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Review Article

SWEET FUTURE OF STEVIA: A MAGICAL SWEETENER

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ABSTRACT

The plant *Stevia rebaudiana* is mainly found in tropical and subtropical regions from western North America to South America. This genus is having near about 240 species of shrubs and herbs in the sunflower family (*Asteraceae*). It exhibits various properties such as antibacterial, antifungal, anti-inflammatory, antimicrobial, antiviral, antiyeast, cardiotonic, diuretic, hypoglycemic, hypotensive tonic, and vasodilator effect. It is an important source of a number of antioxidants, for example, benzoic acid, caffeic acid, chlorogenic acid, ferulic acid, rozmaric acid, protocatechuic acid, salicylic acid, and their derivatives and flavonoids including campherol derivatives, catechin, and its derivatives, epicatechin, luteolin, and its derivatives, rutin, and its derivatives. Day by day, there is remarkable increase in demand of high potency sweeteners. The increasing number of diabetic patients and health conscious individuals would push forward the need for alternatives to sugar. The extract from leaves of Stevia is 200 times sweeter than sugar (glucose, fructose, sucrose, maltose, and lactose). Stevia is a potential alternative source for replacing artificial sweeteners such as saccharin, aspartame, and asulfam.

Keywords: Artificial sweeteners, Stevia, Antioxidant, Flavonoids.

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INTRODUCTION

Stevia rebaudiana Bertoni is a perennial herb of significant economic value due to its high content of natural, dietetically valuable sweeteners in its leaves [1,2]. The sweet taste of Stevia is due to diterpene glycoside; it is calorie free and does not metabolize. Therefore, it is established as natural sweetest plant on earth. Stevia possesses many beneficial properties as compared to other sweeteners such as stevia has calorie value 2.7 kcal/g, whereas glucose has calorie value 3.80 kcal/g. Stevia is thermostable and can withstand temperature range of 200°C. Being non-fermentable, it is used in cooking and baking. It is less expensive as compared to other sweeteners. Stevia is used in the treatment of diabetes and obesity by suppressing appetite and reduces the urge for sweets. Further, it is helpful in the management of weight or to reduce weight [3].

Stevia products are approved in more than 100 countries, and about 5 billion consumers have access to Stevia products (Fig. 1) [4]. The total value of global sweetener market, sugar, high-fructose corn syrup, and non-natural high-intensity sweeteners is about $70, $60, $7, and $1.2 billion USD, respectively. The global sale of high-purity Stevia extracts in 2013 was about $150 million USD and the estimated growth in 20 years is more than $10 billion USD [4].

STEVIA CULTIVATION

A number of countries showing their enthusiasm for its cultivation and for research work. The cultivation of Stevia is mainly done by intensive study and according to its agronomic abilities. Stevia has been considered as a beneficial product due to the high content of sweetness, adaptive nature of the plant in various climates and its medicinal uses. In future, the demand for this beneficial sweetener is relied on progress. The herb is native of the Amambay region, in northeastern Paraguay [5]. The various countries of world which are growing this sweetener are India, Egypt, California, Western Georgia, Italy, Abkhazia, Korea, Slovakia, Czech Republic, Canada, Russia, Indonesia, Brazil, and Argentina [1]. Long-term potential of Stevia leaf production is around 2 million tones showing agricultural industry potential about $3-4 billion USD [4].

CHEMICAL CONSTITUENTS OF STEVIA

S. rebaudiana comprise more than 100 chemical constituents, but the most abundant compounds found are steviol glycosides, mainly rebaudioside A and stevioside (Fig. 2) [6].

STEVIOL GLYCOSIDES

In *S. rebaudiana,* there are more than 30 steviol glycosides with different concentrations of the total steviol glycosides up to 20% of the dry leaf weight are reported (Tables 1 and 2). The most profound steviol glycosides are stevioside and rebaudioside A, which are present in high amounts [7-17].

NON-GLYCOSIDE DITERPENES (STEREBINS)

These constituents mainly belong to Labdane-type diterpenes. These compounds were identified using ^{1}H, ^{13}C nuclear magnetic resonance (NMR), ultraviolet and infrared spectroscopy, and MS. The low-polarity sterebins do not possess any known pharmaceutical effects. Therefore, the concentration of low-polarity sterebins can be minimized by developing new Stevia lines, and the levels of sweet diterpenes glycosides can be enhanced (Table 3) [18-22].

POLYPHENOLS

Polyphenols were analyzed as an additional parameter by Folin–Ciocalteu colorimetric method. The total phenolic content obtained was expressed in gallic acid, tannic acid, or catechin equivalents/g or mg of extract or dried leaves. Quantitatively, the phenolic compounds can be analyzed by the use of high-performance liquid chromatography (HPLC) on a C18 column with gradient elution and diode array detection (DAD). The main phenolic compounds analyzed were pyrogallol with 951.27 mg/100 g dry base water extract, 4-methoxybenzoic acid (33.80 mg/100 g), p-coumaric acid (30.47 mg/100 g), 4-methylcatechol (25.61 mg/100 g), and sinapic

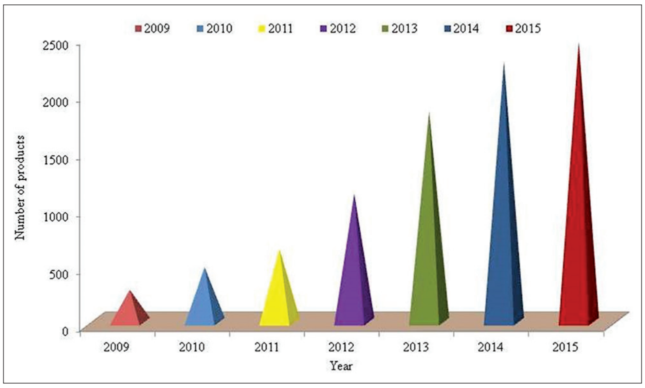


Fig. 1: Number of products launched by year

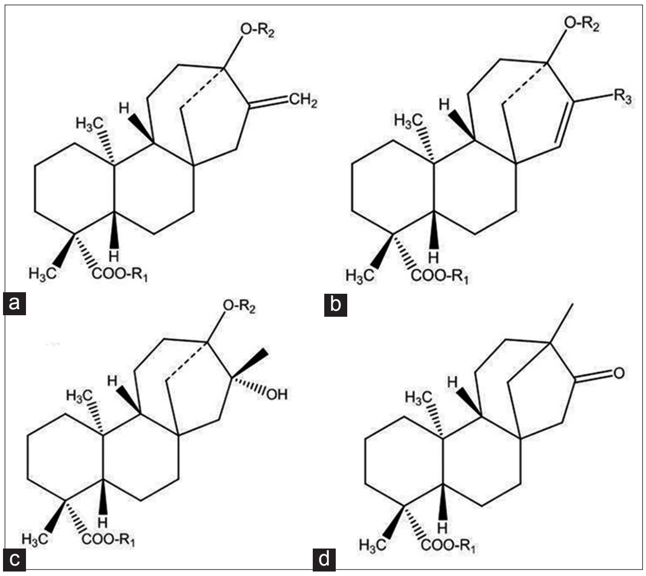


Fig. 2:(a-d) Different ent-kaurene body structures of steviol glycosides

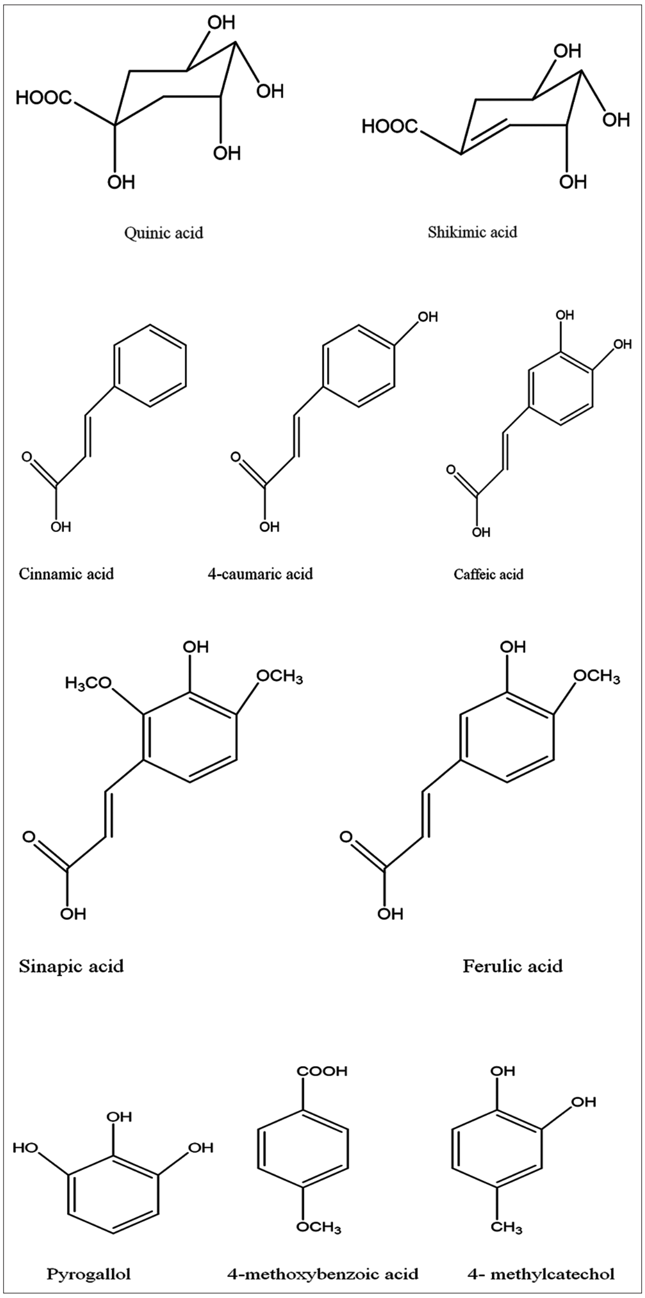


Fig. 3: Substructures of chlorogenic acids

and cinnamic acid (Fig. 3). Various chlorogenic acid and other phenolic compounds found in *S. rebaudiana* are enlisted in Table 4 [23,24].

FLAVONOIDS

In leaves of Stevia, the observed flavonoids are concerned with subgroups of flavonols and flavones (Table 5). These were recognized utilizing two-dimensional UHPLC-DAD34 and LC-MS/MS and spectroscopic techniques (^{1}H, ^{13}C NMR, IR, and 2D NMR). Quantitatively, they were detected as total flavonoid content using technique of aluminum chloride colorimetric and the Folin–Ciocalteu assay. Quantitatively, they were broke down as aggregate flavonoid content utilizing an aluminum chloride colorimetric technique and the Folin–Ciocalteu measure [25-28].

POLYHYDROXY INDOZILIDINE ALKALOID

The steviamine an indozilidine iminosugar alkaloid (Fig. 4) was extracted from leaves of stevia plant. Alkaloids of this type belong to Hyacinthaceae family, but never found in Asteraceae. Different pharmacological and biomedical properties have been reported in iminosugars like the inhibitory effect against glucosidase [29,30].

Natural sweeteners in a human diet [31-34]

Table 6 shows the natural sweeteners (Sugar alcohols and Other natural sweeteners)

TRADITIONAL MEDICINAL USES OF STEVIA

Stevia has potential uses such as cardiotonic (strengthens, tones, and balances the heart), sweetener, antimicrobial activities, hypotensive (reduces blood pressure), and hypoglycemic (Table 7) [35]. Due to various natural constituents, stevia is very beneficial for human health.

COMMERCIALIZATION OF STEVIA

The use of stevia is prohibited for human food because it has not been included in GRAS (Generally Recognized as Safe) status indicated in the documents provided by Dietary Supplement Health and Education Act. On the premise of authentic use and logical proof, Doun Kinghorn of the Herb Research Foundation gave a review for American Herbal Products Association that has proved the safe use of stevia. After this proof, many researchers have studied that stevia possesses a number of medicinal uses and does not have any side effects. As studied by GD Searle and Company, near about 200 reviews stated stevia as "NutraSweet" is safe. Diverse administrative bodies like FDA reassessed the papers and as named new sweetener Neotame is to be promoted by the organization. In the USA, steviol glycoside got the

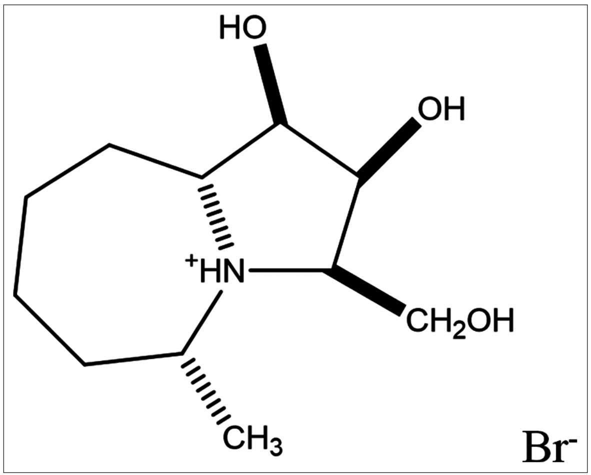
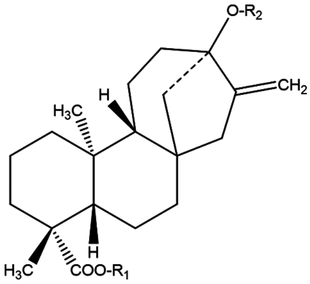


Fig. 4: Structure of steviamine

Table 1: New steviol glycosides



Steviol glycosides	R_1	R_2
Steviolmonoside	H	Glcβ1-
Rubusoside	Glcβ1-	Glcβ1-
Steviolbioside	H	Glcβ1-2Glcβ1-
Dulcoside A	Glcβ1-	Rhaα1-2Glcβ1-
Stevioside	Glcβ1-	Glcβ1-2Glcβ1-
Rebaudioside G	Glcβ1-	Glcβ1-3Glcβ1-
Rebaudioside B	H	Glcβ1-2(Glcβ1-3) Glcβ1-
Dulcoside B	H	Rhaα1-2(Glcβ1-3) Glcβ1-
Rebaudioside A	Glcβ1-	Glcβ1-2(Glcβ1-3) Glcβ1-
Rebaudioside C	Glcβ1-	Rhaα1-2(Glcβ1-3) Glcβ1-
Rebaudioside L	Glcβ1-	Glcβ1-6Glcβ1-2(Glcβ1-3) Glcβ1-
Rebaudioside H	Glcβ1-	Glcβ1-3Rhaαβ1-2 (Glcβ1-3) Glcβ1-
Rebaudioside F	Glcβ1-	Xylβ1-2(Glcβ1-3) Glcβ1-
Rebaudioside E	Glcβ1-2Glcβ1-	Glcβ1-2Glcβ1-
Rebaudioside D	Glcβ1-2Glcβ1	Glcβ1-2(Glcβ1-3) Glcβ1-
Rebaudioside I	Glcβ1-3Glcβ1-	Glcβ1-2(Glcβ1-3) Glcβ1
Rebaudioside K	Glcβ1-2Glcβ1-	Rhaα1-2(Glcβ1-3) Glcβ1-
Rebaudioside J	Rhaα1-2Glcβ1-	Glcβ1-2(Glcβ1-3) Glcβ1-
Rebaudioside N	Rhaα1-2(Glcβ1-3) Glcβ1-	Glcβ1-2(Glcβ1-3) Glcβ1-
Rebaudioside M	Glcβ1-2(Glcβ1-3) Glcβ1-	Glcβ1-2(Glcβ1-3) Glcβ1-
Rebaudioside O	Glcβ1-3Rhaα1-2 (Glcβ1-3) Glcβ1-	Glcβ1-2(Glcβ1-3) Glcβ1-

Where Glc: Glucose, Rha: Rhamnose, Xyl: Xylose

GRAS status in 2008 and 2009 [3]. Some of its products in the market of the USA are given in Table 8 [3].

CONCLUSION AND FUTURE PERSPECTIVES

Stevia is now being used worldwide for its natural sweetening activity and pharmaceutical properties. Some extensive high throughput

Table 2: New steviol glycosides with changes in the ent-kaurene backbone

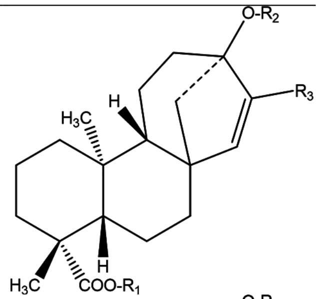
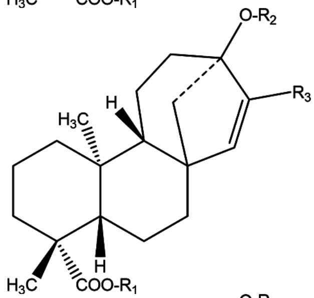
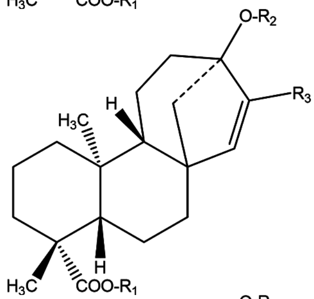
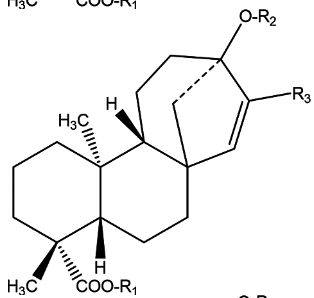
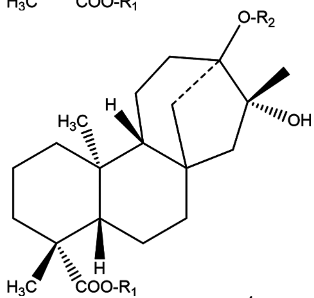
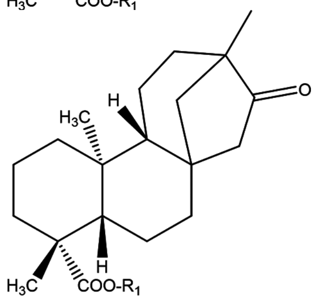
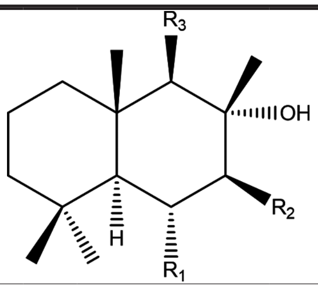
R_1	R_2	R_3	Chemical structure
Glcβ-	Glcβ1-2Glcβ1-	CH_2OH	
Glcβ1-	Glcβ1-2Glcβ1-	CHO	
Glcβ1-	Glcβ1-2Glcβ1-	CH_3	
H	Glcβ1-2 (Glcβ1-3) Glcβ1-	CH_3	
H	Glcβ1-2 (Glcβ1-3) Glcβ1-	-	
Glcβ1-	-	-	

Table 3: Substituent for different sterebins (A-N)



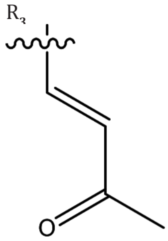
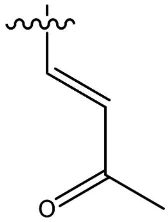
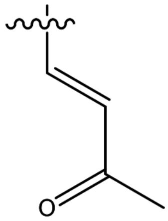
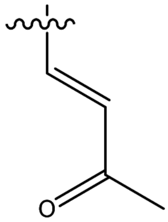
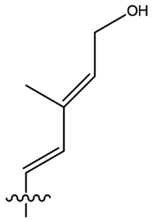
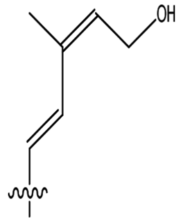
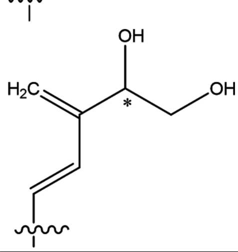
Sterebins	R_1	R_2	R_3
Sterebin A	OH	OH	
Sterebin B	OAc	OH	
Sterebin C	OH	OAc	
Sterebin D	H	OH	
Sterebin E	OH	OH	
Sterebin F	OH	OH	
Sterebin G, sterebin H (sterebin G and H are C-14 epimers)	OH	OH	

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Table 3: *(Continued)*

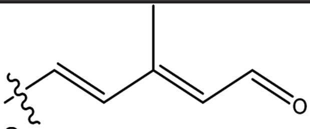
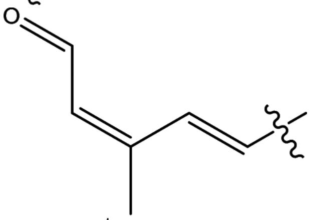
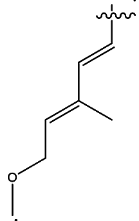
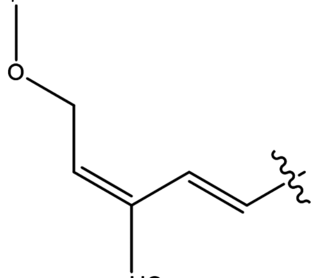
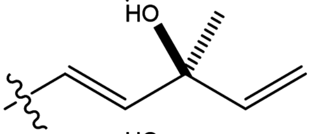
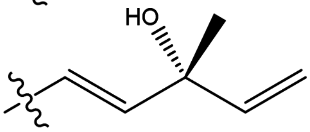
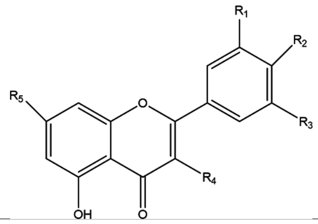
Sterebin I	OH	OH	
Sterebin J	OH	OH	
Sterebin K	OH	OH	
Sterebin L	OH	OH	
Sterebin M	OH	OH	
Sterebin N	OH	OH	

Table 4: List of chlorogenic acid and other phenolic compounds found in *Stevia rebaudiana*

Name
3-caffeoylquinic acid (3-CQA)
5-caffeoylquinic acid (5-CQA)
4-caffeoylquinic acid (4-CQA)
3,5-dicaffeoylquinic acid (3,5-diCQA)
3,4-dicaffeoylquinic acid (3,4-diCQA)
4,5-dicaffeoylquinic acid (4,5-diCQA)
A cis-3,5-dicaffeoylquinic acid (a cis -3,5-diCQA)
A cis-4,5-dicaffeoylquinic acid (cis -4,5-diCQA)
Cis-4,5-dicaffeoylquinic acid (cis -4,5-diCQA)
A cis-4,5-dicaffeoylquinic acid (a cis -4,5-diCQA)
5-p-coumaroylquinic acid (5-p-CoQA)
Caffeoyl-feruloylquinic acid (CFQA)
4-Caffeoyl-5-feruloylquinic acid (4-C,5FQA)
5-Caffeoylshikimic acid (5-CSA)
4-Caffeoylshikimic acid (4-CSA)
3-Caffeoylshikimic acid (3-CSA)
5-Feruloylquinic acid (5-FQA)
Feruloylquinic acid (FQA)
3,4,5-Tricaffeoylquinic acid (3,4,5-triCQA)
1,3,5-Tricaffeoylquinic acid (1,3,5-triCQA)
Tricaffeoylquinic acid (triCQA)
3,4,5-Tricaffeoylquinic acid (triCQA)
Pyrogallol
4-Methoxybenzoic acid
4-Coumaric acid
4-Methylcatechol
Sinapic acid
Cinnamic acid

S. rebaudiana: Stevia rebaudiana

Table 5: Flavonoids found in leaves of *Stevia rebaudiana*



Flavonoids	R_1	R_2	R_3	R_4	R_5
Flavonols					
Quercetin	OH	OH	H	OH	OH
Quercetin-3-O-β-D-arabinoside	OH	OH	H	O-arabinoside	OH
Quercetin-3-O-β-D-rhamnoside	OH	OH	H	O-rhamnoside	OH
Quercetin-3-O-glucoside	OH	OH	H	O-glucoside	OH
Quercetin-3-O-rutinoside	OH	OH	H	O-rutinoside	OH
Quercetin-3-O-(4-O-trans-caffeoyl)-α-L-rhamno-pyranosyl-(1-6)-β-D-galactopyranoside	OH	OH	H	[4-O-trans-caffeoyl-α-L-rhamno-pyranosyl-(1-6)-β-D-galactopyranoside]	OH
Kaempferol-3-O-rhamnoside	H	OH	H	O-rhamnoside	OH
Flavones					
Apigenin	H	OH	H	H	OH
Apigenin-4'-O-β-D-glycoside	H	O-glycoside	H	H	OH
Apigenin-7-O-β-D-glycoside	H	OH	H	H	O-glycoside
Luteolin	OH	OH	H	H	OH
Luteolin-7-O-β-D-glycoside	OH	OH	H	OH	O-glycoside

Table 6: List of natural sweeteners

S. No.	Substance	Chemical formula	E index	Sweetness	Caloric value kcal/g	Glycemic index[b]
Sugars						
1.	Glucose	$C_6H_{12}O_6$	-	0.75		100
2.	Fructose	$C_6H_{12}O_6$	-	1.7		23
3.	Sucrose	$C_{12}H_{22}O_{11}$	-	1	4	65
4.	Maltose	$C_{12}H_{22}O_{11}$	-	0.3		105
5.	Lactose	$C_{12}H_{22}O_{11}$	-	0.15		45
Sugar alcohols						
1.	Erythritol	$C_4H_{10}O_4$	E968	0.6-0.8		0
2.	Isomalt	$C_{12}H_{24}O_{11}$	E953	0.45-0.65		9
3.	Lactitol	$C_{12}H_{24}O_{11}$	E966	0.3-0.4		6
4.	Maltitol	$C_{12}H_{24}O_{11}$	E965	0.9	2.4	35
5.	Mannitol	$C_6H_{14}O_6$	E421	0.5-0.7		0
6.	Sorbitol	$C_6H_{14}O_6$	E420	0.5-0.7		9
7.	Xylitol	$C_5H_{12}O_5$	E967	1.0		13
Other natural sweeteners						
1.	Stevia (steviol glycoside)	$C_{38}H_{60}O_{18}$[a] $C_{44}H_{70}O_{23}$[b]	E960	200	0	0
2.	*Thaumatococcus danielli* (thaumatin)	Polypeptide (207 amino acids)	E957	2000	4	0

[a]Stevioside, [b]rebaudioside A

Table 7: Ethnomedical uses of stevia

Country	Ethnomedical uses
United States	Diabetes, candida, hyperglycemia, hypertension, vasodilator, infections
South America	Hypertension, diabetes, obesity, infections
Brazil	Depression, urinary insufficiency, tonic, hyperglycemia, diabetes, infections, sweet cravings, obesity, hypertension, cavities, wounds, fatigue
Paraguay	Diabetes

biotechnological techniques and other toxicity studies are essential for the establishment of biomedical potentials of Stevia. Being a natural product, with virtually calorie free status causing less harm, Stevia benefits several health conditions reflecting its bright future with other medicinal values apart from its use as a sweetener.

Table 8: Commercially available stevia products in the USA market

Product	Dosage form	Manufacturer
Stevia tablets	Tablets	Stevia Now (Shrub Oak, USA)
Stevia pure powder extracts	Powder extract	Stevia Now (Shrub Oak, USA)
Stevia dark liquid concentrate	Liquid concentrate	Stevia Now (Shrub Oak, USA)
Stevia	Crystals	Stevia LLC (Valley Forge, PA, USA)
Stevia extracts	Powder	Life extension foundation (FL, USA)
Stevia liquid extract	Liquid	Barr Products, Inc. (Downingtown, PA, USA)
JAJA stevioside	Powder	JAJ Group, Inc. (Jacksonville, FL, USA)

AUTHORS CONTRIBUTIONS

All the author have contributed equally.

CONFLICTS OF INTERESTS

All authors have none to declare.

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