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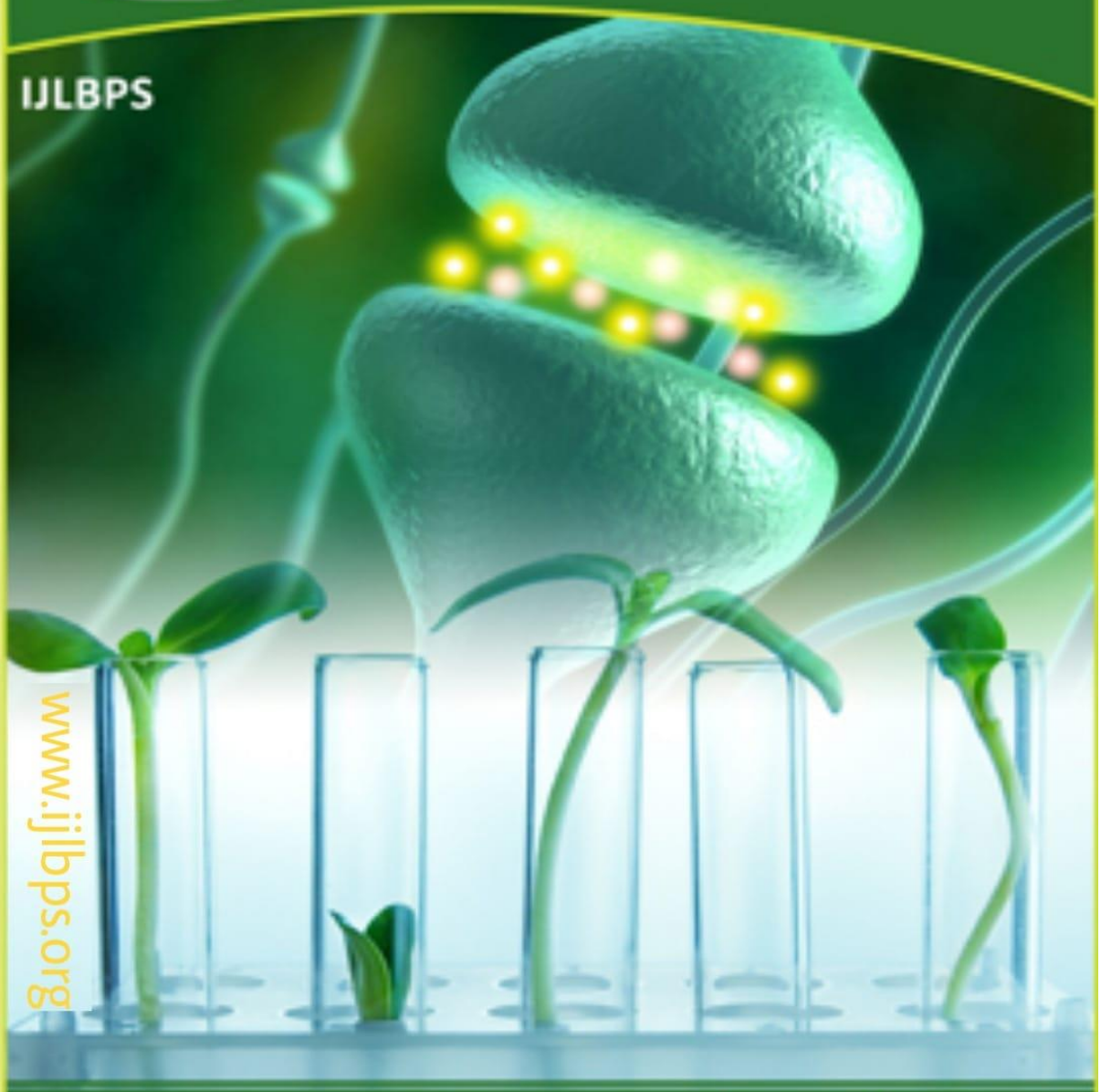

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Sweet gold for diabetics: Stevia rebaudiana, a plant with medical and nutraceutical uses.

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Abtract

The rising rates of obesity and diabetes have sparked widespread interest in natural sweeteners that may replace sucrose. We consider stevia (Stevia rebaudiana) to be a foreign plant. It's usefulness extends to both the economy and medicine. In recent years, it has emerged as a promising commercial sweetener for the expanding organic food industry. The growing interest in foods that are low in carbohydrates and sugar has brought more attention to this plant. Most people use sugar, also known as sucrose, as their primary source of sweetness. However, in recent years, interest in and the hunt for no-calorie natural sweeteners have increased due to concerns about the negative health consequences of sucrose and other well-known artificial sweeteners. Fortunately, stevioside was discovered, and it can sate the sweet tooth of diabetics. Different steviol glycosides, with stevioside being the most abundant, may be found in Stevia rebaudiana leaves. Diterpenoid glycoside stevioside consists of an aglycone (steviol) and three glucose molecules. Stevia rebaudiana yielded various additional sweet compounds other from stevioside, including steviobioside, rebaudioside A, B, C, D, E, and ducoside A. This analysis explores this wild herb's potential therapeutic and nutritional value in the context of health care management and its application to the needs of diabetes patients.

Mean arterial blood pressure (MABP), Streptozotocin (STZ), stevioside (SV), and DM (diabetic rats).

Introduction

One of the world's most widespread health issues is diabetes. Diabetes Mellitus is the proper medical term. Diabetes mellitus is the most critical metabolic condition. Almost every bodily system may be impacted. Hyperglycemia is a condition in which the blood sugar level rises uncontrollably, posing a number of health risks. Uncontrolled blood glucose increases, detectable even in the urine 1, are the result of insulin level disruptions. Despite the incredible scientific achievements seen this century, medical science still cannot claim to know all there is to know about diabetes mellitus, including its treatment. This is the primary basis for the worldwide fascination in treatments from so-called "alternative systems" of medicine2. The ancient Indian doctors were familiar with the illness. Madhumeha or Ikshumeha (both of which literally translate to "sugar in the urine") is the name given to this condition in all of the well-known ancient books of Ayurveda, including the Charaka Samhita (1000 B.C.), the Sushruta Samhita (600 B.C.), and other publications. In Ayurveda, the management of diabetes includes not only a detailed description of its etiopathogenesis (according to Ayurvedic concepts), but also the two types of diabetic patients (obese and lean), a definite familial prediction to the disease, and the importance of dietary regulations, physical exercises, and baths.There is a pressing need for high-potency, low-calorie sweeteners that can replace sugar in food and medicine. The natural sweetener stevia has 0 calories 5.

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Both stevioside and rebaudioside, two types of sweet-tasting deterpene glycoside, may be found in stevia leaves. 6. The derived stevioside from the plant has a sweetness level 300–500 times that of sugar. It has been carefully tested for flavor on animals and has been used by people with no negative effects, thus it is safe to suggest it for diabetes. 7.
Stevioside is a diterpene carboxylic alcohol8 complex consisting of three glucose molecules and one steviol aglycone molecule. Japan, Brazil, South Korea, and Paraguay have all adopted it as a sugar alternative because of its zero-calorie nature. 9. Several studies have demonstrated that stevioside has therapeutic potential as a contraceptive10, as well as cardiovascular11a and metabolic effects, in addition to its usage as a sweetener. Stevia leaf extracts have been shown to be beneficial for patients with diabetes because of its established antibacterial, antifungal, antiinflammatory, antimicrobial, antiviral, antiyeast, cardiotonic, diuretic, and hypoglycemic effects. 12.

Stevia rebaudiana's antibacterial and colonel-propagating properties have been discussed in detail by Debnath 13. What they unearthed

Stevia rebaudiana leaf extracts were shown to be hospitable by all tested bacterial species, including E. coli (MT CC 41), B. subtilis (MT CC 41), S. mutans (MT CC 479) and S. aureus (MT CC 737), however a few fungi exhibited inhibition to the extracts. The only sugar substitute with anti-diabetic effects is stevia rebaudiana.

Hypertension and high cholesterol are only two of the many ailments that the plant is used to cure. Paragraphs taken from

Traditional diabetic therapy in South America has long included the use of Stevia rebaudiana Bertoni leaves. When administered orally, extracts have a modest effect on lowering plasma glucose levels in healthy people. Oral administration of Stevia rebaudiana Bertoni extracts results in a 35% decrease in blood glucose in diabetic patients. Eggshell breakage may be decreased by 75% when stevia leaf powder is added to poultry feed, and blood calcium15 levels in pigs are doubled when fed 2.0% stevia leaf powder. This raises the possibility that stevia leaf powder might be used to treat osteoporosis.

Effects on Reducing Hyperglycemia

Researchers have undertaken several research on various cell lines to determine whether or not stevioside contributes to the glycemic action of extract of Stevia rebaudiana. Type-2 diabetic gotokakizaki (GK) rats were studied by Jeppensen et al. for any possible antihyperglycemic benefit. Stevioside (0.025 g.Kg-1.d-1) was given to rats for six weeks at this dosage. After 5 weeks, an intra-arterial catheter was placed in the rats, and in week 6, the rats underwent an arterial tolerance test (2.0g.Kg-1). Japanese adult male GK and Wistar rats were utilized in the study. The antihyperglycemic impact of stevioside was measured by measuring the IAUC (incremental area under the glucose response curve). Stevioside increased insulin levels in INS-1 cell lines, suggesting that it may stimulate insulin release by activating genes involved in glycolysis (16).

Herbal and alternative medicine is widely used for the treatment of diabetes, as documented by Kinghorn and Soejarto. Stevia rebaudiana preparations have been used to treat diabetes for a long time, as these researchers demonstrated in South America17. After 4 weeks of treatment18, rats fed a diet containing 0.5 g% stevioside and 10% powdered stevia leaves saw a substantial decrease in blood glucose level.Humans were given 5 g% aqueous extracts of stevia leaves at 6-hour intervals over the course of three days to determine the impact of this supplement on a glucose tolerance test. During a glucose tolerance test, plasma glucose levels dropped significantly. Stevioside and steviol's effects on

glucose absorption have been studied 19 times. According to their findings, hamster jejunal stevioside at 1 and 5 mm did not limit glucose absorption, whereas steviol at 1 mm did inhibit glucose absorption by roughly 30% without affecting intestinal Na+/K+ ATPase activity. Both the ATP content and the absorbent surface area of the intestinal mucosa are diminished.

Stevioside's impact on glucose production has been investigated in two models of diabetes in rats: type-1 (insulin-dependent) and type-2 (non-insulin-dependent).

, which requires insulin, and type 2, which does not. Both type -1 and type-2 diabetic rats benefit from stevioside's ability to bring down elevated blood sugar levels. Oral administration of stevioside (1, 2, or 10 mg/kg/BW/Day) to streptozotocin (STZ)-induced diabetic rats for 15 days resulted in hyperglycemia.

Table1: Effect of Stevioside and extracts of *Stevia rebaudiana* on the serum insulin and plasma glucagon concentrations in both normal and diabetic rats

S/No.	Group	Serum insulin concentration (µlU/mL)	Plasma glucagon concentration (pg/mL)
1.	Control(n=7)	5.13±0.19	45.89±6.59
2.	Control-SVS (n=8)	6.19±0.15	48.30± 6.62
3.	Control-SR (n=8)	5.17±0.36	47.08±4.95
4.	Dm(n=8)	2.66±0.19	76.04±5.38
5.	Dm-SVS(n=8)	3.29±0.11	75.21±3.12
6.	Dm-SR(n=9)	3.87+0.45	49.43+3.45

All values are mean ±SEM[20.]

The mechanism of glycemic action of SV and *Stevia rebaudiana* in both serum insulin and plasma glucagon levels is shown in table below. The serum insulin level in normal rats treated with stevio side or *Stevia rebaudiana* Bertoni was not significantly different from normal rats fed with water. The serum insulin level was raised from 2.66 ±0.19 ml U/Ml in normal diabetic rats to 3.29 ±0.11mlU/ml ($p<0.05$) in DM-stevioside and to 3.87±0.45 µlu/ml ($p<005$) in DM *Stevia rebaudiana* Bertoni.

Hypertension Effect

Early studies bath in animals and humans demonstrated that stevioside and stevia extract decreases mean arterial blood pressure (MABP) by including vasolilation and diuresis as well as n aturiuresis, which leads to decreased plasma volume [21, 22]. The antihypertensive effect of crude stevia extract (2.67g of dry leaf/day) taken orally is time- dependent and requires prolonged administration. There is no significant change in blood pressure for first 20 days. Indeed the hypertensive effect of the extract was observed 40 and 60 days following administration [23]. Reduced blood pressure occurs in rats following repeated oral dose of stevioside at 25 mg/kg BW/ day for 6 weeks. A double blind, placebo controlled studies in Taiwan to hypertensive subjects in ranging from 28-15 years. Each subject was given capsule containing 250 mg stevioside or placebo three times daily and followed up at monthly intervals for one year. After three months the systolic and diastolic blood pressure of the stevioside group decreased by about six points and the effect persisted during the whole year.

Antirotavirus Activity of Stevia

Tokahashi *et al.*, found that the *Stevia rebaudiana* had inhibitory activity against the replication of Anti-human rotavirus (HRV). Anti-human rotavirus activity of hot water extracts from inhibited the replication of all four serotypes of HRV in-vitro. They showed that the *Stevia rebaudiana* inhibited the binding of anti VP7 monoclonal antibody to HRV-infected MA-104 cells. The inhibitory components of *Stevia rebaudiana* were found to be heterogenous anionic polysaccharide with different in charges. The component analyses suggested that the purified fraction named as Stevian with the highest inhibitory activity consists of the anionic polysaccharide with molecular weight of 9800, and contains Ser and Ala as amino acids. Analyses of sugar residues suggest uronic acid(s) as sugar components. It did not contain amino and neutral sugars and sulfate res idues[24].

Antioxidant Activity

Contents of flavonoid and other phenolic substance

have been suggested to play a preventive role in the development of cancer and heart disease[25]. In the present study the Folin-Ciocalteu method was used to determine the total phenolic compound and flavonoid content of stevia leaves and callus. The phenolic compound in Stevia leaves and callus were extracted by using HCL -methanol. Total phenolic compounds was wound to be 25.18 and 35.86 mg/gram of stevia leaves and callus on dry weight basis, respectively flavonoid content was 31.99 mg/gram for stevia callus on dry weight basis. They also selected the FRAP and DPPH assay to evaluate the antioxidant activities of leaves and callus of stevia. Gallic acid was the strongest antioxidant in both water and methanol whereas trolox was proved to be a weak antioxidant in water. The ICSO for Gallic acid, trolox and BHA observed was 11.04, 41.04 and 57.14ug /ml respectively

Table 1: Inhibitory effect of *Stevia rebaudiana* against rotaviruses on plaque formation

Serotype	Strain	EC50 (dilution)a	CC50 (dilution)b	Selectivity index
1.	Wa	118 121 (pH 2)	32 35	4 4
2.	DS-1 S2	137 153	32 32	4 5
3.	MO	138	32	4
4.	Hochi	114	32	4
Rhesus rotavirus	SA11	32	32	nd

a. EC50 was expressed as the mean value from triplicate experiments of plaque assays.
b. CC50, cytotoxicity of SE was determined by an 3-(4, 5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide MTT assay in the MA104 cell culture which was exposed to SE for 1 h (adsorption period) and incubated for 3 days. CC50 was expressed as the reciprocal of dilution of SE that reduced the absorbance of control cells (without SE) by 50%c. nd, not determined [24.]

Table 2: Antioxidant activity of water and methanolic extracts of *Stevia rebaudiana* leaves and callus equivalent to gallic acid or ascorbic acid BHA or Trolox

Mg equivalent per gram on dry weight basis	Leaf extract		Callus extract	
	Water	Methanolic	Water	Methanolic
Gallic Acid	$09.66^{a} \pm 0.09$	$11.03^{b} \pm 0.47$	$09.44^{a} \pm 0.13$	$10.14^{a} \pm 0.18$
Ascorbic Acid	$25.70^{a} \pm 0.24$	$35.16^{c} \pm 0.49$	$25.11^{a} \pm 0.35$	$32.32^{b} \pm 0.56$
BHA	20.19 ± 0.19	$35.16^{b} \pm 1.49$	$19.72^{a} \pm 0.27$	$18.27^{a} \pm 0.32$
Trolox	38.24 ± 0.36	$37.40^{ab} \pm 1.58$	$37.36^{ab} \pm 0.51$	34.37 ± 0.60

(Values are a mean of three trials ±SEM (n=3)) [26].

Anti-Inflammatory and Anticancerous Effects

There are evidences that show the anti-inflammatory effect of stevioside both in vitro and in vivo. Boonkaewwan *et al*., observed the effect of stevioside and steviol as anti-inflammatory agent. Stevioside at 1.0 mm significantly surprised lipopolysaccharide (LPS) induced released of TNF- and IL-1β and slightly suppressed nitric oxide released in THP-1. They suggested that stevioside attenuates synthesis of inflammatory mediatory in LPS- stimulated THP-1 cells by interfering with IKH- and NF- kappa signaling pathway and stevioside induced TNF - secretion[27].

In addition, the anti-tumor effect of stevioside was investigated as TPA (12-0-tetradecanoylphorbol-13-acetate) is known to induce cancer formation in mammalian cells [28]. Stevioside inhibits TPA-induced tumor promotion in a skin cancer model of two stage carcinogenesis in mice. Mizushina *et al*., (2005) showed that isosteviol inhibits DNA polymerases and human DNA topoisamerase -II, Cellular targets for pharmacotherapy of cancer as well as inflammatory diseases.

Antimicrobial Activity

Jayaraman *et al*., has evaluated the antimicrobial and antitumor activity of *Stevia rebaudiana* leaf extracts[29]. They showed the antibacterial and antifungal activity by preparing nutrient broth (Hi Media) and by transferring a loopfulof culture to 10 ml of nutrient broth and incubated at 37^0C for 24 hours for bacterial proliferation. The plant extract was introduced into the Agar-well and plates were incubated at 37^0C for 24 hours, the antibacterial activity of the

plant extract was determined by measuring the diameter of the inhibition zone. For determining the antifungalactivity potato dextrose agar (Hi Media) was prepared and 1ml (50 mg/ml) of plant extract was added to the
medium. Then cultures were placed, and all plates were incubated at 25^0 for 4 days

Table 3: Antibacterial activity of the extracts of *Stevia rebaudiana* leaves[29]

Test	Zone of inhibition (mm)			
	Ethyl acetate	Acetone	Water	Chloroform
Staphylococcus aureus	10	19	-	-
Salmonella typhii	11	13	-	7
Escherichia coli	10	10	-	6
Bacillus subtilus	11	18	-	8
Aeromonas hydrophila	11	14	-	-
Vibrio cholerae	18	10	-	6

Das *et al*., has also reported the Comparative antimicrobial potential of different extracts of leaves of *Stevia rebaudiana* Bertoni leaf extracts, procured from Indian acidic and basic soil zones. Separately Stevia leaves were extracted with aqueous, methanol and ethanol solvents and their micro -biocides were diffusion technique compared against few selected gram positive (*Bacillus substilis* and *Staphylococcus aureus*) and gram negative bacteria (*Escherichia coli*, *Salmonella typhi*) by disc diffusion technique. The in vitro antimicrobial activity of aqueous, methanol and ethanol extracts of dried *Stevia* leaves (collected from acidic and basic soil field), stevia extracts showed high significant activities ($p < 0.001$) against *B. subtilis* and *S. aureus* whereas no activities found against *E. coil* and *S. typhi*. Among the extracts, only aqueous extract shows higher activities against *B. subtilis* and *S. aureus* (10.5 mm and 11.5 mm respectively) than methanolic and ethanolic extracts. However methanolic extract showed little higher activity against S. aureus (10.5 mm) than ethanolic extract (10.2 mm) at 300 mcg/ml concentration, whereas reverse activity shown against *B. subtilis* (9.9 mm for ethanolic extract and 9.8 mm for methanolic extract) at 300 mcg/ml concentration, but there were no significant variation in methanolic and ethanolic extracts against *B. subtilis* and *S. aureus*[31.] In other way, the extracts obtained from the basic soil zone the same trend followed as earlier where aqueous extract gave significant high activity than other two extracts. But interestingly, aqueous and ethanolic extracts showed activities against *S. typhi*, *B. subtilis* and *S. aureus*, whereas no activity shown against *S. typhi* with none of the former extracts collected from the acidic soil zone . Aqueous extract was significantly active against *S. typhi* (10.03 mm) at 300 mcg/ml concentration where as ethanolic ext ract was active significantly at 200 mcg/ml concentration (9.43 mm) but as per zone of inhibition measured, aqueous extract showed 9.7 mm where as ethanolic extract showed 9.43 mm at 200 mcg/ml concentration. These observations clearly highlighted that amo ng the extracts, aqueous extract shown higher activities ($p<0.05$) against *S. typhi* (10.03 mm), *S. aureus* (11.23 mm) and

B. subtilis (10.3 mm) followed by methanolic and ethanolic extracts. Methanolic extract showed higher activities against *S. aureus* and *B. substilis* (10.06 mm and 9.96 mm respectively) than ethanolic extracts for the same (9.49 mm and 9.68 mm respectively). Totally negative activity showed against *E. coli* with all the extracts collected from both the zones[31].

Cardiovascular Action

Cardiovascular action of stevia and stevioside on man and animals have been done 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 long term use of stevia would probably have a cardiotonic action, i.e. would produce a mild strengthening of the heart and vascular system[27].

Antihistamine Action

Histamine is a chemical substance existing widely in the tissues of animals, but excessive existence in a human body cases allergy, activates secretion of gastric acid, causes platelets aggregation and blood vessels contraction. Stevia extract liquid was found to detoxify histamine. It was found that extract of stevia was clinically useful for Age related disease, atopic dermatitis or allergic. Dermatitis and has antihistaminic effect (H1 receptor). Kazuhiro *et al.*, showed stem extract of Stevia contributed to the gastro protective activity of the extract in animal fed dietary histamine by studying the contractile response of the smooth muscles of the guinea pig ileum[32.]

Conclusion

rebaudiana (Stevia) Small and perennial, Bertoni is a member of the Asteraceae family and has green leaves. Stevia is mostly found in the Paraguayan Andes, although over 150 distinct species have been discovered so far. It has recently gained popularity as an alternative to sugar since it is a safe, all-natural sweetener that may be obtained in the form of a concentrated liquid, crushed leaf, or concentrated white powder. No adverse effects have been reported in either human or animal trials, leading to the recommendation for diabetes treatment. As the market for natural foods continues to expand, stevia is poised to become a significant supplier of high-potency sweeteners. Native Brazilians and Paraguayans have used Stevia leaves for hundreds of years as a natural sweetener and medicine for a variety of conditions, including obesity, hypertension, heartburn, and gout.Stevia leaf extract is 300 times sweeter than sugar and has been shown to have antimicrobial, antifungal, antiyeast, cardiotonic, diuretic, and hypoglycemic effects, making it a godsend for those with diabetes. Because of its pleasant licorice flavor, fresh stevia leaves are popular among those following

low-carb diets, including those with diabetes. [15].

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