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Stevia Rebaudiana Bertoni: Phytochemistry, Ethnomedicinal Uses and Therapeutic Potential of A Natural Non-Caloric Sweetener

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Abstract: *Stevia rebaudiana Bertoni*, a perennial herb belonging to the family Asteraceae, has gained global attention as a natural non-caloric sweetener and a medicinal plant with diverse therapeutic benefits. Traditionally used by indigenous communities of South America, stevia has been widely adopted in modern food and pharmaceutical industries due to the presence of intensely sweet diterpene glycosides such as sativoside and rebaudioside. This review provides a comprehensive overview of Stevia rebaudiana, including its botanical description, geographical distribution, ethnomedicinal applications, phytochemical constituents, and biochemical and nutritional properties. The plant is rich in bioactive compounds such as steviol glycosides, flavonoids, phenolic acids, tannins, alkaloids, sterols, and volatile constituents, which contribute to its antioxidant, antidiabetic, anti-inflammatory, antimicrobial, antihypertensive, and cardioprotective activities. Additionally, stevia exhibits favorable nutritional characteristics, including low caloric value and beneficial carbohydrate and protein content, making it suitable for diabetic and health-conscious individuals. The growing scientific evidence supports the traditional claims of stevia and highlights its potential as a safe natural alternative to synthetic sweeteners, as well as a promising candidate for pharmaceutical and nutraceutical applications.

Keywords: *Stevia rebaudiana Bertoni:* steviol glycosides, rebaudioside , flavonoids , phenolic acid, anti diabetic activity , anti hypertensive activity

1. INTRODUCTION

1.1 HERBAL MEDICINE

The WHO has recently defined traditional medicine (including herbal drugs) as comprising therapeutic practices that have been in existence, often for hundreds of years, before the development and spread of modern medicine and are still in use today. Traditional medicine is the synthesis of therapeutic experience of generations of practicing physicians of indigenous system of medicine. Traditional preparations comprise medicinal plants, minerals and organic matter etc. Herbal drugs constitute only those traditional medicines which primarily use medicinal plant preparations for therapy. The earliest recorded evidence of their use in Indian, Chinese, Egyptian, Greek, Roman and Syrian texts dates back to about 5000 years. The classical Indian texts include Rigveda, Atharvaveda, Charak Samhita and Sushruta Samhita. The

herbal medicines / traditional medicaments have therefore been derived from rich traditions of ancient civilizations and scientific heritage.[1]

1.2 POLYPHARMACOGNOSY

Because of their complimentary and potentiating properties, polyherbal medicine which contain two or more herbal ingredient are frequently more successful than single medications. Compared to conventional medicine, the combination of two or more herbal extracts results in greater therapeutic efficacy, improved pharmacological actions, quicker alleviation, and fewer side effects because the dosage is lower. Due to their high efficacy, easy accessibility, low toxicity, and environmental friendliness, polyherbal medicines are now widely used and preferred worldwide. They also shorten treatment times and lower the cost of individual anti-inflammatory and antimicrobial medications, which lowers prescription costs. In allopathic treatment, the idea of polyherbal combination is well-established and has shown amazing results, giving patients fresh hope. [2]

1.3 TRADITIONAL CHINESE MEDICINE

Although the origin of TCM remains uncertain, some evidence points to more than 5000 years of history. Indeed, some archaeological findings of acupuncture needles and traces of herbal treatments suggest 4000 to 8000 years of existence. The "Yijing" ("I Ching" or The Book of Changes) and the "Huangdi Neijing" (The Yellow Emperor's Classic of Internal Medicine) are the oldest known written sources of information in TCM philosophy and clinical application. The "Yijing", dating back 3000 to 5000 years, describes the course of life systematically based on a mathematical model of regulation. It describes its changes and modalities, offering advice on personal emotional lifestyle and guidance, while the "Huangdi Neijing" is comparable in importance to the Hippocratic Corpus in Greek medicine.

The main TCM theories include the teaching of "yin" and "yang" and the Five tres passes Phases ("Elements"). They describe the activity of effects and functional powers involved in body function such as the "qi", the "blood" or "xue", as well as the effects of active and resting fluids "jin ye", and the differential diagnosis of syndromes, while the primary practices include acupuncture and moxibustion, the use of Chinese herbs and dietetics, and "Tuina", "Qigong" and "Taijiquan", commonly known as Tai Chi. Ancient Chinese physicians postulated that everything is made of the same "substance", the "qi". This philosophy stands for oneness and wholeness as part of the same paradigm, considering that all existing things are symbiotically connected through the system of "qi". One of the main goals of TCM is to balance the effects of the body's "qi", known in the West as the "Vital Force", to live in harmony with the surrounding "qi". According to ancient Chinese culture, this includes the energies of "Heaven", such as the energy of the sun, moon, planets, and constellations, and the energies of "Earth", such as the effects of geographical location, the energy of the plants, soil, water, animals, and natural formations.[3]

2. PLANT PROFILE

Stevia rebaudiana Bertoni is a medicinal plant widely used as a natural sweetener due to its minimal side effects compared to synthetic chemicals. With increasing health concerns such as diabetes caused by excessive sucrose consumption, plant-based sweeteners like stevia have gained significant importance in the global natural food market. Stevia, commonly known as sweet leaf, honey leaf, or candy leaf, belongs to the family Asteraceae. The plant contains steviosides and rebaudiosides, which are 150–300 times sweeter than sucrose. In addition, stevia contains various bioactive compounds such as diterpenes, triterpenes, sterols, flavonoids, tannins, and vitamins A, B, and C. These compounds contribute to its numerous therapeutic properties including hypoglycaemic, antihypertensive, antimicrobial, anti-inflammatory, antiviral, antifungal, and anticancer activities. Stevia is also used for the management of gastrointestinal and skin disorders. Several varieties of Stevia rebaudiana have been developed worldwide to suit different climatic conditions, and the sativoside and rebaudioside content in leaves largely determines its market value and commercial importance.[4]

2.1 PLANT DESCRIPTION

- Plant name: Stevia rebaudiana Bertoni
- Common name: Stevia, Sweet leaf, Sugar leaf, Honey leaf
- Family: Asteraceae(composite family)

Fig 1: Stevia Rebaudiana

- Synonyms : Eupatorium rebaudianum
- Stevia rebaudiana (Bertoni) Hemsl.
- Stevia rebaudiana var. bertoni
- Stevia rebaudiana Bertoni forma rebaudiana
- Stevia rebaudiana var. rebaudiana
- Stevia rebaudiana var. candida
- Stevia teuberi
- Stevia rebaudiana f. rebaudiana
- Eupatorium rebaudiana B.L.Rob.
- Sweet Herb of Paraguay (vernacular synonym)

2.2 VERNACULAR NAMES

- Arabic: Istifia Ribaudiana
- English: Sweet Leaf, Sugar Leaf, Honey Leaf
- Bengali: Mishti Pata
- Hindi: Meethi Patti, Meethi Thulasi
- Greek: Stevia
- Gujarati: Mithi Pan, Jadibuti Mithi
- Kannada: Shi Tulasi
- Kokani: Goad Paana, Mithe Paano
- Malayalam: Madhura Ilai
- Manipuri: Chanam Atingba
- Napalese: Mitho Paat
- Oriya: Mitha Pata
- Persian: Osotovia
- Sanskrit: Madhura Patra
- Tamil: Inippu ilai, Thene Ilaigal
- Telugu: Teepi Aku, Madhu Tulasi

2.3 TAXONOMICAL CLASSIFICATION

Table 1

Kingdom	Plantae
Subkingdom	Tracheophyta
Super Division	Spermatophyta
Division	Magnoliophyta
Class	Magnoliopsida
Order	Asterales
Family	Asteraceae
Genus	Stevia

2.4 GEOGRAPHICAL DISTRIBUTION

Stevia rebaudiana is endemic to the mountainous regions of Paraguay and Brazil, where it traditionally flourishes in subtropical climes. It naturally occurs in wet grasslands, woodland borders, and mild-altitude regions of South America.

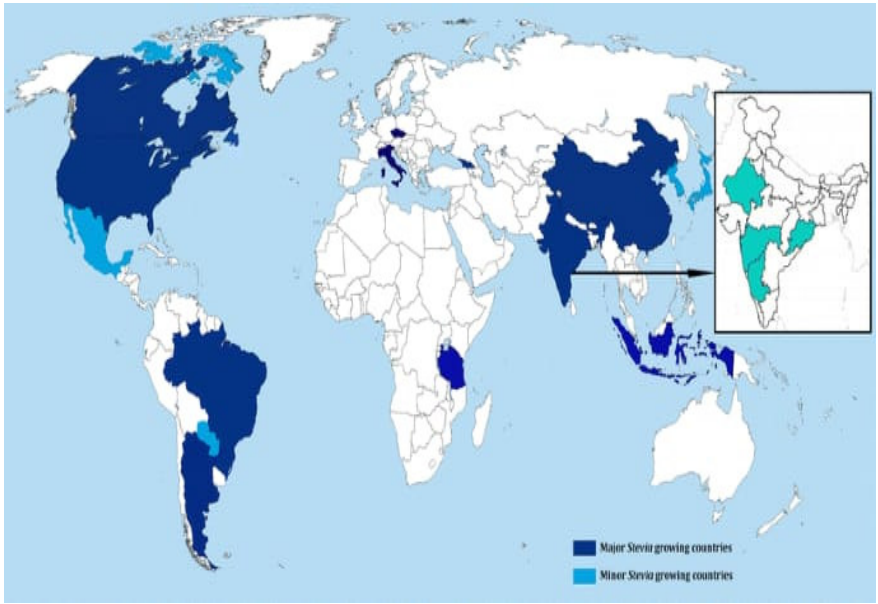


Fig 2: Distribution Of Stevia Rebaudiana

The plant is now widely grown throughout Asia, particularly in China, India, Thailand, and Japan, because of its sweetness. It is also produced in North America, Europe, and Africa in conditions suited for subtropical crops. Overall, stevia has become a worldwide spread crop, extending well beyond its native South American habitat.[5-11]

2.5 BOTANICAL DESCRIPTION

Stevia is a genus consisting of nearly 200 species of herbs and shrubs belonging to the family Asteraceae. Stevia rebaudiana is a perennial herb that grows up to about 1 m in height and possesses an extensive root system with brittle stems and small elliptic leaves. The leaves are sessile, 3–4 cm long, lanceolate in shape with serrated margins, and slightly pubescent on the upper surface. The plant bears small white pentamerous flowers arranged in loose panicles, and the fruit is a five-ribbed spindle-shaped achene. Stevia grows well in a variety of soils with adequate moisture and good drainage and is cultivated widely in subtropical regions. It is native to northern South America, particularly Paraguay and Brazil, and is now cultivated in several countries including China, Taiwan, Thailand, Korea, Brazil, and Malaysia. The plant has high water requirements but can recover quickly from short periods of water stress. Under cultivation, stevia can be harvested multiple times per year and remains productive for up to eight years. Approximately 1000–1200 kg of dried leaves can be produced per hectare, yielding about 60–70 kg of sativoside, a natural sweetener nearly 300 times sweeter than sucrose. [12]

2.6 ETHNO-MEDICINAL USES OF STEVIA REBAUDIANA

Fig 3: Ethnomedicinal Uses

Stevia rebaudiana Bertoni has a long history of traditional and ethnomedical use, particularly among indigenous communities of South America, where it is commonly known as "ka'a he'ê," meaning sweet herb. Traditionally, the leaves were used as a natural sweetener to improve the taste of herbal teas and medicinal preparations. Beyond its sweetening property, *S. rebaudiana* has been used in folk medicine for the management of various ailments due to its perceived therapeutic benefits.

In traditional Paraguayan and Brazilian medicine, *S. rebaudiana* leaves have been used to regulate blood sugar levels and manage symptoms of diabetes. Indigenous healers consumed fresh or dried leaves or prepared infusions to reduce excessive thirst, fatigue, and other symptoms associated with hyperglycaemia. These traditional claims are supported by later scientific findings demonstrating the antihyperglycemic effects of steviol glycosides.

Stevia has also been employed ethnomedically for the treatment of gastrointestinal disorders. Leaf infusions were traditionally used to alleviate stomach discomfort, heartburn, indigestion, and gastric acidity. Its mild antimicrobial and anti-inflammatory properties were believed to support digestive health and improve gut function.

In several traditional practices, *S. rebaudiana* has been used to manage cardiovascular conditions such as hypertension. Decoctions prepared from stevia leaves were consumed to help regulate blood pressure and improve overall cardiovascular health. This ethnomedical use aligns with modern pharmacological evidence demonstrating the vasodilatory and antihypertensive effects of sativoside.

Traditional healers have also utilized *S. rebaudiana* for its antimicrobial and wound-healing properties. Crushed fresh leaves or leaf extracts were applied topically to minor wounds, burns, and skin infections to promote healing and prevent microbial growth. These practices are supported by studies reporting the antibacterial and anti-inflammatory activities of stevia extracts. Additionally, stevia has been used in folk medicine to address oral and dental problems. The leaves were traditionally chewed or used as mouth rinses to prevent dental caries and improve oral hygiene. Unlike sugar, stevia does not promote tooth decay and has been traditionally valued for maintaining dental health.[13,14]

2.7 PHYTOCHEMICAL CONSTITUENTS

Medicinal plants are of great importance to the health of individuals and communities. The medicinal value of these plants lies in some chemical substances that produce a definite physiological action on the human body. The phytochemicals present in *S. rebaudiana* are austroinullin, β-carotene, dulcoside, niacin, rebaudi oxides, riboflavin, steviol, sativoside and thiamine

2.7.1 DITERPENE GLYCOSIDES

Glycosides are a group of organic compounds containing a carbohydrate molecule (sugar) bound to a non carbohydrate moiety. These compounds are mainly found in plants, and they can be converted, by hydrolytic cleavage, into a sugar and a non-sugar component (aglycone). Stevia, the common name for the extract sativoside from the leaves of *S. rebaudiana*, is a new promising renewable raw food stuff on the world market and is a natural, sweet tasting calorie free botanical that may also be used as a sugar substitute or as an alternative to artificial sweeteners. The natural sweeteners of stevia leaves, called steviol glycosides, are diterpenes, isolated and identified as sativoside, steviolbioside, rebaudioside A, B, C, D, E, F and dulcoside. Depending on growth conditions, cultivation and tillage techniques their contents range from 4 to 20% fresh leaf weight.

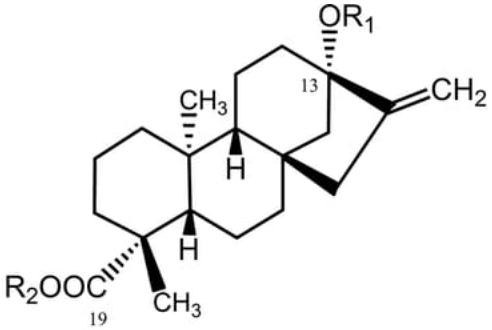
Sativoside was reported to be the most abundant stevia glycoside (4-13% w/w) found in the plant leaves. It is followed by rebaudioside A (2-4% w/w), rebaudioside C (1-2% w/w) and dulcoside A (0.4-0.7% w/w). Steviolbioside, rebaudioside B, D, E and F were also identified in the leaf extracts, but as minor constituents. The sativoside is the main sweetening compound found in the leaf of plant Stevia rebaudiana (from 5-15% dry weight), followed by rebaudioside (3 6%). The sativoside and the other stevia glycosides have high chemical stability because of their Tri dimensional chemical form which produces resistance to acid and enzymatic hydrolysis ensuring their inalterability even under biochemical and physiological aspects.

All diterpene glycosides isolated from *S. rebaudiana* leaves have the same steviol backbone and differ mainly in the content of carbohydrate residues (R1 and R2), mono-, di-, and tri saccharides containing glucose and/or rhamnose at positions C13 and C19.

The sweetness of any of the stevia compounds is greater than that of saccharose: rebaudioside A (250-450 times); rebaudioside B (300-350 times); rebaudioside C (50-120 times); rebaudioside D (250-450 times); rebaudioside E (150-300 times); dulcoside A (50-120 times); and steviolbioside (100–125 times).

On average, the sweetness of the steviol glycosides is 250-300 times greater than that of saccharose, with low water solubility and high melting points. Sativoside, the most abundant steviol glycoside in the leaf of the plant, has become well known for its intense sweetness (250-300 times sweeter than solutions containing 0.4% saccharose), and is used as a non-caloric sweetener in several countries. And compared stevia leaf powder and stevia white extract with granulated sugar.[15]

Table 2: Chemical Constituents Of *Stevia Rebaudiana*



Compound name	R_1 (C-13)	R_2 (C-19)	Formula	Mass
Steviol	H	H	$C_{20}H_{30}O_3$	318.22
Steviol mono-glucoside	β-Glc	H	$C_{26}H_{40}O_8$	480.27
Steviol mono-glucosyl ester	H	β-Glc	$C_{26}H_{40}O_8$	480.27
Rubusoside	β-Glc	β-Glc	$C_{32}H_{50}O_{13}$	642.33
Steviolbioside	β-Glc-(2→1)-β-Glc	H	$C_{32}H_{50}O_{13}$	642.33
Stevioside	β-Glc-(2→1)-β-Glc	β-Glc	$C_{38}H_{60}O_{18}$	804.38
Rebaudioside A	β-Glc-(2→1)-β-Glc \(3→1)-β-Glc	β-Glc	$C_{44}H_{70}O_{23}$	966.43
Rebaudioside B	β-Glc-(2→1)-β-Glc \(3→1)-β-Glc	H	$C_{38}H_{60}O_{18}$	804.38
Rebaudioside C	β-Glc-(2→1)-α-Rha \(3→1)-β-Glc	β-Glc	$C_{44}H_{70}O_{22}$	950.44
Rebaudioside D	β-Glc-(2→1)-β-Glc \(3→1)-β-Glc	β-Glc-(2→1)-β-Glc	$C_{50}H_{80}O_{28}$	1128.48
Rebaudioside F	β-Glc-(2→1)-β-Xyl \(3→1)-β-Glc	β-Glc	$C_{43}H_{68}O_{22}$	936.42
Dulcoside A	β-Glc-(2→1)-α-Rha	β-Glc	$C_{38}H_{60}O_{17}$	788.38

Table 3: Comparison of stevia leaf powder and stevia white extract with granulated sugar

Granulated Sugar	Stevia Leaf Powder	Stevia White Extract
1 Tablespoon	1\8 Teaspoon	Dust on spoon
1 Tablespoon	3\8 Teaspoon	1\2 Pinch
1\4 Cup	1\2 Teaspoon	Pinch
1\2 Cup	1 Tablespoon	1\8 Teaspoon
1 Cup	2 Tablespoon	1\4 Teaspoon
3.75 Pounds	7.2 Ounces	0.3 Ounces
10 Pounds	19.2 Ounces	0.8 Ounces

2.7.2 FLAVONOIDS

Flavonoids constitute an important group of polyphenolic compounds present in *S. rebaudiana* leaves. Reported flavonoids include quercetin, kaempferol, luteolin, apigenin, rutin, and catechin. These compounds contribute significantly to the antioxidant activity of stevia by scavenging free radicals and inhibiting lipid peroxidation. Flavonoids are also known to possess anti-inflammatory, antimicrobial, hepatoprotective, and anticancer properties, thereby enhancing the therapeutic value of *S. rebaudiana* .[16]

2.7.3 PHENOLIC ACIDS

Phenolic acids represent another major class of bioactive compounds found in *Stevia rebaudiana*. The commonly identified phenolic acids include chlorogenic acid, caffeic acid, ferulic acid, gallic acid, rosmarinic acid, and p-coumaric acid. Chlorogenic and caffeic acids are the most abundant and are mainly responsible for the strong antioxidant and antidiabetic activities of stevia. These compounds play a vital role in reducing oxidative stress, improving glucose metabolism, and protecting against metabolic and cardiovascular disorders.[17]

2.7.4 TANNINS

Tannins are present in moderate quantities in *S. rebaudiana* leaves and contribute to its medicinal significance. These compounds possess astringent, antimicrobial, antioxidant, and anti-inflammatory activities. Tannins help inhibit the growth of pathogenic microorganisms and protect biological tissues from oxidative damage, thereby supporting the traditional medicinal use of stevia.[18]

2.7.5 ALKALOIDS

Alkaloids have been reported in *Stevia rebaudiana* in smaller amounts but contribute to its overall pharmacological activity. These compounds exhibit antimicrobial, anti-inflammatory, and analgesic properties. Alkaloids may also support metabolic regulation and enhance the bioactivity of other phytoconstituents present in stevia leaves .

2.7.6 STEROLS AND TRITERPENOIDS

Plant sterols and triterpenoids such as β-sitosterol and stigmasterol have been identified in *S. rebaudiana*. These compounds are well known for their cholesterol-lowering, anti-inflammatory, and anticancer effects. The presence of sterols further contributes to the cardioprotective and therapeutic potential of stevia-based formulations.

2.7.7 VOLATILE COMPOUNDS

Volatile compounds are present in *Stevia rebaudiana* in relatively low concentrations compared to aromatic plants. Essential oil analysis has revealed the presence of monoterpenes and sesquiterpenes such as linalool, β-caryophyllene, germacrene D, and spathulenol. These volatile constituents exhibit antimicrobial and antioxidant activities and influence the sensory properties of stevia extracts. The composition of volatile compounds varies with geographical origin, harvesting time, and extraction methods.[19,20]

2.8 BIOCHEMICAL AND NUTRITIONAL ASPECTS OF STEVIA

The dry extract from the leaves of stevia contains flavonoids, alkaloids, water-soluble chlorophylls and xanthophylls, hydroxycinnamic acids (caffeine, chlorogenic, etc.), neutral water-soluble oligosaccharides, free sugars, amino acids, lipids, essential oils and trace elements. Analysis of stevia leaves on a dry weight basis and calculated an energy value of 2.7 kcal g 1 , moreover, Khiraoui being analyzed were found to be (3.05 - 3.17 kcal g-1) This means that stevia may be granted the status of a low calorie sweetener. Calorie contribution to the diet by the commonly used saccharose, which is considered high since it is metabolised completely by the body, has a potential to escalade towards overweight status. In this context, the use of stevia as a low calorie sweetener could be of immense help in restricting or controlling calorie intake in the diet. stevia leaf presents values of bulk density of 0.443 g ml-1, water holding capacity of 4.7 ml g-1, fat absorption capacity of 4.5 ml g-1, emulsification value of 5.0 ml g-1, swelling index of 5.01 g g-1, solubility of 0.365 g g-1 and pH of 5.95. The study showed an increased water holding capacity of the stevia leaf powder, which appears to be advantageous and may be due to high protein content. Proteins would increase water holding capacity, thus enhancing the swelling ability, an important function of protein in the preparation of viscous foods such as soups, gravies, dough and baked products. The ability of the protein to aid the formation and stabilization of emulsion is also critical in many foods applications, such as cake, batters, coffee whiteners, milk, frozen desserts and others. Stevia leaf powder seems to possess an adequate fat absorption capacity, allowing it to play an important role in food processing since fat acts on flavor retainers and increases mouthfeel of foods. The benefits associated with stevia leaf are principally due to their biochemical and nutritional composition (Table 1), which is a good source of carbohydrates, protein and crude fibre that promotes wellness and minimize the risk of certain diseases.

2.8.1 CARBOHYDRATES

Carbohydrates are the principal sources of energy and they are found as structural components of cellular elements. The advantages associated with stevia leaf are mainly due to their nutritional composition (Table 1), which is a good source of carbohydrates. Carbohydrates perform numerous essential roles in living beings. Thus, monosaccharides are the major source of energy in human metabolism, while polysaccharides serve as the storage of energy and can act as structural components. Other beneficial health effects have also been linked to these compounds. This includes a prebiotic effect as well as other less common antioxidant or anti-inflammatory activities. In *S. rebaudiana* roots and leaves, inulin-type fructo-oligosaccharides at 4.6%, a naturally occurring plant polysaccharide with important functional properties related to prebiotics, dietary fibre, role lipid metabolism and diabetes control, have been isolated.

2.8.2 PROTEINS

Proteins, peptides and/or amino acids are found in a great variety of matrices including animals, fungi, vegetables, cereals, etc. The study identified eight essential amino acids in stevia leaves, namely glutamic acid, aspartic acid, lysine, serine, isoleucine, alanine, proline, tyrosine . had found still more amino acids in the stevia leaves. Altogether seventeen amino acids were determined and classified as essential and non-essential amino acids, unfortunately including arginine as one of the indispensable amino acids.

2.8.3 CRUDE FIBRE

Dietary fibre is the comestible parts of plants or analogous carbohydrates that are resistant to digestion and absorption in the human small intestine with complete or partial fermentation in the large intestine. Dietary fibre includes polysaccharides, oligosaccharides, lignin and associated plant substances. In addition, an analogous carbohydrate is defined as those carbohydrates-based food ingredients that are non digestible and non-absorbable, and which are similar to plant dietary fibre. Dietary fibre has been widely studied for its health benefits. It is considered a preventive factor for cancer, serves as a substrate for colonic bacteria, promotes intestinal food transit, and decreases bile acid reabsorption thereby altering micelle formation and contributing to lowering blood cholesterol levels

2.8.4 MINERALS

Minerals have many important functions in the human body. The main elements are sodium, magnesium, phosphorus, sulphur, chlorine, potassium, and calcium which are classified as macronutrients and the minor elements, considered micronutrients, are chromium, manganese, iron, cobalt, copper, zinc, selenium, molybdenum and iodine. Stevia contains substantial amounts of these important nutrients, which further establishes it as a mineral loaded ingredient needed to protect the body, regulate and maintain the various metabolic processes. Potassium, calcium, magnesium, and sodium which are nutritionally important, were found in reasonable amount in stevia leaves.

2.8.5 LIPIDS

Lipids are a large group of natural compounds. Their main biological functions include energy storage. In the leaf oil of stevia, Tadhani and Subhash had identified six fatty acids using methyl ester standards. Palmitic, palmitoleic, stearic, oleic, linoleic and linolenic acids were identified in the leaf oil.

2.8.6 VITAMINS

Studies shows that the amounts of water-soluble vitamins in the stevia leaf extracts, and determined that the contents of folic acid, vitamin C and vitamin B2 in the leaf extracts were significantly higher than those of the callus extracts. In the leaf extract, folic acid was found to be the major compound, followed by vitamin C. In the callus extract, vitamin C was the major compound, followed by vitamin B.[21]

3. PHARMACOLOGICAL ACTIONS

3.1 ANTIDIABETIC ACTIVITY

Several studies have revealed that compounds found in stevia can reduce plasma glucose levels. Sativoside, which is the main compound of stevia decreases blood glucose levels through several mechanisms: increasing insulin secretion and sensitivity, reducing glucagon secretion. Another study showed that stevia extract increasing the expression of peroxisome proliferator-activated receptor-γ (PPARγ) and insulin mRNA. Also, sativoside and steviol compounds have increased activity in

gene expression and glucose transporter type 4 proteins (GLUT4). Increased expression of PPARγ and GLUT4, will increase glucose intake into cells so that glucose in the blood is metabolized and blood glucose levels will decrease. Research conducted by Lestari, et al. 2019 also showed that the water extract of stevia leaves at a dose of 3.125 mg/kg BW, 6.25 mg/kg BW, and 12.5 mg/kg BW could reduce blood glucose levels significantly. Natural medicines that can be used to prevent and reduce obesity and type 2 diabetes mellitus are the plants that contain secondary metabolites.

3.2 ANTIHYPERTENSIVE ACTIVITY

Natural compounds that have hydrophobic terpenes such as steviol glycosides from stevia can inhibit or block one of the 3 active sides of Angiotensin-Converting Enzyme (ACE). Research compared the activity of ACE inhibitors from ethanol extracts, steviol glycosides, and protein hydrolysate from stevia, and captopril. ACE inhibitory activity from the largest to the smallest is captopril > protein hydrolysate > steviol glycosides > ethanol extract of stevia. Although the ACE 2 inhibitory activity of protein hydrolysate and steviol glycosides is lower than captopril, it shows better toxicity results than captopril.

3.3 ANTIHYPERLIPIDEMIC ACTIVITY

Sativoside has been reported to exhibit significant hypolipidemic effects. Several studies indicate that it reduces total cholesterol, triglycerides, LDL, and VLDL levels while increasing HDL levels. The reduction in cholesterol is mainly attributed to enhanced bile acid excretion and increased conversion of hepatic cholesterol into bile acids. Sativoside also decreases triglyceride levels by stimulating liver lipase activity, which promotes lipid catabolism and faecal excretion of triglycerides. Additionally, the hypolipidemic effect is associated with activation of PPAR receptors, which regulate lipid metabolism by increasing lipoprotein lipase expression and fatty acid oxidation. Stevia also inhibits key lipogenic enzymes such as acetyl-CoA carboxylase and fatty acid synthase. Furthermore, sativoside enhances LDL receptor activity, facilitating the removal of LDL cholesterol from blood circulation. Studies have also shown that stevia extracts can reduce VLDL levels and increase HDL levels, possibly through enhanced activity of lecithin–cholesterol acyltransferase (LCAT), thereby contributing to improved lipid regulation.

3.4 ANTI OBESITY ACTIVITY

Obesity has achieved worldwide plague extents with high prevalence. It is associated with various metabolic, cardiovascular, musculoskeletal, and respiratory disorders like obstructive sleep apnea. Consumption of low-calorie sugar substitutes can play a role in weight loss because it will not stimulate the appetite, so it does not increase calorie intake. This is supported by several studies, when hyperlipidaemic rats are given stevia extract with a certain dose can reduce the body weight of rats that previously had increased. The inhibition of weight gain is caused by the ability of sativoside to reduce rat food intake. Also, sativoside can decrease weight gain by reducing glucose levels, fat absorption, and lipogenic enzymes, increasing insulin sensitivity, and fat excretion.

3.5 ANTICANCER ACTIVITY

Sativoside has been reported to exhibit significant anticancer activity, particularly against breast and colon cancer cells. It induces apoptosis by activating caspase-3 and caspase-9 enzymes and by increasing pro-apoptotic proteins (Bax) while decreasing anti-apoptotic proteins (Bcl-2). Sativoside also inhibits DNA synthesis, reduces cell viability, and promotes mitochondrial-mediated apoptotic pathways. In colon cancer cells (HT29), sativoside induces apoptosis through increased expression of MAPK pathways (ERK and p38) associated with reactive oxygen species (ROS). Additionally, steviol has demonstrated inhibitory activity against several human digestive cancer cell lines with effects comparable to 5-fluorouracil (5-FU). The anticancer mechanism involves regulation of tumor suppressor proteins such as p21 and p53 and modulation of the Bax/Bcl-2 ratio. Furthermore, stevia extracts exhibit antiproliferative effects by inhibiting cyclin-dependent kinases (CDK4), thereby suppressing cell cycle progression in cancer cells.

3.6 ANTIOXIDANT AND ANTI INFLAMMATORY

The incorporation of active ingredients into nano-systems to increase their shelf life, bioactivity, and bioavailability without inducing

immune-system reactions has become a research hotspot. The compounds contained in Stevia extracts such as steviol glycosides, flavonoids, quinic acid, caffeic acid, and their derivatives are biologically active molecules and capable to suppress the expression of inflammatory proteins and cytokines through the removal of Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) with antioxidant capacity. Flavonoids and proanthocyanidins contained in stevia can inhibit the production of Nitric Oxide in macrophages stimulated by lipo-polysaccharides (LPS) / gamma interferon (IFNγ). Natural diterpenoids (austroinulin and 6-O-acetyl austroinulin) in stevia can inhibit the production of nitric oxide synthase (iNOS), proinflammatory cytokines (TNF-α, IL-6, IL-1β, and mast protease-1 cells), and prostaglandin E2. The mechanism that occurs is the inhibition of NF-κB activation and (MAPK) phosphorylation.

3.7 ANTIMICROBIAL ACTIVITY

Stevia extracts have demonstrated significant antibacterial and antifungal activities in various in vitro studies. Chloroform and ethanol extracts of stevia showed antibacterial effects against pathogens such as Ralstonia solanacearum, Pseudomonas syringae, and Erwinia amylovora. Antifungal activity has also been observed against Alternaria alternata, Colletotrichum gloeosporioides, and Fusarium moniliforme, with reduced fungal growth and structural deformation of hyphae. Studies comparing different extraction methods revealed that ethanol extracts exhibited strong antibacterial activity against Staphylococcus albus, Klebsiella aerogenes, Escherichia coli, and Enterobacter aerogenes, while aqueous extracts were more effective against Bacillus subtilis and Candida albicans. Certain fungi such as Aspergillus niger and Penicillium chrysogenum were effectively inhibited using column extraction methods. These findings suggest that stevia contains potent antimicrobial compounds, although the exact mechanisms of action are still not fully understood.

3.8 ANTIVIRAL ACTIVITY

Several studies have reported the antiviral activity of polysaccharides (primary metabolites) from stevia in Herpes Simplex Virus-1 (HSV-1). Antiviral activity against HSV-1 was verified from two fractions containing arabinogalactans with unusual main chains (1 → 6) -d-galactan, isolated from stevia leaves. These two fractions (homogeneous alkaline fraction, SSFK, and crude fraction, SFW) can inhibit HSV-1 infection in Vero cells in vitro. The mechanism of the two fractions (SSFK and SFW) in stevia which has antiviral activity by inhibition of adsorption, penetration, and lateral spread of the virus. The virucidal effect shows that this activity is directly related to interactions between polysaccharides from Stevia and viral glycoproteins, not from cellular receptors. Other studies have reported that sativoside and Sophora flavescens (SV) extracts have antiviral activity for rotavirus in pigs. Part of the SV given orally can increase the absorption of sativoside into the intestinal lumen, thereby inhibiting rotavirus replication and preventing rotavirus re-infection into new epithelial cells. Sativoside showed in vitro activity by inhibiting the binding of rotavirus VP7 to cellular receptors.

3.9 EFFECT ON KIDNEY FUNCTION

Stevia extract in diabetic rats showed a significant decrease in Glomerular Filtration Rate (GFR). Rats given Stevia showed a significant protective effect against kidney failure. Serum creatinine and blood urea levels are reduced after previously given Gentamicin (toxic effects on the kidneys). Gentamicin increases intracellular Ca2+ levels and activates calcium entry from both an external source and internal Ca2+ release which causes mesangial cellular contraction of the kidney. Stevia has a hypotensive effect by interfering with the entry of Ca2+, so it can also protect kidney damage.

3.10 EFFECT ON LIVER FUNCTION

Stevia can prevent liver cirrhosis in rats (CCl4-induced) by maintaining markers of serum necrosis (ALT), cholestasis (AP, γ-GTP, and bilirubin), and the normal structure of the liver parenchyma. The mechanism that occurs due to the antioxidant effect of stevia through its ability to prevent increased lipid peroxidation and 4-HNE, (oxidative stress marker in the membrane) and prevent downregulation of liver Glutathione Peroxidase (GSH, oxidative stress marker in the cytosol). Other studies reported that the effects of stevia on decreasing marker enzymes for

impaired liver function, SGOT, and SGPT, after previously being given alloxan.[22]

4. MARKETED PREPARATION

Here are some well-known marketed stevia formulations available in the market:

1. **Truvia:** A mixture of erythritol and stevia extract (Reb A) used to replace sugar in food preparation and drinks.
2. **Stevia In The Raw**: Packaged or packaged as a sugar substitute, this stevia-based sweetener contains dextrose.
3. **Pure Via:** A sweetener made from stevia and erythritol that is sold for use in food and drink.
4. **Sweet Leaf Stevia:** A variety of stevia products without additional sugar or calories, such as liquid drops, sachets, and stevia blends.
5. **Better Stevia:** Now Foods' portfolio of stevia products includes powders, liquid drops, and stevia blends with natural sweeteners.
6. **Stevita**: Pure stevia extract in liquid, powder, and tablet form.
7. **Zevia:** Stevia is used by this company to sweeten sodas and other drinks.
8. **Kirkland Signature Stevia:** This combination of stevia powder is frequently found at bulk retailers like Costco.
9. **Natura Stevia:** A stevia product for baking and drink sweetening that comes in liquid and powdered versions.

To enhance taste and texture, these formulations come in a variety of formats, including powder, liquid, pills, and blends with additional sweeteners.

4.1 DIFFERENT FORMS: [23]

Table 4: Marketed Available Stevia Tablet Products

S. No	Product Name	Dosage Form	Chemical Constituents	Route of administration	Pictures
1.	Stevia drops	Liquid drops	Steviol glycosides (sativoside, rebaudioside A)	oral	
2.	Stevia powder	Powder	Concentrated steviol glycosides	Oral	

3.	Stevia liquid extract	Liquid extract	Steviol glycosides(may contain food- grade alcohol as solvent)	Oral	
4.	Stevia tablets	Tablets	Purified steviol glycosides (sativoside, rebaudioside A)	Oral	

CONCLUSION

Stevia rebaudiana Bertoni represents a valuable medicinal plant with significant therapeutic and nutritional importance. Its high content of steviol glycosides provides intense sweetness without caloric burden, making it an ideal natural substitute for sugar, particularly for individuals suffering from diabetes and metabolic disorders. Beyond its sweetening property, stevia possesses a wide range of pharmacological activities, including antioxidant, anti-inflammatory, antimicrobial, antihypertensive, and cardioprotective effects, which are attributed to its diverse phytochemical profile. The ethnomedicinal uses of stevia are strongly supported by modern scientific studies, validating its traditional applications in managing diabetes, gastrointestinal disorders, cardiovascular conditions, and oral health. Furthermore, its favorable biochemical and nutritional composition enhances its potential in food, pharmaceutical, and nutraceutical industries. Overall, *Stevia rebaudiana* emerges as a safe, effective, and multifunctional natural resource, warranting further research and clinical studies to explore its full therapeutic potential and expand its commercial applications.

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