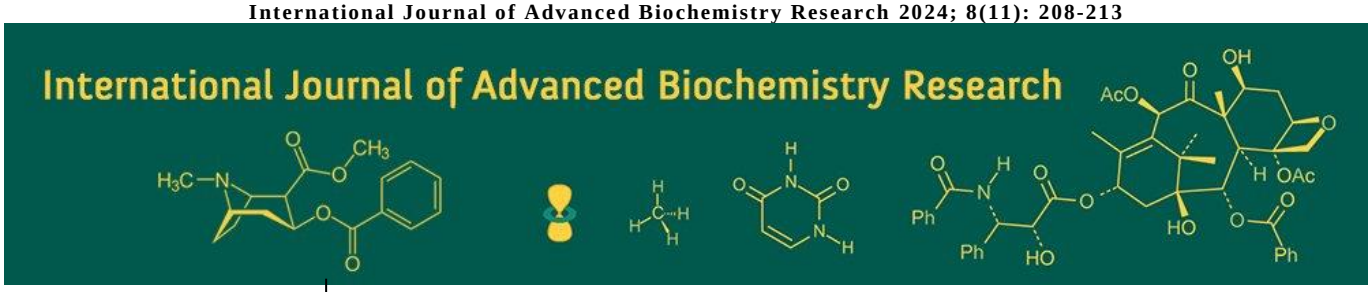

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A review on chemical properties and medicinal potential of *Stevia rebaudiana*

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Abstract
Stevia rebaudiana, a perennial plant, has gained global attention due to its natural sweetness and medicinal properties. The primary sweetening compounds, steviol glycosides, particularly stevioside and rebaudioside A, are up to 300 times sweeter than sucrose and are non-caloric, making *S. rebaudiana* a preferred alternative to synthetic sweeteners. This review focuses on the chemical properties of steviol glycosides and their metabolic pathways, highlighting their stability under various pH and temperature conditions, as well as their impact on human health. Beyond its sweetening capabilities, *S. rebaudiana* exhibits numerous medicinal potentials, including antidiabetic, antihypertensive, anti-inflammatory, and antioxidant effects. The plant's leaves contain phytochemicals such as flavonoids, phenolic compounds, and essential oils that contribute to these therapeutic properties. Clinical studies have shown that *S. rebaudiana* may improve insulin sensitivity, lower blood pressure, and provide cardioprotective benefits. Despite its promising health effects, safety concerns, particularly regarding long-term consumption and its impact on gut microbiota, require further investigation. This review aims to provide an updated synthesis of the chemical characteristics and medicinal applications of *S. rebaudiana*, with a focus on its role in promoting human health and its potential as a natural therapeutic agent.

Keywords: *Stevia rebaudiana*, steviol, natural sweetener, antidiabetic, antioxidant

Introduction
Stevia rebaudiana, a plant belonging to the Asteraceae family, has garnered global recognition for its unique natural sweetness and potential health benefits. Indigenous to the tropical regions of Paraguay and Brazil, *S. rebaudiana* has been traditionally used by the Guarani people for centuries to sweeten beverages and foods, as well as for medicinal purposes (Gantait *et al*., 2018) [14]. Known locally as "kaa-he-e," meaning "sweet herb," it was used to treat ailments such as high blood pressure, heartburn, and obesity (Latha *et al.*, 2017) [30]. The story of *S. rebaudiana* in the scientific world began in the late 19th century when Paraguayan scientist Dr. Moisés Santiago Bertoni, who had heard of the plant's sweetening capabilities from the native Guarani tribes, first described it in 1899. However, it was not until 1931 that two French chemists, Bridel and Lavieille, successfully isolated the plant's sweetening compounds, naming them steviol glycosides (Almeida, 2021) [4]. The most prominent of these compounds, stevioside and rebaudioside A, were found to be significantly sweeter than sucrose, setting the stage for *S. rebaudiana* to be considered as a natural alternative to artificial sweeteners (Muñoz *et al.*, 2024) [38]. Throughout the mid-20th century, Japan became one of the first countries to adopt *S. rebaudiana* as a commercial sweetener, in response to concerns over the safety of synthetic alternatives such as saccharin and cyclamate. Japan's widespread adoption of stevia in food products propelled it to international attention. Unlike synthetic sweeteners, steviol glycosides were found to be non-caloric, heat-stable, and pH-stable, making them suitable for various food and beverage applications (Iannicelli *et al.*, 2018) [22]. Today, *Stevia rebaudiana* is cultivated and used worldwide as a natural sweetener in beverages, foods, and medicinal products. Countries such as Japan, the United States, and those in the European Union have approved stevia extracts for use in food products, following extensive safety evaluations by organizations such as the World Health Organization (WHO) and the U.S. Food and Drug Administration (FDA) (Wang *et al.*, 2020) [51]. Despite some controversy over long-term safety, particularly concerning gut microbiota,

stevia continues to gain popularity as a safer, natural alternative to synthetic sweeteners like aspartame and sucralose (Saad *et al.,* 2014) [46]. The sweetness of *S. rebaudiana* is attributed to its steviol glycosides, a group of diterpenoid compounds, of which stevioside and rebaudioside A are the most abundant and well-studied (Peteliuk *et al.,* 2021) [43]. These glycosides are 200 to 300 times sweeter than sucrose, yet they do not contribute calories or affect blood sugar levels, which makes them highly desirable for individuals with diabetes or those seeking to reduce caloric intake (Singh *et al.,* 2019) [47]. It also contains a variety of other bioactive compounds, including flavonoids, phenolic acids, and volatile oils, which contribute to its medicinal properties (Mathur *et al.,* 2017) [33]. These compounds exhibit antioxidant, anti-inflammatory, and antimicrobial activities, further enhancing the plant's appeal as a medicinal agent (Li *et al.,* 2023) [32]. As awareness of its properties spreads, *S. rebaudiana* stands poised to play an increasingly significant role in promoting healthier lifestyles and providing therapeutic options, showcasing the intersection of traditional knowledge and modern science (Gupta *et al.,* 2017) [19]. This review aims to provide a comprehensive overview of the chemical properties and medicinal potential of *S. rebaudiana*, underscoring its significance in contemporary health and wellness.

Botanical Properties *S. rebaudiana*

S. rebaudiana is a perennial herb native to South America, characterized by its broad, green leaves and small, white flowers. The plant typically reaches heights of 60 to 100 centimeters and thrives in well-drained, sandy soils with plenty of sunlight. *S. rebaudiana* has a complex root system that aids in moisture retention, making it resilient in various climates (Alamgir and Alamgir, 2017) [2]. The plant blooms in late summer, producing clusters of tiny white flowers that attract pollinators. Its growth cycle is influenced by temperature and light, with optimal growth occurring in warm, tropical environments. The robust nature and adaptability of *S. rebaudiana* make it suitable for cultivation in diverse agricultural settings.

Phytochemicals of *S. rebaudiana*

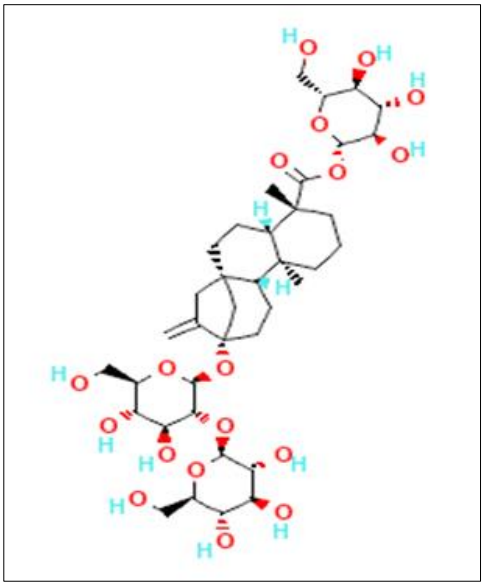
Stevia rebaudiana is rich in a variety of phytochemicals that contribute to its medicinal properties and health benefits. According to Mlambo *et al.* (2022) [35], stevia leaves have been shown to have a variety of compounds in some investigations and tests. Found nine essential amino acids *viz*. glutamate, aspartate, methionine, tyrosine, proline, alanine, isoleucine, lysine, and serine. Abdul *et al.* (2019) [1] reported that all essential amino acids are present in the leaves of Stevia with an exception of tryptophan. In addition to that, fatty acids, namely, linoleic acid, linolenic, oleic, stearic, palmitoleic, and palmitic acid, were found present. Moreover, vitamins such as vitamin B12, vitamin C, and folic acid were also present, along with minerals such as calcium, phosphorus, magnesium, iron, sodium, zinc, and potassium (Deshmukh *et al.,* 2019) [11]. Furthermore, the plant leaves were found to contain phytochemicals such as β-carotene, thiamine, steviol, stevioside, riboflavin, rebaudi oxides, nilacin, dulcoside, and austroinullin (Lemus-Mondaca *et al.,* 2012) [31]. Secondary metabolites are unavoidably present. The majority of studies and publications state that the leaves of stevia include anthraquinones, reducing chemicals, triterpenes, sterols, saponins, cardiac glycosides, alkaloids, and tannins. The biochemical composition of stevia leaves is mainly composed by terpenes and flavonoids. Steviol glycoside is the collective classification for the common backbone structure of glycosides found in stevia. These substances are four-ringed diterpenes. The C-19 carboxyl group and the C-13 hydroxyl group produce the sweet flavor (Gerwig *et al.,* 2016) [16]. The main glycosides found in the plant are stevioside, steviolbioside, isosteviol, and rebaudiosides A, B, C, D, E, and F. 250–300, 50–120, and 250–450 times sweeter than can sugar are stevioside and rebaudioside C and A, respectively. Under alkaline hydrolysis, rebaudiosides A and D can be converted to rebaudioside B. Both substances are extremely soluble and safe for the human body to metabolise (Kazmi *et al.,* 2019) [27]. The two are most appealing because they are pH stable, highly water soluble, thermostable (up to 200 °C), and do not ferment. *S. rebaudiana* also contains flavonoids, such as quercetin and kaempferol, which are known for their antioxidant and anti-inflammatory properties (Ghanta *et al.,* 2007) [17]. Essential oils and other volatile compounds found in the leaves contribute to its aroma and may possess antimicrobial properties. Collectively, these phytochemicals not only provide sweetness without calories but also offer a range of therapeutic advantages, making *S. rebaudiana* a valuable addition to both dietary and medicinal practices (Zaidan *et al.,* 2018) [54].

Table 1: Phytochemicals of S. rebaudiana

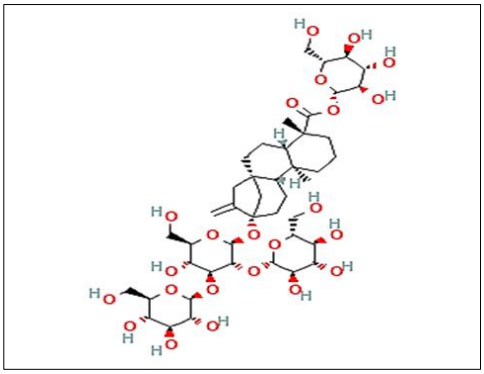
Phytochemical	Description	Reference
Glycosides	Stevioside, Rebaudioside A, Steviol, and Steviolbioside	Ascrizzi *et al.* (2022) [6]
Flavonoids	Quercetin, Kaempferol and Apigenin	Karaköse *et al.* (2015) [26]
Triterpenes	β-Amyrin, α-Amyrin, Lupeol, Oleanolic acid, Taraxerol, Friedelin and Ursolic acid	Ghosh, (2016) [18]
Phenolic acids	caffeic acid, chlorogenic acid	Fu *et al.* (2015) [12]
Diterpenes	Isosteviol, Dulcoside A, Kaurenoic acid	Yadav *et al.* (2012) [53]
Xanthophylls	Lutein and β-carotene	Pirgozliev *et al*., (2022) [44]

Table 2: The substituents of steviol glycosides

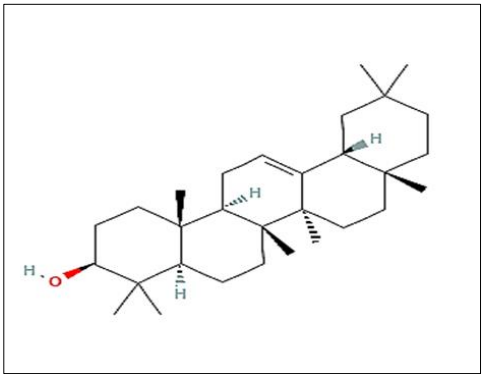
Steviol glycoside	R1 constituent	R2 constituent
Dulcoside A	*β*-Glc	*β*-Glc-*α*- Rha(2 → 1)
Rebaudioside A	*β*-Glc	β-Glc-β-Glc(2→1), β-Glc(3→1)
Rebaudioside B	H	β-Glc-β-Glc(2→1), β-Glc(3→1)
Rebaudioside C	*β*-Glc	β-Glc-α-Rha(2→1), β-Glc(3→1)
Rebaudioside D	β-Glc-β-Glc(2 → 1)	β-Glc-β-Glc (2→1), β-Glc (3→1)
Rebaudioside E	*β*-Glc-*β*-Glc(2 → 1)	*β*-Glc-*β*-Glc(2 → 1)
Rebaudioside F	*β*-Glc	β-Glc-β-Xyl(2→1), β-Glc(3→1)
Stevioside	*β*-Glc	*β*-Glc-*β*-Glc (2 → 1)
Steviolbioside	H	*β*-Glc-*β*-Glc (2 → 1)
Steviol	H	H



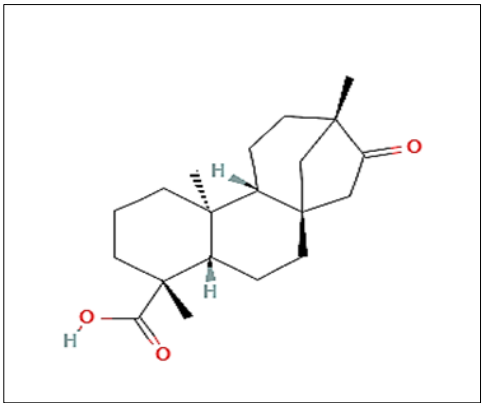
Stevioside ($C_{38}H_{60}O_{18}$)



Rebaudioside A ($C_{44}H_{70}O_{23}$)



Steviol ($C_{20}H_{30}O_3$)



Isosteviol ($C_{20}H_{30}O_3$)

Medicinal Activity of *S. rebaudiana*

Antioxidant activity

Stevia rebaudiana exhibits strong antioxidant activity due to its rich composition of bioactive compounds such as flavonoids, phenolic acids, and diterpenes (Gaweł *et al.*, 2015) [15]. Key antioxidants include quercetin, kaempferol, caffeic acid, and chlorogenic acid, which are known for their ability to neutralize free radicals and reduce oxidative stress (Pacifico *et al.*, 2019) [42]. The steviol glycosides, particularly stevioside and rebaudioside A, also contribute to this effect through their potential to scavenge reactive oxygen species (ROS) (Gutiérrez *et al.*, 2021) [20]. The antioxidant potential of *Stevia rebaudiana* has been demonstrated in various studies, showing significant protective effects against lipid peroxidation and DNA damage (Hanna *et al.*, 2023) [21]. This antioxidant activity is important in preventing chronic diseases, including cardiovascular disorders and cancer, which are associated with oxidative stress. Research highlights the plant's capacity to modulate antioxidant enzymes, enhancing overall cellular defense mechanisms (Ganjiani *et al.*, 2020) [13]. These findings emphasize *S. rebaudiana's* role as not only a natural sweetener but also a potential functional food with health-promoting benefits.

Antidiabetic activity

Several studies demonstrate glucoregulation activity through its steviol glycosides, primarily stevioside and rebaudioside A, which have been shown to help regulate blood glucose levels. These compounds enhance insulin secretion from pancreatic β-cells in a glucose-dependent manner, aiding in the proper uptake and utilization of glucose (Jahangir *et al.*, 2020) [25]. Additionally, steviol glycosides improve insulin sensitivity by activating insulin receptors and modulating glucose transporter proteins, such as GLUT4, facilitating glucose uptake into muscle and adipose tissues (Deenadayalan *et al.*, 2021) [10]. Stevioside may also inhibit gluconeogenesis in the liver, reducing endogenous glucose production. The suppression of glucagon release, a hormone that raises blood sugar, further contributes to its hypoglycemic effect (Kurek *et al.*, 2022) [29]. Studies in diabetic animal models and humans have confirmed these mechanisms, showing that Stevia intake helps maintain normal blood glucose levels and improves glucose tolerance (Chowdhury *et al.*, 2022) [9]. This makes *Stevia rebaudiana* a promising natural therapeutic agent for managing diabetes and metabolic disorders.

Antihypertensive effects

S. rebaudiana has been shown to have blood pressure-lowering effects, primarily through the action of its steviol glycosides, particularly stevioside. Stevioside exerts antihypertensive effects by acting as a vasodilator, relaxing blood vessels and reducing peripheral vascular resistance. This occurs through the inhibition of calcium ion influx into vascular smooth muscle cells, which prevents contraction and promotes vasodilation (Orellana *et al.*, 2023) [39]. Additionally, stevioside enhances the production of nitric oxide (NO), a potent vasodilator that helps maintain vascular tone and lowers blood pressure (Chatsudthipong and Muanprasat, 2009) [8]. Stevia also has diuretic properties, which facilitate the excretion of excess sodium, further contributing to reduced blood pressure (Kotowicz *et al.*, 2024) [28]. Clinical studies in hypertensive patients have

demonstrated significant reductions in systolic and diastolic blood pressure after chronic consumption of Stevia extract, without affecting heart rate. These findings suggest that *S. rebaudiana* can be a beneficial natural supplement for managing hypertension and promoting cardiovascular health.

Anti-cancer activity

S. rebaudiana exhibits anticancerous activity, attributed to its bioactive compounds, particularly steviol glycosides, flavonoids, and diterpenes. Stevioside and rebaudioside A have been shown to induce apoptosis (programmed cell death) in cancer cells by activating caspases, enzymes crucial for apoptotic pathways (Iatridis *et al.,* 2022) [23]. These compounds also inhibit cancer cell proliferation by arresting the cell cycle in the G1 phase, preventing further division of malignant cells (Sun *et al.,* 2024) [48]. Flavonoids like quercetin and kaempferol in Stevia enhance these effects by scavenging free radicals and reducing oxidative stress, which is a key factor in cancer development (Al-Ishaq *et al.,* 2023) [3]. Furthermore, steviol glycosides modulate inflammatory pathways by downregulating pro-inflammatory cytokines, such as NF-κB, which play a role in tumor growth and metastasis (Ilias *et al.,* 2021) [24]. Studies have shown that Stevia extracts exert cytotoxic effects on various cancer cell lines, including breast, colon, and pancreatic cancers, suggesting its potential as a natural anticancer agent (Munir *et al.,* 2024) [37].

Renal Protective

S. rebaudiana has shown renal protective activity, largely due to its antioxidant and anti-inflammatory properties. The steviol glycosides, particularly stevioside, help reduce oxidative stress in kidney tissues by scavenging reactive oxygen species (ROS) and enhancing the activity of endogenous antioxidant enzymes like superoxide dismutase (SOD) and catalase. This prevents damage to renal cells caused by oxidative stress, a key factor in the progression of kidney diseases (Xu *et al.,* 2023) [52]. Additionally, Stevia's anti-inflammatory effects are linked to the downregulation of pro-inflammatory markers such as TNF-α and IL-6, which reduces inflammation in the kidneys (Othman *et al.,* 2023) [40]. Stevioside has also been shown to improve kidney function by reducing proteinuria (excess protein in the urine) and glomerular damage in diabetic nephropathy models (Ozbayer *et al.,* 2011) [41]. Moreover, its mild diuretic effect helps in maintaining electrolyte balance and preventing kidney strain. These findings suggest that *Stevia rebaudiana* can offer significant protection against renal injury, particularly in diabetic or hypertensive conditions (Ray *et al.,* 2020) [45].

Obesity regulation

Stevia rebaudiana aids in obesity regulation through its steviol glycosides, which provide sweetness without contributing calories, making it an ideal substitute for sugar in weight management (Wal *et al.,* 2019) [50]. Stevioside and rebaudioside A influence glucose metabolism by reducing blood glucose spikes, lowering insulin levels, and improving insulin sensitivity, all of which are key in preventing fat accumulation (Antonik *et al.,* 2020) [5]. These compounds also regulate appetite by modulating satiety hormones such as leptin and ghrelin, potentially reducing food intake (Mehmood *et al.,* 2022) [34]. Furthermore, Stevia promotes fat breakdown (lipolysis) and inhibits fat production (lipogenesis) in adipocytes, reducing overall fat storage (Verma *et al.,* 2019) [49]. Its antioxidant properties also help counteract inflammation associated with obesity, lowering the risk of obesity-related complications such as metabolic syndrome (Mohd-Radzman *et al.,* 2013) [36]. Studies on animal models and human trials suggest that regular consumption of *S. rebaudiana* as a sugar alternative helps in controlling weight gain, making it a valuable tool in obesity prevention and management.

Conclusion

S. rebaudiana, renowned for its natural sweetness derived from steviol glycosides, presents a promising avenue in both culinary and medicinal fields. Its chemical properties, primarily attributed to steviol glycosides such as stevioside and rebaudioside A, contribute to its intense sweetness without adding calories, making it a favorable alternative to synthetic sweeteners. Medicinally, Stevia demonstrates potential in managing diabetes and hypertension due to its ability to regulate blood glucose levels and lower blood pressure. Nonetheless, studies are still going on to understand fully the herb. Therefore, not all that is known about the plant is included in the conclusion drawn. The chemical composition of *S. rebaudiana* is highlighted in this paper, along with its medicinal properties, which include antioxidant, antihypoglycemic, anticancer, renal, obesity management and antihypertensive activities.

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