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# Review on *Stevia Rebaudiana*: A Comprehensive Analysis of its Properties and Applications

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**Abstract**

The perennial plant Stevia rebaudiana, also referred to as stevia, is indigenous to South America, especially Brazil and Paraguay. It is a member of the Asteraceae family. Stevia, a natural, calorie-free sweetener, has drawn a lot of attention in recent decades and is frequently promoted as a healthy substitute for sugar and artificial sweeteners. The purpose of this review article is to present a thorough examination of the characteristics, health advantages, extraction processes, and uses of stevia in a variety of industries, with a focus on food and drink. Steviol glycosides (SGs) are low in calories and high in sweetness, thus creating SGs with better flavor profiles is a major priority. Because of its increased sweetness, rebaudioside M8 (Reb M8), a novel non-natural SG derivative made by glycosylating rebaudioside D (Reb D) at the C-13 position with glycosyltransferase UGT94E13, shows promise for future development. However, additional research and commercialization are hampered by UGT94E13's low catalytic activity. By using a semi-rational design, this work sought to increase the enzymatic activity of UGT94E13. A variation, UGT94E13-F169G/I185G, was produced with a 13.90-fold increase in catalytic activity. Uridine diphosphate glucose was recycled using a cascade reaction including UGT94E13-F169G/I185G and sucrose synthase, which produced an effective preparation of Reb M8 with a 98% yield. Additionally, in accordance with the using molecular dynamics simulations to analyze the distances between the substrate Reb D and the enzymes and between Reb D and the glucose donor, it is discovered that the enhanced catalytic activity of UGT94E13-F169G/I185G is due to the beneficial effect of reducing the distance on glycosylation reaction activity. As a result, this study tackles the obstacle to the effective manufacturing of Reb M8 and lays the groundwork for its extensive use in the food sector.

**Keywords:** Stevia Rebaudiana, Natural Sweetener, Steviol Glycosides, Pharmacological Properties, Health Benefits, Applications

## 1. Introduction

The science of cultivating plant cells, tissues, or organs that have been separated from the mother plant is known as plant tissue culture. It has a number of useful goals and incorporates research methodologies and approaches from a variety of botanical areas. This experimental method creates a mass of cells from the tissue of the explant. The resulting callus can be extracted or used to modify certain primary and secondary metabolites, or it can be used directly to regenerate plantlets. The fundamental methods for producing the necessary plant metabolites are callus culture and suspension culture (Vyas and Dixit, 1999).

The primary commercial barrier for the stevia sector used to be the United States' prohibition on using it as a food additive in food items, even though the Food and Drug Administration had authorized its use as a nutritional supplement in 1995 (Bespalhok-Filho and Hattori 1997). Studies on the plant's adaptability were started after it was brought to India in the late 1990s at the University of Agricultural Sciences in Bangalore. Research was more concerned with cultivation than crop enhancement. Two accessions were later introduced for domestication and cultivation in Himachal Pradesh by the Institute of Himalayan Bioresource Technology (CSIR), located in Palampur. In addition to agriculture, research has recently focused on crop improvement using biotechnology and conventional breeding methods. Items such as stevia sweetener will be in greater demand as a result of consumers' desire for natural products. Stevia cultivars that have been enhanced for agronomical

qualities and for greater amounts and quality of iterpene glycosides, including rebaudioside-A, which doesn't have a bitter aftertaste, will be required to meet this demand. In order to establish a baseline for future advancements, this review aims to compile the body of research on stevia enhancement using both traditional plant breeding and selection techniques and contemporary biotechnological methods. Stevia, a beautiful gift from nature, is a member of the Asteraceae family. Stevia rebaudiana Bertoni, a naturally sweet herb with no calories, is a useful substitute for sugar, particularly for the world's diabetic population. WHO (2011). Stevia is indigenous to South America, specifically Brazil and Paraguay. The tiny plant Stevia rebaudiana shrub with oppositely oriented leaves that can reach a height of 65 to 80 cm. Like any vegetable crop, stevia is a semi-humid subtropical plant that is simple to grow. Well-drained red soil and sandy loam soil with a pH of 6.5 to 7.5 are ideal for stevia plants. In India, there is a growing need for stevia plants for cultivation. The class of glycosides that have been isolated from stevia are called diterpene glycosides. Stevia plant leaves contain 9.1% stevioside, 3.8% rebaudioside A, 0.6% rebaudioside C, and 0.3% dulcoside. According to the majority of earlier research, stevia has no negative effects on people [1,2]. The food and pharmaceutical industries have just begun using Stevia rebaudiana (Bert.) Bertoni. Stevia is an indigenous plant that has long been used as a herbal cure and sweetener in the highlands of Paraguay and Brazil.

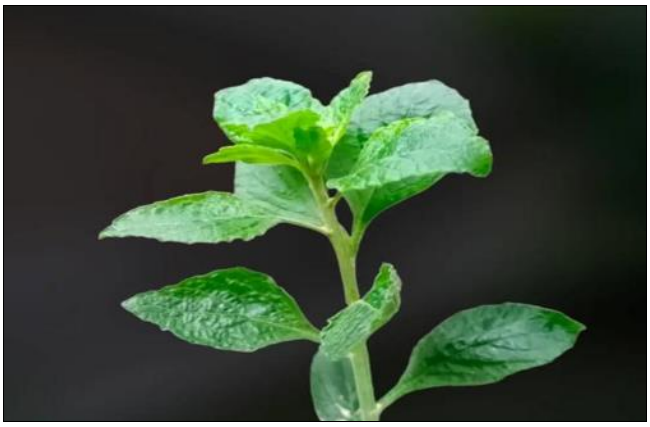

**Fig 1:** Stevia rebaudiana

## 2. History of Stevia

People have known about stevia from ancient times. Stevia was referred to by the Guarani Indians as "Ka-a He-e," or "sweet grass," and was used to flavor harsh beverages like mate. According to some accounts, stevia was already well-known in 16th-century Spain. But it wasn't until the botanist Moises Santiago Bertoni introduced and promoted stevia in the late 19th century that other Europeans became aware of the plant. It was termed Stevia rebaudiana by Bertoni from Euphoria rebaudianum. Bertoni claimed in 1901 that a big cup of tea could be sweetened with just a few leaves of stevia grass. Large-scale stevia cultivation on plantations in Brazil and Paraguay started in 1920. In 1931, the glycoside that gives stevia its sweet flavor was discovered by French researchers Briedel and Lavieille. Stevioside is the name given to this chemical. Due to limitation of sugar use and shortages during World War II, stevia became widely consumed in the UK.

When stevia was first introduced in Japan in the 1970s, studies were conducted to see whether it could improve human health. Since then, Japan has become one of the world's leading producers of stevia and actively uses it in a wide range of foods. The Coca-Cola Company began producing beverages with 30% fewer calories and stevia instead of sugar in 2013. These beverages are currently offered for sale in several nations across the world. Stevia is grown commercially in several other nations, including Ukraine, in addition to Brazil, Japan, and Paraguay.

## 3. Origin and Antiquity

There are about 150200 species of herbaceous, shrub, and sub-shrub plants in the genus Stevia Cav. (Gentry 1996). It is one of the most unique genera in the tribe Eupatorieae due to the uniformity of its flowers and capitula, which have five tubular flowers and five involucral bracts (King and Robinson 1987). It is found in Mexico and Central America, extending southward from the southwestern United States. According to King and Robinson (1987), it can also be found in non-Amazonian South America and extends south to Central Argentina. There are 36 species in Brazil, most of which are found in the central and southern regions (Frederico *et al*. 1996). The highland areas of northern Paraguay (around the Brazilian border) between latitudes 238 and 248S are where Stevia rebaudiana first appeared.

For hundreds of years, the Guarani Indians in the area have been aware of the plant's therapeutic qualities and sweetening capacity (Chan *et al*. 1998; Melis 1999; Jeppensen *et al*. 2002, 2003; Srimaroeng *et al*. 2005). The Guarani Indians employed the plant, which they named "kaa he-he," which means "sweet herb," as a flavor enhancer and to sweeten their green herbal tea, "mate" (Soejarto *et al*. 1983). In its natural habitat, grasslands with shallow watertables or the fringes of marshes are where it thrives (Shock 1982). It is native to the A mambay mountain region's Rio Monday Valley, which is between 200 and 500 meters above sea level. The temperature ranges from 6 to 438 degrees Celsius, making the climate semi-humid subtropical.

an average temperature of 238°C and 1500–1800 mm of annual precipitation. The first seeds were shipped to the UK in 1943, but they were unable to be planted there. After being brought to Japan in 1968, the plant's cultivation and awareness expanded globally (Lewis 1992). Brazil, Korea, Mexico, the United States, Indonesia, Tanzania, Canada, and India are among the countries that have already adopted the crop (Lee *et al*. 1979; Donalisio *et al*. 1982; Shock 1982; Goenadi 1983; Saxena and Ming 1988; Brandle and Rosa 1992; Fors 1995).

## 4. Phytochemical Composition

The main steviol glycosides found in stevia leaves—stevioside and rebaudioside A in particular—are what give stevia its sweet flavor (Zhang *et al*., 2021). These compounds are a good sugar substitute because their sweetness intensity is thought to be 50–300 times higher than sucrose's. Notably, steviol glycosides have become more well-known because of their low glycemic index, which makes them especially desirable for people with diabetes or those trying to cut back on calories (Mäkelä *et al*., 2022) [9].

**Biologically Active Compounds of Stevia**

More than 30 distinct steviol glycosides are found in S. rebaudiana leaves, with stevioside and rebaudioside A being the most abundant (Fig 1). The primary sweet ingredients in

stevia are also stevioside and rebaudioside A. The chemical structure of stevioside was determined in 1952 after it was initially separated from stevia in 1931. Three glucose molecules and a glucone moiety called steviol make up stevioside, a diterpene glycoside. The percentage of steviosides in stevia ranges from 4% to 13% of all glycosides (Marcinek and Krejpcio, 2015). The sweetness of Rebaudioside A, another steviol diterpene glycoside, ranges from 30% to 40%, making it approximately 180–400 times sweeter than sugar (Kaplan and Turgut, 2019). Stevioside and rebaudioside A are present in concentrations of 6.5% to 9.1%. between 2.3% to 3.8% (Atteh *et al*., 2011; Goyal *et al*., 2010).

Glycosides, stevioside, various rebaudiosides, steviolmonoside, rubusoside, dulcoside A, and steviolbioside are the most well-known chemicals that have been identified from stevia leaves overall (Starratt *et al*., 2002; Savita *et al*., 2004). Hexa-glucoside rebaudioside M and penta-glucoside rebaudioside D are less frequent (Olsson *et al*., 2016). Dried S. rebaudiana leaves contain very small amounts of rebaudioside D and rebaudioside M, 0.2% and 0.1%, respectively (Neuwirth, 2020). Nevertheless, Pure Circle Limited and the Coca-Cola Company market rebaudioside M for use in food and beverages (Prakash *et al*., 2014). As a non-caloric sweetener, Rebaudioside D can also be utilized in the food business (Allen *et al*., 2013).

**Glycosides in *S. rebaudiana***

Stevia leaf tissues contain eight diterpene glycosides that have been found to have sweetening qualities. Gibberellic acid, a crucial plant hormone, is generated, at least initially, by the same process as these (Singh and Rao, 2005). Stevioside, which typically accounts for 5–10% of the dry weight of the leaves, and rebaudioside-A (Reb-A), which accounts for 2–4%, are the two primary glycosides and the tastiest substances. Minor glycosides such rebaudioside-B, rebaudioside-C (1–2%), rebaudioside-D, and others are likewise related substances.

Flavonoid glycosides, coumarins, cinnamic acids, steviolbioside, rebaudioside-E, rebaudioside-F, dulcoside-A, dulcoside-C, and some essential oils (Erik *et al*., 1956; Erich *et al*., 1961; Harry *et al*., 1956; Hiroshi *et al*., 1976; Masur *et al*., 1977; Yohei and Masataka, 1978; Rajbhandari and Roberts, 1983; Makapugay *et al*., 1984; Crammer and Ikan, 1986; Kinghorn, 1987; Tsanava *et al*., 1989; Shaffert and Chebotar, 1994; Putieva and Saatov, 1997; Dzyuba, 1998; Dacome *et al*., 2005; Sekaran *et al*., 2007). (Crammer and Ikan, 1986; Yadav) Stevioside, rebaudioside-A, rebaudioside-B, rebaudioside-C, rebaudioside-D, rebaudioside-E, dulcoside-A, and steviolbioside are 250–300, 350–450, 300–350, 50–120, 200–300, 520–300, 50–120, and 100–125 times sweeter than sucrose, respectively.

**Biosynthesis of Steviol Glycosides**

At kaurene, the gibberellin and steviol glycoside routes split off. The primary sweeteners in stevia are formed via glucosylating or rhaminosylating kaurene, which is transformed into steviol, the "backbone" of the sweet glycosides. Following their synthesis in the chloroplast, the precursor chemicals are transferred to the Golgi apparatus, endoplasmic reticulum, and finally vacuolated. Although the exact function of these compounds in the stevia plant is still unknown, the fact that they are highly concentrated in the leaf and that the pathway is conserved within the species suggests that, at some point during the evolutionary process, their presence gave those who possessed them a considerable advantage. While some researchers believe they work to keep particular insects away, others hypothesize that it's a complex way to regulate gibberellic levels.

Van-Stadin and Smith (1992). One effective technology that has come from genomics research is expressed sequence tags (EST). Collections of expressed sequence tags can provide information about sequence diversity, gene regulation, and patterns of gene expression. With the widespread availability of enriched libraries and successful high-throughput sequencing, ESTs have also emerged as a useful tool for gene discovery in certain metabolic contexts (Sterky *et al*. 1998; Ohlrogge and Benning 2000). Van de Loo *et al*. (1995) used this idea for the first time when they isolated oleate hydroxylase from castor. Since then, more genes from several crops' 1-deoxy-D-xylulose 5-phosphate (DXP) pathway have been discovered using ESTs. It is now evident that highly expressed genes involved in a wide range of metabolic processes can be found via transcriptome analysis. (Brandle and others, 2002). Seven distinct glycosides that are produced from the tetracyclic diterpene steviol can accumulate in high concentrations (up to 30%) in the leaves of Stevia rebaudiana (Brandle *et al*. 1998a). Steviol glycoside production and metabolism have attracted attention due to their extreme sweetness, structural similarity to gibberellic acid, and the pathway's high activity (Richman *et al*. 1999; Totte´ *et al*. 2000). Within S. rebaudiana, these substances cannot be found in the roots and are only produced in the mesophyll cells of leaves. Steviol glycosides' adaptive relevance is unknown, but it is evident that S. rebaudiana devotes a significant amount of its overall metabolism to their synthesis, which makes it a strong contender for an EST-based gene discovery project. Only a small number of genes involved in the manufacture of steviol glycosides have been identified and isolated, despite their remarkable metabolic capacity (Richman *et al*. 1999; Brandle *et al*. 2002).

**5. Pathway of Biosynthesis**

The biosynthesis of Stevia rebaudiana's steviol glycosides is a sequence of enzyme-catalyzed processes that convert simple sugars into complex steviol glycoside molecules. This is a simplified overview of the biosynthetic route.

1. **Glycolysis:** Glycolysis, a biochemical mechanism found in plant cells' cytosols, converts glucose into pyruvate.
2. The pentose phosphate route converts pyruvate into pentoses, which are 5-carbon sugars.
3. **Isoprenoid biosynthesis:** The pentoses are transformed into isoprenoids, which are chemicals that act as building blocks in the synthesis of steviol glycosides.
4. **Geranylgeranyl diphosphate (GGPP) production:** Isoprenoids are transformed into GGPP, a 20-carbon compound that acts as a precursor to steviol glycoside synthesis.
5. Steviol synthase converts GGPP to steviol, a 20-carbon molecule that is the aglycone (non-sugar) component of steviol glycosides.
6. **Glycosylation:** Steviol is glycosylated (adhered to a sugar molecule) by a series of enzyme-catalyzed processes, resulting in the creation of stevioside.

7. **Glycoside modification:** Steviol glycosides are further changed by enzyme-catalyzed processes, yielding rebaudioside A and other steviol glycosides.

**6. Pharmaceutical Action**

**1. Anti-Diabetic Action**

**Hypoglycemic Effects:** It has been demonstrated that steviol glycosides, especially stevioside and rebaudioside A, enhance insulin secretion and sensitivity, hence improving glucose metabolism.

**Mechanism:** It improves insulin production and tissue uptake of glucose by influencing the activity of pancreatic β-cells.

**Mechanism**

**Control of Blood Glucose Levels:** The main glycosides in stevia, stevioside and rebaudioside, increase the amount of insulin secreted by pancreatic β-cells in reaction to glucose, which helps control blood sugar levels.

**Increased Insulin Sensitivity:** Stevia's constituents increase tissues' sensitivity to insulin, encouraging the absorption of glucose and lowering insulin resistance.

**Glucose Absorption Inhibition:** Stevia lowers postprandial (after-meal) blood sugar rises by decreasing intestinal glucose absorption.

**Antioxidant Properties:** Stevia's antioxidants fight oxidative stress, a major cause of problems from diabetes.

**Anti-Inflammatory Effects:** Stevia promotes improved insulin action by lowering tissue inflammation, especially in the pancreas.

**2. Action Against Hypertension**

Stevioside has been shown to reduce blood pressure in hypertensive people while having no discernible effect on participants with normotension.

**Mechanism:** By encouraging the generation of nitric oxide and preventing calcium influx in vascular smooth muscle, it causes vasodilation.

**3. Antioxidants Activity**

**Free Radical Scavenging:** Polyphenolic substances with potent antioxidant qualities have been found in Stevia rebaudiana extracts.

**Protective Role:** These antioxidants can lessen oxidative stress and guard against conditions like cancer and cardiovascular disorders that are linked to damage from free radicals.

**4. Effects on Inflammation**

**Inflammation Modulation:** Stevia rebaudiana contains compounds that inhibit pro-inflammatory cytokines and pathways, hence lowering inflammation.

**Potential Use:** It might help with chronic inflammatory disorders, inflammatory bowel diseases, and arthritis.

**5. Antifungal and Antimicrobial Properties**

Stevia extracts have been demonstrated to suppress the growth of bacteria and fungus, such as Candida albicans and Escherichia coli.

**Mechanism:** The rupture of bacteria membranes may be the cause of the antimicrobial actions.

**Health Benefits**

Stevia's possible health advantages have been extensively studied. According to recent research, stevia may have antibacterial, antioxidant, and anti-inflammatory qualities (Thangaraj *et al*., 2020) [22]. It has also been demonstrated to support weight management and glycemic control without the negative side effects typically linked to artificial sweeteners. Stevia's potential as a functional food ingredient is highlighted in a review by Dhingra *et al*. (2021) [2], which highlights its ability to lower blood pressure and improve cholesterol levels.

**Extraction and Processing Methods**

Steviol glycosides can be extracted from Stevia rebaudiana leaves using a variety of techniques, such as supercritical fluid extraction, organic solvent extraction, and aqueous extraction. Because of its effectiveness and capacity to maintain the bioactive components without the use of hazardous solvents, supercritical CO2 extraction has become more and more popular among these (González *et al*., 2023) [4]. It is now simpler to create high-purity stevia extracts that satisfy customer tastes and food safety laws because to technological advancements in the extraction and purification of steviol glycosides.

**Applications in Food and Beverage Industries**

Stevia's adaptability has led to its incorporation into a broad range of culinary items, including dairy products, baked foods, and beverages. Numerous case studies on product formulations using stevia in a variety of applications are included in the study by He *et al*. (2022) [5]. It points out that although though stevia comes from nature, using it in food products frequently presents problems with aftertaste and taste masking, which researchers are attempting to resolve by combining it with other sweeteners (formerly known as the "bitter aftertaste") (López *et al*., 2021) [8].

**Safety and Regulatory Status**

The European Food Safety Authority (EFSA) and the Food and Drug Administration (FDA) have both assessed the safety profile of stevia and determined that high-purity steviol glycosides are safe to eat (FDA, 2019) [3]. This support is essential to increasing stevia's market acceptance worldwide as consumer interest in natural products keeps growing.

**7. Conclusion**

To sum up, Stevia rebaudiana makes a strong argument for itself as a natural sweetener with a host of health advantages and culinary technological uses. Its promise goes beyond simple sweetening agents, according to ongoing study, which highlights the need for more investigation into its functional qualities and consumer acceptability. Stevia has a bright future ahead of it, with rising demand expected in the upcoming years due to the global trend towards cleaner-label products and healthy eating. This study offers up-to-date information on stevia's phytochemicals, industrial uses, safety, and possible function in various medical disorders. Furthermore, there has been discussion of recent data about the amphiphilic nature and self-assembly behavior of steviol glycosides. Stevia is a nutrient-dense, sweet plant that has

been grown for commercial purposes in several nations. It's been utilized in food, drink, and medication, and its uses and advantages are still debatable.

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