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A Brief Account of Phytochemical and Pharmacological Properties of Stevia Rebaudiana Bertoni

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Abstract

Stevia rebaudiana Bertoni (Asteraceae) is a shrub like plant.it is also known as candy leaf plant because its leaves contain sweeteners like glycoside – stevioside, steviolbioside, rebaudiosides A, B, C, D, and E and also Dulcoside which is 100-300 more time sweetner than sucrose. *Stevia rebaudiana* is a versatile herb. Its leaves powder and extract are extremely intensive natural health promoting sweetener. Its high phenolic and flavonoid content are used as a good source of antioxidant. There are many minerals like sodium, potassium, copper, manganese, phosphorus, iron, nickel etc. present in the leaves of stevia. It is beneficial in the regulation of blood pressure, regulation of glucose, control the obesity and multiple health benefits to humans including hypotensive, antidiabetic, anticariogenic, antioxodative, antimicrobial, anti-tumor and anti-inflammatory.

Keywords: Stevia, Stevioside, Steviolbioside, Rebaudiosides, Antidiabetic, Anticariogenic, Antioxodative.

Introduction

Stevia rebaudiana appertains to a genus of Asteraceae family. It is one of the 154 known members of this family. It is also known as Sweet leaf, Sweet herb of Paraguay, honey leaf and candy leaf. It is found as perennial semi-shrub with height of 30cm. its leaves are sessile and 3-4cm long, lanceolate or spatulate shape with blunt tipped lamina, its margin is serrate in middle to the tip. The stem is weak and woody. Its rhizome has branched roots. Flowers are composite surrounded by inolucre of epicalyx. Flowers are purple, pentamerous and fruits are five ribbed spindle shape achene.

Stevia leaves are loaded with different types of chemicals. Among the chemicals are nine essential amino acids viz. glutamate, aspartate, methionine, tyrosine, proline, alanine, isoleucine, lysine, and serine. All essential amino acids are present in the leaves of Stevia with an exception of tryp tophan. In addition to that, fatty acids, namely, linoleic acid, linolenic, oleic, stearic, palmitoleic, and palmitic acid, were found present. Moreover, vitamins such as vitamin B12, vita min C, and folic acid were also present, along with minerals such as calcium, phosphorus, magnesium, iron, sodium, zinc, and potassium. Not only that, phytochemicals, namely, β-carotene, thiamine, steviol, stevioside, riboflavin, rebaudi oxides, nilacin, dulcoside, and austroinullin, were detected in the plant leaves. According to experiments the anthraquinones, reducing compounds, triterpenes, sterols, saponins, cardiac glycosides alkaloids, and tannins are found in the Stevia leaves. Terpenes, phenols, coumarins and flavonoids dominate in terms of chemical composition in the Stevia leaves.

Glycosides found in Stevia have a common backbone structure, which are given an umbrella term, steviol glyco side. These chemicals are diterpenes with four rings. The sweet taste is rendered by the C-13 hydroxyl group and C 19 carboxyl group. Stevioside, steviolbioside, isosteviol, and rebaudioside A, B, C, D, E, and F are the major glycosides present in the herb. Stevioside and rebaudioside C and A are 250-300, 50-120, and 250-450 times sweeter than can sugar, respectively. Rebaudioside A and D are convertible to rebaudioside B under alkaline hydrolysis. The duo is highly soluble and can be metabolized in the human body without side effects. The most attractive attributes of the two are that they are thermostable (up to 200°C), highly water soluble, pH stable, and do not ferment.

THERAPEUTIC VALUES OF *Stevia Rebaudiana*

Leaves *of Stevia rebaudiana* has been recommended as a treatment against various chronic and non-chronic diseases like diabetes, cardiovascular disease, cancer, renal disease, obesity, inflammatory bowel disease and dental caries. Glucoregulation Diabetes mellitus (DM) is a group of diseases characterized by hyperglycemia and varying degrees of an insufficient insulin effect. According to the World Health Organization (WHO, 2004), there are approximately 177 million people with diabetes worldwide. The global prevalence of diabetes will go up from 8.6% in 2012 to 9.8% in 2030 and the numbers of people affected with diabetes will go up from 285 to 435 million. India leads the world with the largest number of diabetic subjects, earning the dubious distinction of being termed the ―diabetes capital of the world‖. Stevia leaf extract has been used traditionally in the treatment of diabetes (Megeji et al., 2005; Soejarto et al., 1982). Their ingestion causes a slight suppression of plasma glucose levels and significantly increased glucose tolerance in normal adult humans (Curi et al., 1986). Steviol glycosides have an enhancing effect on insulin secretion by directly acting on β-cells without altering the K+ - ATP channel activity and cAMP level in the islets, thus documenting stevioside and steviol as potent antihyperglycemic agents (Jeppesen et al., 2000). Stevioside regulate blood glucose levels by enhancing not only insulin secretion, but also insulin utilization in insulin-deficient rats; which was due to decreased phosphoenolpyruvate carboxykinase (PEPCK) gene expression in rat liver by stevioside's action of slowing down gluconeogenesis suggested by Chen et al. (2005). Study conducted in diabetic humans, where a single acute dose of stevioside (1,000 mg) was able to reduce the postprandial area under the curve (AUC) of glucose by 18% relative to control (1 g corn starch) and appeared to benefit the insulin:glucose ratio in serum by 40% (Gregersen et al., 2004). The medicative effects of medium-polar (benzene:acetone, 1:1 v/v) extract of leaves from S. rebaudiana (family Asteraceae) on alloxan-induced diabetic rats was studied. Medium-polar leaf extract of S. rebaudiana (200 and 400 mg/kg) produced a delayed but significant ($P < 0.01$) decrease in the blood glucose level, without producing condition of hypoglycemia after treatment, together with lesser loss inthe body weight as compared with standard positive control drug glibenclamide (Misra et al., 2011). Stevioside also enhances glucose-stimulated insulin secretion, but does not affect fasting insulinemia (Xiao and Hermansen, 2005; Chen et al., 2006). In a 6-week study, stevioside- fed diabetic rats displayed significantly enhanced first phase insulin responses with concomitant suppression of glucagon secretion and attenuation of blood glucose concentration excursions (Jeppesen et al., 2003). The effects of Stevia leaves and its extracted polyphenols and fiber on streptozotocin induced diabetic rats were studiedand found that Stevia leaves have a significant role in alleviating damage in the streptozotocin-diabetic rats besides its hypoglycemic effect and it also reduce the risk of oxidative stress (Shivanna et al., 2013). Overall, Stevia possess the ability to increase the insulin effect on cell membranes, increase insulin production, stabilize glucagon secretion and blood sugar levels, and improve glucose

tolerance to ingested carbohydrates and lower post-prandial blood sugar levels in both animals and humans. In other words, Stevia is shown to provide a comprehensive set of mechanisms that counter the mechanics of type II diabetes and its eventual complications. Thus, sugars can be replaced with steviol glycosides or stevioside of Stevia leaf to support healthy glucoregulation. The addition of leaves of Stevia, dried or in powder form in supplementary food products of diabetic patients aid in increasing the natural sweetness and also help in rejuvenating the pancreatic gland.

Renal function

Globally, there are nearly 70 million people with kidney disease of varying severity levels. Chronic kidney disease resulted in 400,000 deaths in 1990 and 735,000 deaths in 2010 (Lozano, 2012). The kidneys are essential organs for maintaining many aspects of the internal environment of the body. The main function of kidney is to maintain homeostatic balance with respect to fluids, electrolytes, and organic solutes. Various disease conditions may affect the kidney and disturb the normal functioning of the nephrons. Melis (1992) studied the effect of stevioside from the leaves of S. rebaudiana on renal function of normal and hypertensive rats. Analysed stevioside acts as a typical systemic vasodilator which provoked hypotension, diuresis and natriuresis in both the normal and hypertensive rats. Constant administration of stevioside in both normal and hypertensive rats increase the glomerular filtration rate (GFR) and renal plasma flow (RPF) which was due to vasodilation of both the afferent and efferent arterioles. Study was designed to explore the direct effect of stevioside on transepithelial transport of p-aminohippurate (PAH) in isolated S2 segments of rabbit proximal renal tubules using in vitro micro perfusion. Findings suggest that stevioside, at a pharmacological concentration of 0.70 mM, inhibits transepithelial transport of PAH by interfering with the basolateral entry step, the rate-limiting step for transepithelial transport. The lack of effect of stevioside on transepithelial transport of PAH on the luminal side and its reversible inhibitory effect on the basolateral side indicate that stevioside does not permanently change PAH transport and should not harm renal tubular function at normal human intake levels (Jutabha et al., 2000). Yuajit et al. (2013) studied the inhibitory effect and detailed mechanisms of steviol and its derivatives on cyst growth using a cyst model in Madin-Darby canine kidney (MDCK) cells. Results revealed that steviol retards MDCK cyst progression, first by directly inhibiting cystic fibrosis transmembrane conductance regulator (CFTR) chloride channel activity and second by reducing CFTR expression, in part, by promoting proteasomal degradation of CFTR. Steviol and its analogs represent promising natural plant-based drug candidates for treatment of polycystic kidney disease.

Obesity

Obesity is the most common nutritional disorder; it is a state of excess accumulation of fat in the body. In clinical terms, obesity is a condition of excess body weight more than 20% above the ideal body weight. In recent years, overweight and obesity have increased markedly and contributing factors include a social environment that supports physical inactivity, excessive food consumption, and unhealthy food choices. Overweight and obesity, is a major risk factor associated with a wide number of health problems including hypertension, hyperlipidemia, dia betes, surgical risks, pulmonary and renal problems, pregnancy complications and certain type of cancer. Increased consumption of sugar leads to several nutritional and medicinal problems such as obesity. Regular consumption of sugar-sweetened snacks and beverages may cause metabolic disorders, such as obesity. Therefore, an efficacious weight management strategy is to substitute sugar with low calorie sweeteners (Stephen et al., 2010). Stevia leaves contain zero-calorie ent-

kaurene diterpene glycosides (stevioside and rebaudiosides) that are not metabolized to produce energy and taste 300 times sweeter than sucrose (Soejarto et al., 1982; Megeji et al., 2005; Walter and Soliah, 2010). In human studies, the measured sweetness of 1 g of crude extract of Stevia leaf dissolved in water ranged from 100 to 150 times that of equivalent concentrations of sucrose (Cardello et al., 1999). Stevia sweeteners in foods and beverages offer low calorie alternative substitute of sugar, assist with weight control and weight loss by restricting or controlling calorie intake in the diet. Ingestion of steviol in high doses showed a reduction in body weight as experimented in rats (Curry and Roberts, 2008). Leaves of S. rebaudiana can also be used as a functional food ingredient and prove beneficial to dietetic practice. In fact, ―replacing intake of added sugars with non-nutritive sweeteners could result in a deficit of 380 cal/day or 1 pound of weight loss in 9 to 10 days, if intake was at 95 g (24 tsp) daily‖ (8 Position of JADA). Stevia can be used in place of sugar as they provide fewer calories per gram than sugar which is not completely absorbed by digestive system. Consumption of Stevia leaves and extract reduce the carving for sweet and fatty foods and are useful in weight loss programme (Jain et al., 2007).

Inflammatory bowel disease (IBD)

IBD is a group of inflammatory conditions of the colon and small intestine. The two major forms are Crohn's disease and ulcerative colitis. The onset of IBD occurs most often in patients between the ages of 15 and 30 years, and both sexes are equally affected. In each case, the cause is unknown but genetic predisposition and immune and autoimmune phenomena are involved (Kornbluth et al., 1998). Stevia and its polyphenolic compounds steviol and stevioside exert anti-inflammatory effects on colonic epithelial cells. Shiozaki et al. (2006) conducted the study on animals and observed that stevioside inhibit intestinal smooth muscle contraction, stimulation of which is linked to hypermotility-associated diarrhea. Pariwat et al. (2008) studied the stevioside and its similar compounds steviol, dihydroisosteviol, isosteviol and isosteviol 16-oxime, on cAMP-regulated chloride (Cl) secretion in human T84 colonic epithelial cells line and in vivo for their antidiarrheal efficacy, results showed that steviol and its analogs, inhibited cAMP activated Cl secretion in intact T84 cells in a dose-dependent manner. The stevioside ineffectiveness could be due to its molecular bulkiness, rendering it relatively impermeable to cell membranes, and thereby exhibiting a promising agent in antidiarrheal treatment. Similar compounds of dihydroisosteviol could be a new class of cystic fibrosis transmembrane conductance regulator inhibitors that may be useful for further development as antidiarrheal agents.

Dental caries

Dental caries, also known as tooth decay, is the most prevalent chronic diseases of people worldwide and individuals are susceptible to this disease throughout their lifetime. It is an oral infectious disease in which organic acid metabolites produced by the metabolism of oral microorganisms lead to gradual demineralization of tooth enamel, followed by rapid proteolytic destruction of the tooth structure. Bacteria are an essential part of the tooth decay process. Several microorganisms are capa ble of fermenting dietary carbohydrate. Streptococcus mutans is the most prevalent followed by Lactobacillus casein and Streptococcus sanguis. Regular consumption of nutritive sweeteners also known as caloric sweeteners or sugars provide energy in the form of carbohydrate, causes cavities which encourage the growth of harmful bacteria in the mouth contributing to plaque formation and gingivitis. There is a requirement to substitute sucrose with natural sweetener which should be nutritionally appropriate and not being detrimental to the overall general health of the individual (Matsukubo and Takazoe, 2010). Stevia, as a non nutritive

sweetener are zero- or low-calorie alternatives to nutritive sweeteners, such as table sugar possess bacteriostatic and bacteriocidal properties benefit oral health by eliminating the cause of dental decay and gingivitis. Stevia is a natural sucrose substitute with high nutritional value beneficial in the battle against dental caries. Extract of Stevia leaves and its major secondary metabolites, steviol, isosteviol, stevioside and rebaudio side A, B, C and E are noncariogenic and have been found to inhibit glucan induced aggregation of cariogenic organism, Thus Stevia have potential of providing oral health benefits (Wu et al., 1998). Studies suggested that development of dental caries in rat pups are triggered in presence of sucrose solution while it is not with stevioside (Das et al., 1992). The major cariogenic organism, S. mutans, experiences growth suppression and secretes less acid when grown on media containing stevioside than when grown on sucrose, glucose or fructose media (Grenby, 1991).

Blood pressure regulation

Essential hypertension‖ is defined as an increase in blood pressure above certain measured levels. The definition of high blood pressure begins at a systolic blood pressure of 140 mmHg and a diastolic blood pressure of 90 mmHg. High blood pressure results in pathological changes accrue in medium sized and small arteries that cause further increases in blood pressure. The pathology is a thickening of the walls of these blood vessels so that effectively the diameter of the vessels is diminished. This causes the heart to work harder to pump enough blood to meet the demands of all the tissues increasing the risk for to heart attack or stroke. Stevia can be used as a heart tonic to normalize blood pressure levels, to regulate heartbeat, and for other cardiopulmonary indications. In humans, a hot water extract of the leaf has been shown to lower both systolic and diastolic blood pressure. Studies on Stevia extracts, as well as its isolated glycosides, demonstrate its hypotensive and diuretic action. Stevia acts at the cell membrane level much in the same way as a type of medication known as a calcium channel blocking agent. These medicines are routinely prescribed to help control high blood pressure by relaxing the muscular walls of the arteries causing the elevation in blood pressure. Studies suggest that Stevia acts to relax arteries and lower blood pressure. Leaves of S. rebaudiana contain non-caloric sweeteners (steviol glycosides) whose consumption could exert beneficial effects on human health (Gardana et al., 2010). Glycosides present in Stevia possess valuable biological properties. Regular consumption of these compounds decreases the content of cholesterol in the blood (Atteh et al., 2008), improves cell regeneration and blood co agulation, suppresses neoplastic growth and strengthens blood vessels (Barriocanal et al., 2008; Jeppesen et al., 2003; Maki et al., 2008; Wingard et al., 1980). The use of stevioside results in a clinically significant hypotensive effect in spontaneously hypertensive rats, without adversely affecting their heart rates or serum catecholamine levels (Chan et al., 1998). Phytosterols present in the wax of Stevia leaves were found to respond against cardiovascular defects (Markovie et al., 2008). Stevioside induces vasorelaxation (Lee et al., 2001; Wong et al., 2004; Liu et al., 2003). This effect was tested in a year-long randomized, double-blind, placebo controlled study of 106 hypertensive subjects who consumed capsules containing either stevioside (750 mg daily) or placebo (Chan et al., 2000). Beginning after 3 months and persisting throughout the remaining 9 months of the study, the subjects consuming stevioside exhibited significantly greater decreases in systolic and diastolic blood pressures. No significant adverse effects occurred. In a longer 2-year study, compared to placebo, 1,500 mg of stevioside daily also produced significantlygreater decreases in systolic and diastolic blood pressures in subjects with mild hypertension (Hsieh et al., 2003). Studies have shown that purified stevioside induces hypotension, diuresis, and natriuresis in rats and these effects are probably related to changes in prostaglandin activity (Melis et al., 1985). The effect of consumption of Stevia extract

on 20 selected hypercholesterolemic women was studied and it was found that consumption of 20 ml extract in a glass of water (200 ml) helps in the reduction of bad cholesterol such as triglyceride and low-density lipoprotein (LDL) with significant increase in good cholesterol that is high density lipoprotein (HDL), and it was concluded that Stevia extract had a hypolipidaemic effect and it maintains cardiovascular health (Sharma and Mogre, 2007). The previous studies prove the clinical efficacy of Stevia leaves in reducing chronic hypertension by relaxing arteries and help prevent the buildup of calcium on artery walls.

CONCLUSION

The sweet herb *Steva rebaudiana* (Bertoni) has a valuable future and is extensively used in various areas of the world. Stevia and its metabolites have commercial value in number of countries as sugar substitutes in foods, beverages and medicines. Studies have reported the health promoting of this magical natural herb Stevia which is well known as therapeutic agent and an efficient medication for curing chronic diseases. Researchers need to work more on Stevia for clinical evidences and demonstration of metabolic pathways regarding benefits to explore its full potential.

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