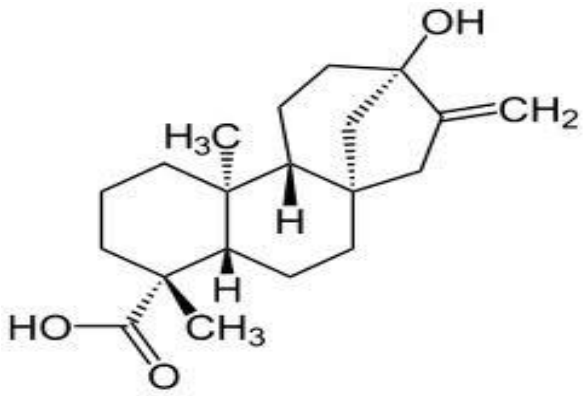
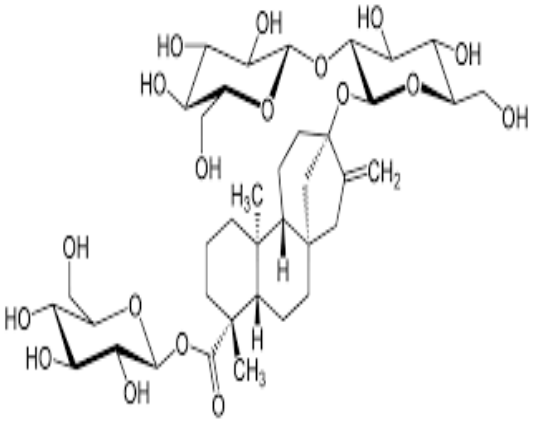


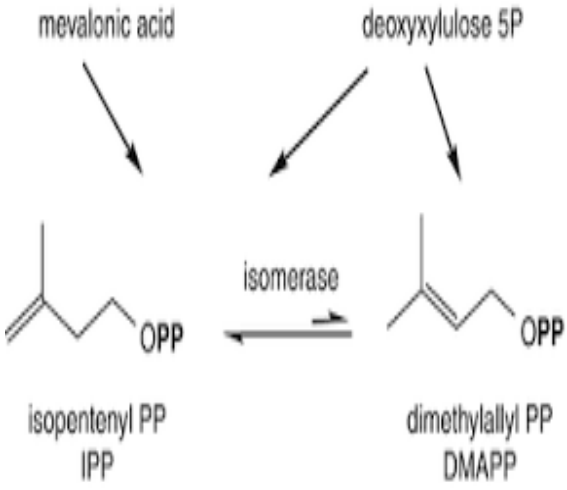
Fig b. Steviol

For hundreds of years, indigenous people in Brazil and Paraguay have used the leaves of Stevia as a sweetener. They have also used Stevia to sweeten other teas and food and have used it medicinally as a cardio tonic, for obesity, hypertension and heartburn and also to help lower uric acid level. In addition to being a sweetener, Stevia is considered to be hypoglycemic, diuretic, cardio tonic and tonic. The leaf is used for diabetics, obesity, hypertension, fatigue, depression, sweet cravings and infection.

CHEMICAL CONSTITUENTS OF *Stevia rebaudiana*

Over 100 photochemicals have been discovered in Stevia. It is rich in terpenes and flavonoids. It consists of eight glycosides named as stevioside (5-10%, Fig b), steviolbioside, rebausiosides A-E (1-2%), and dulcoside A(0.4- 0.7%). of these eight glycoside, the one called stevioside (Fig c) is 300 times sweeter than sugar.





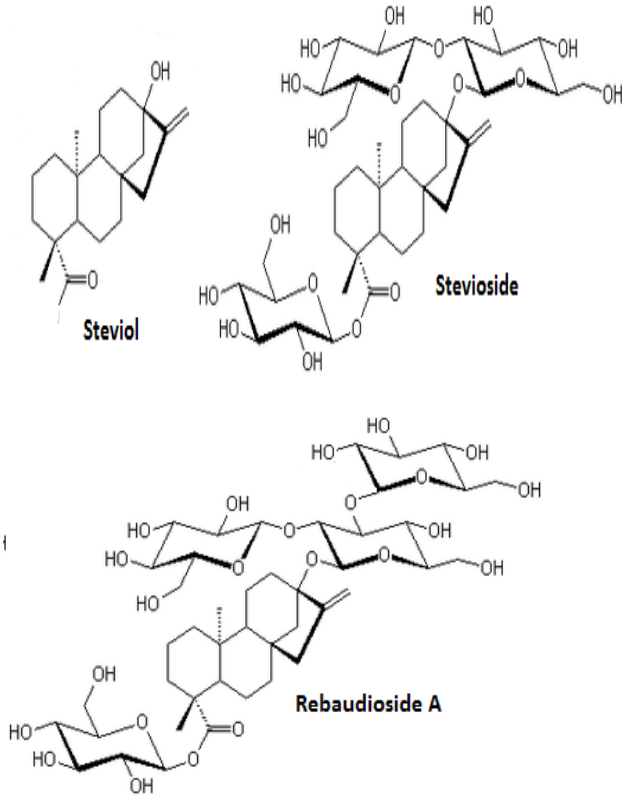


Fig c. Stevioside

The *Stevia* plant has sweet components in leaves called steviol glycosides(Fig d), which share a common steviol backbone. Carbohydrate residues (mainly glucose) are attached to the steviol backbone in various configurations to form the wide variety of sweet compounds found naturally in the stevia leaf. Steviol glycosides are poorly absorbed in the body and pass through the upper gastrointestinal tract, including the stomach and small intestines, fully intact. Once steviol glycosides reach the colon, gut bacteria hydrolyze steviol glycosides into steviol by snipping off their glucose units. Steviol is then absorbed via the portal vein and primarily metabolized by the liver forming steviol glucoronide, and then excreted in the urine Research has shown that there is no accumulation of stevia (or any by-product of stevia) in the body during metabolism. It is a result of this essentially

Table1: Chemical compounds present in Stevia

Trivial name	Formula	MW (g/mol)	Conversion factor X
Steviol	$C_{20}H_{30}O_3$	318.45	1.00
Stevioside	$C_{38}H_{60}O_{18}$	804.87	0.40
Rebaudioside A	$C_{44}H_{70}O_{23}$	967.01	0.33
Rebaudioside C	$C_{44}H_{70}O_{22}$	951.01	0.34
Dulcoside A	$C_{38}H_{60}O_{17}$	788.17	0.40
Rubusoside	$C_{32}H_{50}O_{13}$	642.73	0.50
Steviolbioside	$C_{32}H_{50}O_{13}$	642.73	0.50
Rebaudioside D	$C_{50}H_{80}O_{28}$	804.87	0.40
Rebaudioside E	$C_{44}H_{70}O_{23}$	967.01	0.33
Rebaudioside F	$C_{43}H_{68}O_{22}$	936.99	0.34

poor absorption in the digestive tract which ultimately contributes to the fact that stevia has zero calories and does not raise blood glucose or insulin levels when digested.

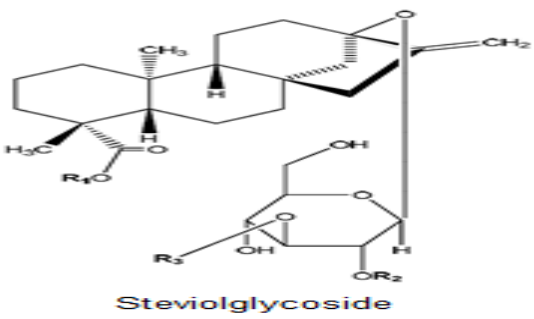


Fig d. Steviol glycoside

There are multiple steviol glycosides that have now been approved for use including those listed in the table below. The formulas and molecular weights vary, as does the conversion factor which allows for the calculation of "steviol equivalents". Notably, global regulatory agencies have created maximum use limits in their respective safety assessments which are expressed as steviol equivalents to account for the varying chemical structures of the steviol glycosides approved for use. Through the use of this conversion factor, the limits are adjusted accordingly to reflect the molecular weight of each given steviol glycoside.

CHEMICALS FOUND IN *Stevia rebaudiana*

Apigenin-4'-o-beta-d-glucoside, austroinulin, avicularin, beta-sitosterol, caffeic acid, campesterol, caryophyllene, centaureidin, chlorogenic acid, chlorophyll, cosmosiin, cynaroside, daucosterol, diterpene glycosides, dulcosides A-B, foeniculin, formic acid, gibberellic acid, gibberellin, indole-3-acetonitrile, isoquercitrin, isosteviol, jhanol,

kaempferol-3-o-rhamnoside, kaurene, lupeol, luteolin-7-o-glucoside, polystachoside, quercetin, quercitrin, rebaudioside A-F, scopoletin, sterebin A-H, steviol, steviolbioside, steviolmonoside, stevioside, stevioside a-3, stigmasterol, umbelliferone, xanthophylls, etc are the common chemicals found in Stevia.

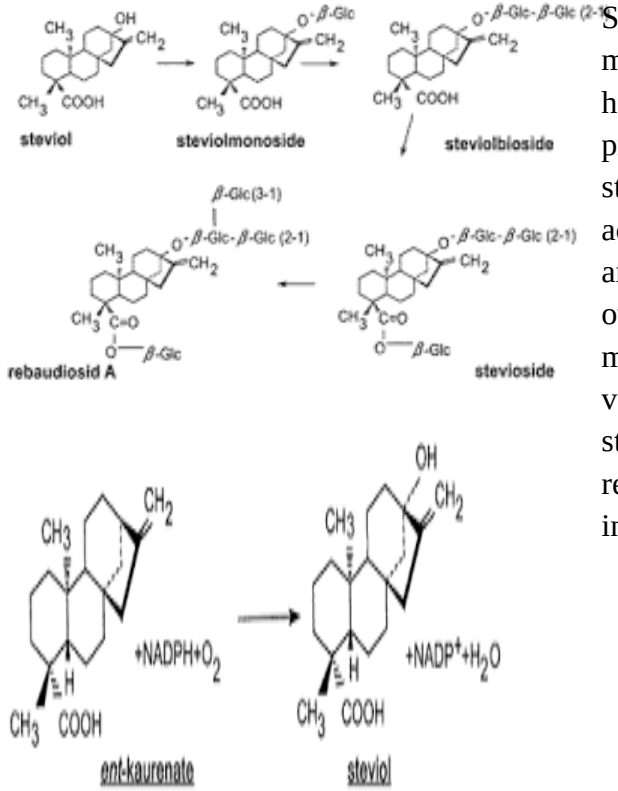


Fig e. Transglycosidation of steviol to form steviollmonoside, stevioside & rebaudiosideA

MODE OF ACTION

Glycosides contain glucose and other non-sugar substances called aglycones. The tongue's taste receptors react to the glucose in the glycosides: those with more glucose (rebaudioside) taste sweeter than those with less (stevioside) (Anonymous, 2015). Some of the tongue's bitter receptors react to the aglycones. In the digestive tract, rebaudiosides are metabolised into stevioside which is subsequently broken down into glucose and steviol. The glucose released in this process is used by bacteria in the colon and not absorbed into the bloodstream (Koyama et al, 2003). Steviol cannot be further digested and is excreted.

MEDICINAL AND ETHNO-MEDICINAL IMPORTANCE

Stevia has its legendary due to its various mode of actions such as, sweetener, hypoglycemic, hypotensive (lowers blood pressure), cardiotonic (tones, balances and strengthens the heart), antimicrobial activities (Taylor, 2005). Different studies and documents proved that stevia has its own and natural constituents which are very much helpful for human health. Among various uses, sweetener is the main use of stevia. Some ethnological uses has been recorded (Taylor, 2005) which are enlisted in the table (Table 2):

Table2: Ethnomedicinal uses of stevia in different countries

Country	Ethnomedicinal uses
Brazil	Usually used for cavities, depression, diabetes, fatigue, heart support, hypertension, hyperglycemia, infections, obesity, sweet cravings, tonic, urinary insufficiency, wounds
Paraguay	Diabetes
South America	diabetes, hypertension, infections, obesity
United States	candida, diabetes, hypertension, hyperglycemia, infections, and as a vasodilator

THERAPEUTIC IMPLICATIONS

Anti-hyperglycemic effect

Stevia has a revitalizing effect on the beta cells of pancreas, also improves insulin sensitivity and promotes additional insulin production. Chen *et al*., 2005 revealed that stevioside was able to regulate blood glucose levels by enhancing not only insulin secretion but also insulin utilization in insulin deficit rats. The later was due to decreased phosphophenol pyruvate carboxykinase gene expression in rat liver by stevioside's action of slowing down glucogenesis. Stevioside reduces the postprandial blood glucose levels. Several human trials conducted in normal healthy volunteers have shown that extracts of *Stevia rebaudiana* leaves could increase glucose tolerance in humans. Therefore stevia may be advantageous in the treatment of type 2 diabetes (Jeppesen *et al*., 2006, Chen *et al*., 2005, Anton *et al.,* 2010, Gregersen *et al.,* 2004 and Barriocanal *et al*., 2008).

Anti hypertensive effect

Physiological and Pharmacological experiments have suggested that stevioside from the leaves of stevia act as a typical systemic vasodilator. Melis MS et al in their studies have demonstrated that stevioside from *Stevia rebaudiana* leaves provoked hypotension, diuresis and natriuresis in both normal and hypertensive rats. An increase in the renal plasma flow and glomerular filtration in rats had been observed in normal rats and the effect was attributed to the vasodilatation of afferent and efferent arterioles (Melis, 1996 and Melis, 1995). Human studies have also suggested its beneficial role in hypertension for its vasodilator property. It was suggested that 750 – 1500 mg/ day of stevioside, reduces systolic blood pressure by 10 – 11 mmHg and diastolic blood pressure by 6 -14 mmHg within one week of starting the treatment (Ferri *et al*., 2006 and Maki *et al*., 2008). It is found that stevioside causes vasorelaxation by inhibition of Ca^{++} influx into the blood vessels (Ulbricht *et al*., 2010). Therefore, stevia could prove to be beneficial in hypertensive patients.

Anti-oxidant effect

Being natural stevia is potential source of natural antioxidants. Varieties of antioxidants were obtained from the extracts of *Stevia rebaudiana*, they include, opigenin, kaempferol and quereitrin that inhibited DNA strand damage. Isosteviol, a derivative of stevioside inhibits angiotensin II induced cell proliferation and endothelin I secretion while attenuation of reactive oxygen species generation (Ghanta *et al.,* 2004 and Stoyanova *et al.,* 2011). Hence it could be beneficial in a variety of diseases like cancer, reproductive problems and developmental defects.

Anti -cancer effect

Although limited evidence are available, animal studies by Yasukawa *et al* 2006 indicate that the four isolates of steviol glycoside - stevioside, rebaudiosides A & C and ducloside A from *Stevia rebaudiana* have a strong inhibitory effect on 12- 0-tetradecanoylphorbol-13-acetate (TPA) induced inflammation in mice which is suggestive of its anticancer effect (Raskovic *et al*., 2004 and Yasukawa, 2002).

Antimicrobial effect

The ability of Stevia to inhibit the growth and reproduction of bacteria and other infectious organisms is important in at least two respects. First, it may help to enhanced products report a lower incidence of colds and flues, and second, it has fostered the invention of a number of mouthwash and toothpaste products. Tadhani M. B. and Subhash R. (2006) reported that *Streptococcus mutans, Pseudomonas aeruginos, Proteus vulgaris* and other microbes do not thrive in the presence of the nonnutritive Stevia constituents. This fact, combined with the naturally sweet flavour of the herb, makes it a suitable ingredient for mouthwashes and for toothpastes. The patent literature contains many applications for these kinds of Stevia based products. Stevia has even been shown to lower the incidence of dental caries. Evidential research reports indicate that derivatives prepared by stevia isolates which included octa - acetylombuoside, ombuine and retusine were found to have antimicrobial action against few types of gram positive bacteria (Tomita et al., 1997). Jayaraman et al (2008) revealed that the antimicrobial and antitumor activities of Stevia rebaudiana leaves extracted using various solvents, and is therefore, a potential drug that requires further studies and development.

Anti-inflammatory and immuno-modulatory effect

Anti-inflammatory refers to the property that reduces inflammation or swelling. Anti-inflammatory drugs make up about half of analgesics, remedying pain by reducing inflammation as opposed to opioids, which affect the central nervous system. Stevia has been found to attenuate synthesis of the inflammatory mediators in LPS stimulated THP-1 cells by interfering with the I Kappa B kinases (IKKbeta) and Kappa B signaling pathway thus beneficial as anti-inflammatory and immunomodulatory substance (Bookaewan *et al.,* 2006). Stevia is also rich in beta carotene, ascorbic acid, protein, calcium, iron, magnesium, phosphorus and numerous other phytochemicals. Hence the herbal derivative apart from its sweetening property also is beneficial with its nutritive value. Other proposed uses include alcohol abuse, anti-inflammatory, anti-mutagenic, antitumor, diuretic, digestive aid, food additive, immunomodulation and obesity (Chatsudthipong, 2009).

Drug interactions

Stevia has diuretic effect so it decreases the excretion of lithium with resultant increase in plasma lithium concentration and leads to lithium toxicity (Melis, 1996). Given along with antidiabetic agents like glimepride, pioglitazone etc. may cause decrease in blood sugar levels hence needs close monitoring of blood sugar levels. Stevia plant which interact with monoketocholate (a substance that may affect glucose and lipid levels), diuretics, anti-inflammatory, anticancer agents or hypocalcaemia agents (Raskovic *et al.,* 2004).Verapamil tends to increase the renal and systemic effects of stevia (Melis, 1991).

Hypoglycaemic action

Hypoglycemia, is known as low blood sugar is when decreases to below normal and symptoms including clumsiness, trouble talking, confusion, loss of consciousness, seizures, or death. A feeling

of hunger, sweating, shakiness, or weakness may also be present. Hypoglycemia, is known as low blood sugar is when decreases to below normal and symptoms including clumsiness, trouble talking, confusion, loss of consciousness, seizures, or death. A feeling of hunger, sweating, shakiness, or weakness may also be present. (Yanai *et al*., 2015; Schrier, 2007) hypoglycemia caused kidney failure,certain tumors, liverdisease, hypothy roidism, starvation, inborn error of metabolism,severe infections, reactive hypoglycemia, and a number of drugs including alcohol.(Schrier, 2007). Low blood sugar may occur in babies who are otherwise healthy who have not eaten for a few hours. (Perkin, 2008).

It is probably the presence of the steviosides themselves that has made stevia effective for hypoglycemic action. Stevia is believed to be helpful for hypoglycemia and diabetes because it nourishes the pancreas and thereby helps to restore normal pancreatic function. Oviedo, et.al., (1970) reported a 35.2% fall in normal blood sugar levels 6-8 hours following the ingestion of a Stevia leaf extract. Other workers (Singh *et al.,* 2013; Jeppensen *et al.,* 2003; Kinghon *et al* 2002; Chen *et al.,* 2005) have reported similar trends in humans and experimental animals. Peoples of Paraguay use Stevia leaf tea in the treatment of diabetes. Similarly, in Brazil, Stevia tea and Stevia capsules are officially approved for sale for the treatment of diabetes although, Stevia does not normally lower blood glucose levels.Till to date, however, almost all research findings on the effectiveness of stevia remained inconclusive. The mild acting nature of the plant and its total lack of toxic side effects argue against the need for extensive and expensive research programs. However, many of the anecdotes reporting a definite and significant blood sugar lowering action in diabetics, and a pronounced exhilarating effect in hypoglycaemic, are sound enough to justify considerable experimental work in the area.

Cardiovascular action

Significant research work has been done on the effects of Stevia and stevioside on cardiovascular functioning in man and animals. Some of this work was simply looking for possible toxicity, while some was investigating possible therapeutic action. In neither case have significant properties been found. When any action at all is observed, it is almost always a slight lowering of arterial blood pressure at low and normal doses, changing to a slight rise in arterial pressure at very high doses. The most curious finding is a dose dependent action on heartbeat, with a slight increase appearing at lower doses, changing to a mild decrease at higher doses. In both instance is the result remarkable, and it is extremely doubtful that humans would experience any effect at normal doses. The long-term use of Stevia would probably has a cardiotonic action, that is, would produce a mild strengthening of the heart and vascular system.

Digestive Tonic Action

Brazil literature shows that Stevia ranks high among the list of plants used for centuries by the "gauchos" of the southern plains to flavour the bitter medicinal preparations used by that nomadic culture. For example, it was widely used in their "mate." Through much experimentation, these people learned that Stevia made a significant contribution to improved

digestion, and that it improved overall gastrointestinal function. Likewise, since its introduction in China, Stevia tea, made from either hot or cold water, is used as a low calorie, sweet-tasting tea, as an appetite stimulant, as a digestive aid, as an aid to weightmanagement and even for staying young.

Effects on the skin

liquid extract of Stevia has the ability to help remove skin problems. Researchers reported that it is effective when applied to acne, seborrhea, dermatitis, eczema, etc. When placed directly in cuts and wounds a more rapid healing without scarring is evidenced. Frequent application of Stevia poultices and extracts is believed to smoothen skin with softer feelings when touched. Stevia is also known for skin shining and tightening properties, and has found its way in several commercial skin tighting product or anti-wrinkle product.

ADVERSE EFFECTS AND CONTRAINDICATIONS

- Stevia is considered to be safe, with minimal side effects that include; nausea, abdominal fullness, myalgia, muscle weakness, dizziness, asthenia and allergy (Genus, 2003 and Goyal *et al*., 2003) and also used with caution in diabetes as it is known to reduce the blood sugar levels.
- In hypertensive patients it is used with caution as it is likely to reduce the blood pressure.
- It may affect the renal activity and perfusion, sodium excretion and urinary flow hence, cautious use is indicated in patients with renal disease or with impaired renal function (Melis, 1996).
- With lack of evidence for its effect on pregnancy and lactation. Stevia is not recommended during pregnancy and lactation.

CONCLUSION

Stevia is now being used worldwide. Its medicinal values and stimulating actions are time tested. The busy and stressful life styles of present days alarmingly increase the incidence of diabetes, hypertension and obesity particularly affecting the young adults. These are to be addressed properly or a serious consequence is inevitable. Among various chemical constituents of stevia, stevioside has a potential mode of actions in controlling type 2 diabetes. Therefore, it has attracted all the attention of people so that it may be used safely. The huge demand, promts the biotechnology companies to produce stevia through tissue culture in a commercial scale and marketing stevia in different form such as leaf powder, liquid and fresh leaves. Moreover, Stevia having a natural sweetening activity and pharmaceutical properties, it can be a part of high throughput biotechnological techniques for animal health studies. Stevia is a natural sweetener with virtually calorie free status causes less harm, benefits several health conditions and has a bright future in the days ahead.

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