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Study of Medicinal Plant Stevia *Rebaudiana* (Bert.) and Biosynthesis of its Chemical Compound as Well as Medicinal Uses and Pharmological Properties

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Abstract : Stevia rebaudiana, renowned for its sweet leaves containing steviol glycosides, offers a organic sugar alternative with potency up to 300 times that of cane sugar. Flourishing in subtropical climates, it enjoys widespread cultivation for its non-caloric sweetness, particularly beneficial for individuals with hyperglycemia. Originating from Paraguay, its global cultivation stems from its economic significance and medicinal attributes, stevia leaves also contain various phytoconstituents, providing diverse health benefits including antidiabetic, antimicrobial, and antioxidant properties. Its dual role as aorganic sweetener and medicinal herb underscores its importance in both the food industry and healthcare sector. Stevia leaves encompass a range of compounds including steviol glycosides, flavonoid glycosides, triterpenes, sterols, and antioxidants. Steviol glycosides, particularly stevioside and rebaudioside A, exhibit promising pharmacological properties. In diabetes management, they enhance insulin secretion, improve glucose metabolism, and mitigate insulin resistance without affecting normal glucose levels. Their antioxidant prowess shields against oxidative stress-induced tissue damage, while their blood pressure-lowering effects include vasodilation and diuresis, suggesting potential benefits for hypertension treatment. Evidence hints at stevioside's selective antihypertensive effects, sparing individuals with normal blood pressure. With minimal adverse effects, steviol glycosides emerge as valuable candidates for further exploration in diabetes, antioxidant therapy, and hypertension management. Steviol glycosides, particularly stevioside and rebaudioside A, display diverse therapeutic properties with potential applications across various health conditions. They exhibit antidiarrheal activity by inhibiting CFTR and regulating intestinal smooth muscle contraction. Their anti-inflammatory effects involve modulating NF-κBsignaling and reducing liver inflammation. Moreover, they hold promise in cancer therapy by inhibiting carcinogenesis and inducing apoptosis in cancer cells. Additionally, steviol glycosides offer benefits against obesity, display antiviral activity against HSV-1 and rotavirus, and modulate lipid levels and gut microbiota. These properties position steviol glycosides as valuable candidates for medicinal and dietary supplementation with minimal adverse effects.

Keywords: Stevia rebaudiana, Steviol glycosidesAntidiabetic, Antimicrobial, Antioxidant

Hypertension management, Antiviral activity

Introduction

Stevia (*SteviarebaudianaBertoni*) is aBlossoming plant belonging to the Stevia genus within the Compositaefamily. Its leaves, recognized for their sweetness, have earned it various names including candy leaf herb, honey leaf as well as sweet leaf.

Sweetness of these leaves comes from Steviol glycosides, chemical compounds that serve as non-caloric sweeteners.(Madan*et al.,*2010).Stevia leaves possess functional and sensory characteristics that surpass those of numerous other high-strength sweeteners, making them a promising candidate to emerge as a primary organic sweetener for the expanding outsider (food market). (Samsher*et al.,*2010; Ahmad*et al.,*2020; Kovačević*et al.,*2018).The green powder derived from Stevia leaf is round about 18 to 20 or less than 25 times sweeter than Beet sugar as well as sugar cane, on the other hand pure extract of Stevioside and it boasts a sweetness level around 300 times greater than that of sugar.Because of its non-caloric sweetness, this plant holds added significance, particularly for individuals with hyperglycemia, offering them an alternative to sugar for consumption. (Sikdar*et al.,*2012).Stevia (*Rebaudianabertoni*) is a tiny eternal shrub, typically reaching heights upto 65 to 80 cm, characterized by leaves organize directly opposite each other. It thrives in semi-steamy subtropical climates and perchance cultivated simply, much type of some alternate kitchen gardens and unform in vegetable crop. The shrub prefers well-pour out red sandy loam soils pH upto 6.5-7.5, and it's advisable to avoid saline soils during its cultivation (Samsher*et al.,* 2010).

(Shalini *et al.,*2013), found stevia flowers are tiny, bleached, with a bright purple throat, and organize in little corymbs.(Kobus-Moryson and Gramza-Michalowska., 2015).indicates that stevia (Rebaudianabertoni) organicly grows in semitropical pasture at altitudes ranging upto 200–500m more than sea level. It tolerates temperatures reach upto –6°C to 43°C, with overall temperature of 23°C. Stevia requires an annual rainfall of 1500–1800 mm, boasting ellipse-shaped leaves and white blooms. Cultivation conditions for stevia vary; it thrives in dark, moist sandy soils, loamy, highly permeable soils, and is also found along swamp banks, on infertile, acidic sands, or muck soils.(Kumar et al., 2011).

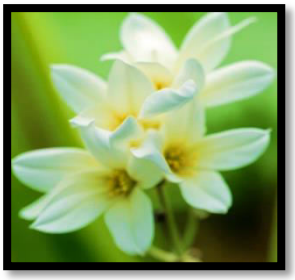
The genus Stevia comprises around 200 species of bloossoming, bush, and sub-bush plants, making it one of the finest distinguishable genera inside the gens Eupatorieae.This distinctiveness arises from the regularity of its capitula and flowers, which typically incorporate of five involucral bracts and five tubular flowers (Shivanna et al., 2013).Stevia is distributed from the Central America, southward through Mexico and southwestern United States, extending into non-Amazonian, South Americareaching as far as south Central Argentina. Up to30 species have been identified in Brazil, predominantly in the central regions and southern. Stevia (*Rebaudianabertoni*) drive from hills areas of northeastern

Paraguay, latitudes are 23⁰ and 24 near the Brazilian border, the local Guarani Indians had recognized many centuries ago the unique sweetening power and medicinal properties of its leaves. United Kingdom exported the first seeds, where cultivation attempts failed. However, in 1968, the seeds were successfully exported to Japan, leading to increased global awareness and cultivation of the plant. Since then, Stevia has been initiated tomany countries, including India, Tanzania, Mexico, Korea, Indonesia, United States of America, Braziland Canada (Simonetti *et al.,* 2003; Ferrazzano*et al.,* 2015; Kumar*et al.,* 2011).

Botanical Classification reported the botanical classification of stevia (*Rebaudianabertoni*) as given in Table.(Kumar*et al.,* 2011).

Kingdom	Plantae
Division	Magnoliophyta
Class	Magnoliopsida
Group	Monochlamydae
Order	Asterales
Family	Asteraceae
Tribe	Eupatorieae
Genus	Stevia
Species	Rebaudiana

Botanical descriptions of stevia Description,



Source: Kumar*et al.,* 2011

Figure 1.Figure 2.Figure 3.

Figure 1. Stevia (*Rebaudianabertoni*) plant.,Figure 2. Stevia *(Rebaudianabertoni)* flowers Figure 3. Stevia *(Rebaudianabertoni)* plant Fresh leaves

(Rieck- Wolwer., 2012), stevia (Rebaudianabertoni) is eternal herb esteemed for its considerable economic value attributed to the abundant organic sweeteners found in its leaves. When stevia leaves dehydrated then they have long served as organic sweeteners, while extracts are approved as food additives in numerous countries worldwide. The utilization of stevia *(Rebaudianabertoni)* plays a significant place in treating various ailments, with no evidence of adverse effects associated with its consumption. Stevia is rich in phenols and flavonoids, endowing it with potent antioxidant properties (Asrani and Thakur., 2020

Stevia is primarily recognized steviol glycosides found in its leaves, which serve as calorie-free and non-sucrose sweeteners in numerous food appilcations. Glycosides are natural compounds comprising two components: a carbohydrate known as the glycone, that is linked through a glycoside bond to defferent component called the a non-sugar group, aglycone. (Orellana*et al.,* 2023). Among the stevioside, steviol glycosides and rebaudioside A (RebA) are the most widely recognized and prevalent glycosides found in the plant. (Chaturvedula et al., 2014., Geuns., 2003). Apart from these sweetening compounds, stevia leaves also contain phenolic compounds, vitamins, essential oils, dietary fibres, water-soluble, lipids, minerals and carbohydrates and. (Tavarini,*et al.,* 2013.,Wolwer*et al*., 2012).

Recent research has revealed numerous advantages associated with consuming stevia leaves for human health. Owing to their abundance of diverse phytoconstituents, stevia leaves demonstrate a wide spectrum of biological effects, including antihypertensive, antioxidant, anti-tumor, antidiabetic, antimicrobial, and anti-inflammatory properties. (Ruiz *et al*., 2017., Borgo*et al*., 2021).

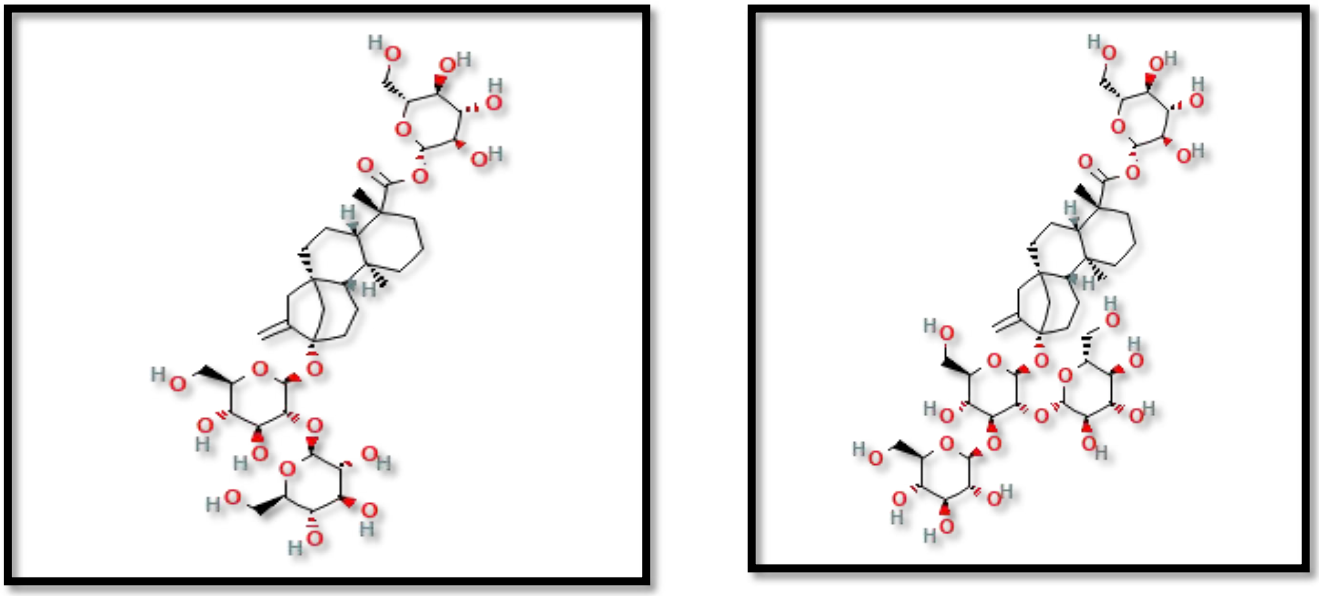
Composition of Chemical

Stevia leaves contain the sweetening compounds known as Steviolglycosides. (Megeji*et al*., 2005).Additionally, there exist other associated compounds such as, coumarins, flavonoid glycosides, phenylpropanoids cinnamic acids and certain essential oils.(Hossain*et al*., 2017).Furthermore, the leaves also bear triterpenes like amyrin acetate and three lupeol esters, along with sterols such as campesterol, , sitosterol, and stigmasterol. Moreover, Stevia is rich in phenols, flavonoids, and antioxidants. (Agostino*et al*., 2023).

Steviol Glycosides and it's Structure

Above the 300 species within the genus Stevia, only 18 possess sweetening character. *Stevia rebaudiana* stands out as the sweetest variety among them. Its leaves organicly contain eight steviol glycosides (ent-kaurene glycosides), including, rebaudiosides A-E, dulcoside A, stevioside and steviolbioside. The total content of these glycosides scale upto 4per cent to 20per cent, based on the genotype and cultivation conditions. The primary sweeteners found in Stevia

rebaudiana are stevioside (~9.1per cent) and rebaudioside A (~3.8per cent). (Tavarini, et al., 2013., Brahmachari*et al*., 2011). (Figure 1).All Steviol glycosides share comparable structures, with Steviol serving as the aglycone for both primary and secondary sweetener compounds.(Wallin., 2004).(Figure 3). aglycone is linked at positions C-13 to mono-, di-, or tri-saccharides and C-4 composed of rhamnose residues and/or glucose. (Ni F*et al*., 2007., Shah*et al*., 2012).(Figure4)



SteviosideRebaudioside A

Figure 1.Structure of the main steviol glycosides in Stevia *rebaudianaBertoni.*

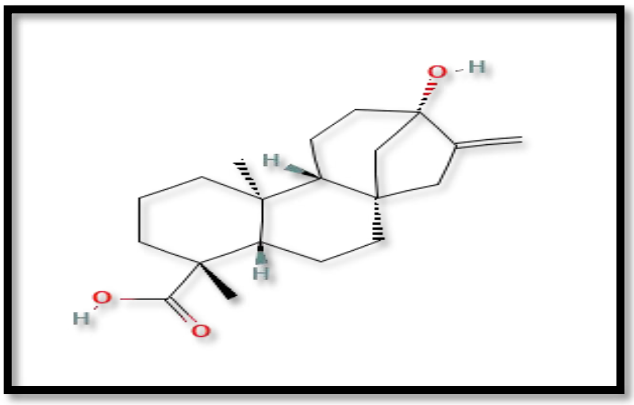


Figure 3. Steviol-the aglycone of sweetner compounds

H : Hydrogen

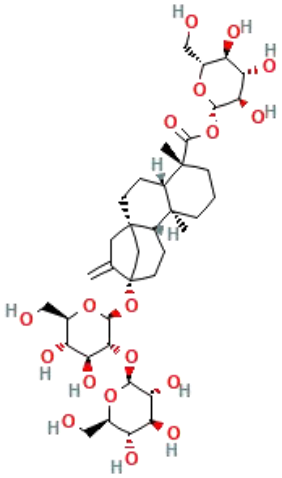
Glc : Glucose Rha : Rhamnose Xyl : Xylose

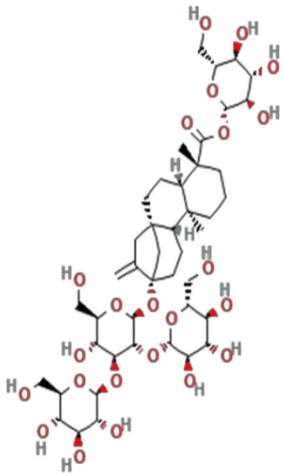
(Wallin, 2004; Shah *et al*., 2012)

Compound Name	R1	R2
DulcosideA	β-Glc	β-Glc-α-Rha(2→1)
RebaudiosideA	β-Glc	β-Glc-β-Glc(2→1)|β-Glc(3→1)
RebaudiosideB	H	β-Glc-β-Glc(2→1)|β-Glc(3→1)
RebaudiosideC	β-Glc	β-Glc-α-Rha(2→1)|β-Glc(3→1)
RebaudiosideD	β-Glc-β-Glc(2→1)	β-Glc-β-Glc(2→1)|
RebaudiosideE	β-Glc-β-Glc(2→1)	β-Glc(3→1)β-Glc-β-Glc(2→1)
RebaudiosieF	β-Glc	β-Glc-β-Xyl(2→1)| Glc(3→1)
Steviol	H	H
Steviolbioside	H	β-Glc-β-Glc(2→1)
Stevioside	β-Glc	β-Glc-β-Glc(2→1)

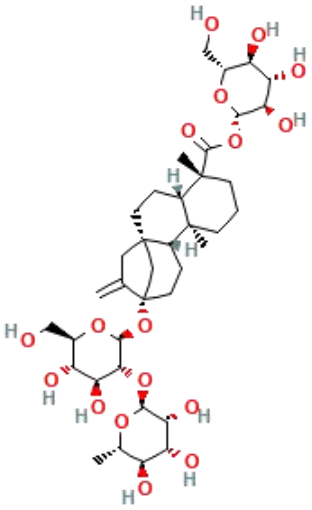
Table 4.Chemical structures of mainsteviol glycosides.

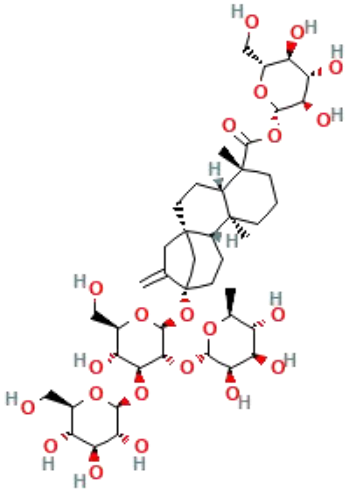
The plant contains approximately ten Steviol glycosides, including Steviolbioside, Rebaudioside A, B, C, D, E, F, Stevioside, and Dulcoside A,. (Madan*et al*.,2010). Among these, the four primary sweeteners are Dulcoside A, Rebaudioside A, , Rebaudioside C, and Stevioside, with sweetness levels comparable to sucrose of 210, 242, 30, and 30 times, mindly. (Kinghorn*et al*.,1987). (Figure 5). The percentage of steviol glycosides drive in the total dehydrated weight of Stevia leaves is as follows: 5-10per cent Stevioside, 2-5per cent Rebaudioside A, 1per cent Rebaudioside C, 0.5per cent Dulcoside A, 0.2per cent Rebaudioside D, E, F, and 0.1per cent Steviolbioside. (Kumar*et al.,* 2011., Wojewoda*et al.,* 2018).





SteviosideRebaudioside A





DulcosideA **RebaudiosideC**

Figure 5.Four main structures of steviol glycosides

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(Available:https://www.sigmaaldrich.com/ca)

Biosynthesis Steviol Glycosides

Stevia rebaudiana generates natural sweet compounds called steviol glycosides in its leaves, with steviol as its basic component. Research suggests that steviol is derived from kaurene via the MEP pathway, as evidenced by multiple studies.The biosynthesis process consists of two primary stages. Initially, compounds sourced from primary metabolic pathways, like Pyruvate and Glyceraldehyde 3-Phosphate (G-3-P), undergo processes to produce isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP) through the 2-C-methyl-D-erythritol-4

phosphate pathway (MEP pathway). Following this, IPP and DMAPP merge to generate Geranylgeranyl diphosphate (GGDP).(Figure 6).

In the subsequent phase, GGDP undergoes a series of conversions to yield steviol glycosides. Initially, GGDP transforms into (-) Copalyldisphosphate through cyclization, followed by the production of Kaurene via ionization-dependent cyclization. Kaurene is then oxidized to kaurenoic acid. At this point, the biosynthesis of Steviol glycosides diverges from the pathway responsible for gibberellin production. The subsequent step involves the hydroxylation of kaurenoic acid to generate Steviol (the aglycone), marking the pivotal initial stage in steviol glycoside synthesis.(Brandle et al 2007.,Kumaret al 2012). (Figure 6).

Steviol glycosides are synthesized within the leaves and subsequently distributed throughout the plant. As noted by Hedden and Phillips (2000), the early phases of steviol glycoside biosynthesis are confined to green tissues.(Bondarev *et al.*, 2003). The presence of steviol glycosides is primarily observed in tissues containing chloroplasts, as indicated by research. The biosynthesis pathway for these glycosides involves various cellular organelles. Initially, the early stages leading to the production of Kaurene, the precursor of diterpenoids, take place within chloroplasts. Following this, Kaurene is transported to the endoplasmic reticulum (ER), where enzymes facilitate its conversion into steviol. (Nakai*et al.,* 1999).Enzymes positioned on the membrane of the endoplasmic reticulum (ER) are responsible for the conversion of kaurene into steviol. Subsequently, steviol is transferred to the cytosol, where the synthesis of steviol glycosides occurs, leading to their eventual accumulation in the vacuole.(Kumar *et al.,* 2012).The involvement of chloroplasts in the leaves is pivotal for the biosynthesis of steviol glycosides, acting as a precursor. Consequently, Stevia leaves exhibit higher concentrations of glycosides compared to other plant parts.(Singh *et al.,* 2005).

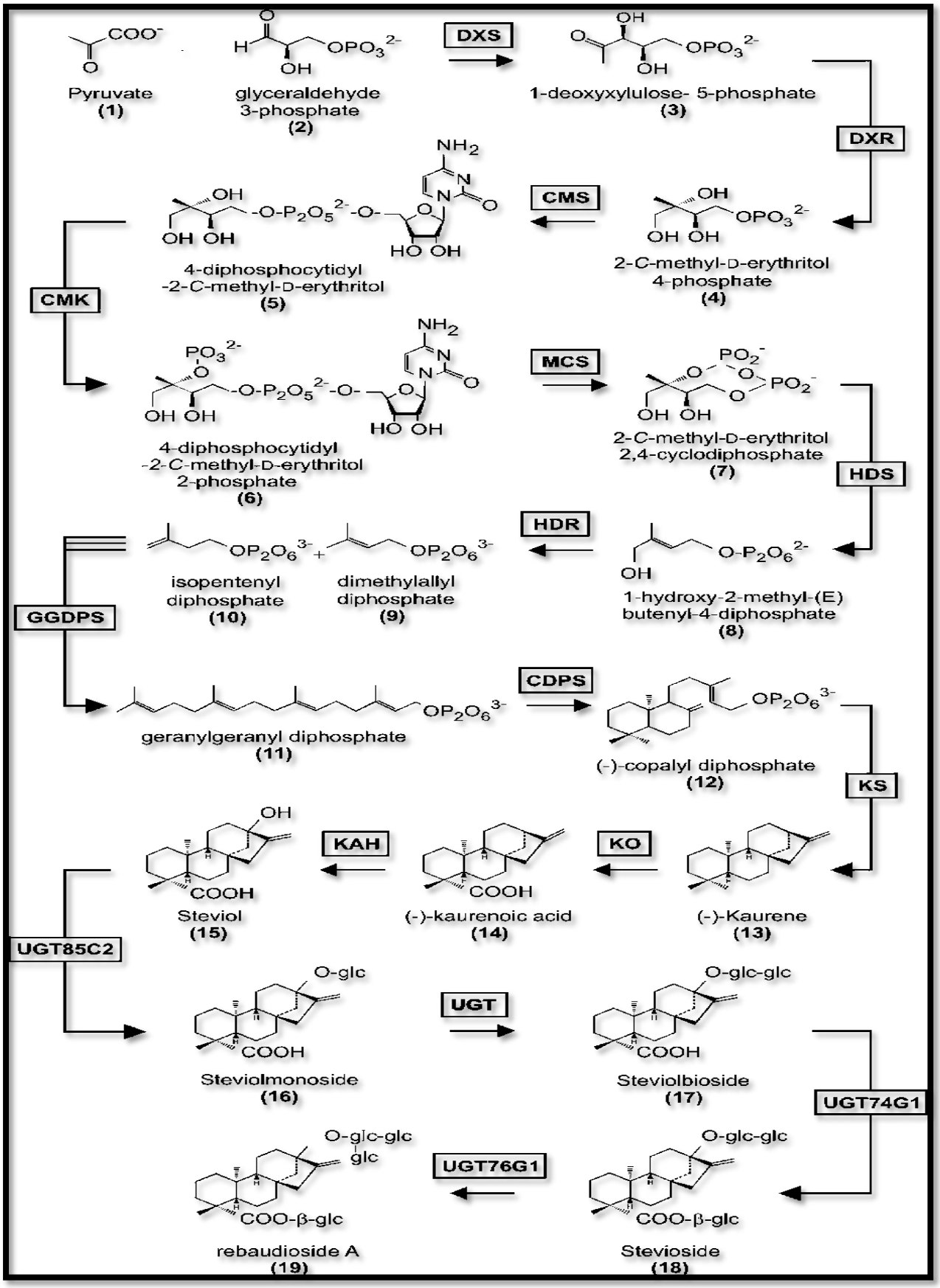

Figure 6.steviol glycoside biosynthesis via MEP pathway. (Brandle et al 2007).

The presence of chloroplasts is vital for glycoside biosynthesis, leading to minimal or absent levels of steviol glycosides in plant parts lacking chloroplasts. Various research have consistently present that steviol glycosides are predominantly found in leaves, with minimal amounts in stems and undetectable levels in roots. (Brandle*et al.,* 1992).affirming this observation. Older leaves tend to have higher sweetener content compared to junior leaves, as steviol glycosides cumulate in tissues as they full grown. The glycoside pacify in leaves decreases during flowering. as it serves as an energy source for the process. (Kumar *et al.,* 2011).

Pharmacokinetics

Preclinical and clinical Bothresearchesare indicating that stevioside remains undecomposed by digestive enzymes and gastric juice. (Koyama*et al*., 2003., Koyama*et al*., 2003).Additionally, ingestion of stevioside orally seems to not undergo absorption in the upper small intestine, likely due to its elevated molecular weight.(Koyama*et al*., 2003).Nonetheless, within the lower gastrointestinal tracts of rats, mice, pigs, and humans, bacterial intestinal flora (particularly from the Bacteroides genus) can break down stevioside, transforming it into free steviol, which is the aglycone form of steviol glycosides.(Koyama*et al*., 2003., Geuns*et al*., 2003).Research involving human volunteers revealed that following the consumption of stevioside at a dosage of 750 mg per day, no measurable levels of free steviol, stevioside, or any other steviol metabolite were detected in bloodstream. However, steviol was found in the fecal matter. (Geuns*et al*., 2007).(Figure2).

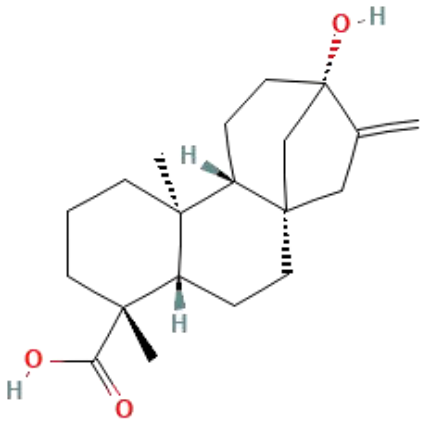

Figure 2.The composition of steviol, which is the typical metabolite resulting from the breakdown of steviol glycosides

In rats, oral administration of stevioside led to the detection of steviol in a portal venous blood sample. (Koyama *et al*., 2003). Studies using everted rat intestinal sacs demonstrated a significantly higher shift rate for steviol compared to

stevioside.comparably, The transport of stevioside is limited in the human intestinal Caco-2 cell line as compared to steviol. (Geunse*t al*., 2003).

Thus, absorption after oral administration primarily involves steviol rather than stevioside. In rats given a single oral dose of radioactive 3H-stevioside (125 mg/kg), the peak blood radioactivity level was 4.8 µg/mL, and an elimination half-life of 24 hours was observed eight hours after administration.(Nakayama*et al.,* 1986).After intravenous injection, the liver exhibited the most significant accumulation of radioactive 131I-stevioside in rats, accounting for 52 percent of the injected dose. High-performance liquid chromatography (HPLC) analysis of bile identified steviol as the primary metabolite, along with several other compounds that remained unidentified.(Cardoso *et al.,*1996). The liver conducts the changing of rebaudioside A and stevioside into steviol (phase I metabolism), which is then excreted through urine. (Geunse*t al*., 2006; Wheeler*et al*., 2008).Steviol undergoes enterohepatic reabsorption and is transformed into steviol glucuronide through phase II metabolism. This primary metabolite is rapidly eliminated from the body. Both in humans and rats, steviol glucuronide is the main blood metabolite. However, their excretion routes differ due to variations in the molecular weight threshold for organic anions excreted via bile. In humans, organic ions weighing more than 600 Da are excreted through bile rather than urine, whereas in rats, those weighing over 325 Da follow the same route. Despite its molecular weight of 512.9 Da, steviol glucuronide is excreted through the kidneys in humans and through bile in rats.(Geunse*t al*., 2006).In experimental studies investigating renal elimination, rats displayed nephrotoxic effects after receiving stevioside via subcutaneous administration at a dosage of 1.5 g/kg, equivalent to 250 times the average daily human intake. Increased levels of urinary glucose and plasma creatinine were observed following stevioside administration. These findings indicate that at very high doses, stevioside might interfere with secretory transport mechanisms. Inhibition of secretory transport systems is warranted to leverage stevioside for prolonging drug clearance and enhancing the efficacy of these systems within the human body. Stevioside remains deemed safe when consumed within ace ptable daily intake (ADI) limits. (Toskulkao*et al.,* 1994).

Pharmacological Properties of Steviol Glycosides

Action against diabetes

Diabetes is a chronic metabolic condition characterized by insufficient insulin levels, which can result from the destruction of pancreatic beta cells (type 1 diabetes) or reduced responsiveness of cells to insulin (type 2 diabetes). (Schmidt*et al.,* 2018). Globally, approximately 536.6 million individuals are impacted by this condition. (Sun *et al.,*2022).Unhealthy dietary habits, sedentary lifestyle, and genetic predisposition are contributing factors to type 2 diabetes mellitus (T2DM).Type 2 diabetes mellitus (T2DM) is distinguished by

compromised glucose regulation in the liver and diminished sensitivity to insulin in peripheral tissues. Furthermore, the emergence of atherosclerosis and cardiovascular ailments represents frequent complications associated with T2DM. (Galicia*et al.,* 2022).A study examined the potential hypoglycemic impacts of stevioside in both type 2 diabetic Goto-Kakizaki (GK) rats and ordinary Wistar rats.(Jeppesen*et al.,* 2002).In diabetic rats, administering stevioside intravenously at a dose of 0.2 g/kg resulted in decreased blood glucose levels, heightened insulin responses, and improved responses in an intravenous glucose tolerance test (IVGT). Conversely, in normal rats, stevioside increased insulin levels during the IVGT but did not affect blood glucose response. These findings suggest that stevioside holds promise as a potential treatment for type 2 diabetes. This is supported by its ability to dose-dependently reduce insulin resistance and induce hypoglycemic effects in diabetic streptozocin (STZ)-induced rats. It is believed that stevioside enhances insulin secretion and sensitivity by inhibiting gluconeogenesis, possibly through downregulating the expression of the phosphoenolpyruvate carboxykinase (PEPCK) gene in the liver of rats.(Chen *et al.,* 2020).Additionally, rebaudioside A increased insulin construction in isolated murine islets of Langerhans, relying on the extracellular Ca2+ concentration for its effectiveness.(Abdulla*et al.,*2004). Both rebaudioside A and stevioside acted as bind for receptors,simulate the effects of insulin. Steviol glycosides (SGs) boosted glucose Absorptionin rat fibroblasts. (Prata*et al.,* 2017).Much like insulin, SGs stimulated heightened glucose transport in HL-60 human leukemia and SH-SY5Y human neuroblastoma cells. Furthermore, both SGs and insulin induced phosphorylation of PI3K and Akt, indicating a correlation between GLUT translocation and modulation of the PI3K/Akt pathway. (Rizzo*et al.,* 2017).Research suggests that stevioside boosts insulin-facilitated glucose transportation into skeletal muscle and enhances insulin sensitivity in rats, regardless of whether they are insulin-resistant or insulin-sensitive.(Lailerd*et al.,* 2004).

Moreover, rebaudioside A and stevioside increased the of TRPM5, a Ca2+-activated cation channel in pancreatic β-cells. As a result, insulin secretion associated with TRPM5 increased, thereby preventing hyperglycemia in mice with diet-induced diabetes. Additionally, rebaudioside A and stevioside enhanced the action of TRPM5, a calcium-trigger cation channel found in pancreatic beta cells. Consequently, insulin release linked to TRPM5 was augmented, thus mitigating hyperglycemia in mice afflicted with diet-induced diabetes.(Philippaert*et al.,* 2017).In both live animal and tissue studies conducted on rats, it was observed that adding rebaudioside A or stevioside to their diets at doses of 500 and 2500 mg/kg did not cause any changes in blood glucose levels, insulin levels, or the index of insulin resistance. Nevertheless, these compounds did regulate lipid metabolism and shielded vital organs from harm in this particular model.(Kureke*t al.,*2020).

The possible negative impacts on metabolism are minimal, since SGs don't function as glucocorticoid receptor (GR) activators and hence don't influence the expression of GR-target genes, levels of GR protein, or GRs on peripheral blood mononuclear cells.(Panagiotou*et al.,*2018). When it comes to regulating typical blood glucose levels, giving normal rats 5.5 mg/kg/day of stevioside orally for 15 days showed no impact. However, providing stevia at a dosage of 20 mg/kg/day led to reduced plasma glucose levels below their initial levels by inhibiting the activity of pyruvate carboxylase and PEPCK.(Ferreira*et al.,* 2006).Stevioside doesn't show a blood sugar-lowering effect when glucose levels are normal but does demonstrate such an effect when blood glucose levels are high in rats with diabetes. Conversely, the hypoglycemic effect of stevia might be due to another component in the extract, separate from stevioside, and not specific to it. Clinical findings back the safe consumption of stevioside over the long term (250 mg, three times/day for three months), with no impact on normal glucose levels or blood pressure.(Geuns*et al.,*2007).

Antioxidant Activity

Excessive generation of reactive oxygen/nitrogen compounds overwhelms the body's antioxidant defenses during oxidative stress, resulting in tissue damage, accelerated cell death, and oxidative modifications of biological macromolecules. Consequently, oxidative stress underpins the pathological basis for numerous diseases. (Trevisan*et al.,* 2001).

Thioacetamide-induced liver damage diminishes antioxidant capacity by suppressing nuclear erythroid factor 2 (Nrf2). In murine models, stevioside administration (20 mg/kg, twice daily) upregulated Nrf2 levels, preventing the rise of oxidative stress markers, mitigating liver injury. (Sael*et al.,*20019).Likewise, a combination of stevioside, rebaudioside A, rebaudioside C, and dulcoside A enhanced the survival of rat cardiac fibroblasts exposed to hydrogen peroxide, while augmenting the concentration and activity of catalase and superoxide dismutase. (Cecilia*et al.,*2017).The antioxidant properties of stevioside and rebaudioside A were exhibited in a fish model, effectively regulating lipid peroxidation and protein carbonylation. (Sánchez*et al.* 2017).Furthermore, stevioside safeguarded against oxidative DNA damage in the livers and kidneys of a murine model of type 2 diabetes. In silico analysis unveiled the potential mechanism of action of stevioside, linked to its capability to inhibit beta-adrenergic and G-protein-coupled receptor kinases (Rotimi*et al.,* 2018).

Additionally, the antioxidant properties were evaluated in food applications. Steviol glycosides (SGs) at concentrations of 50, 125, and 200 mg/L reduced the degradation rates of antioxidants (ascorbic and dehydroascorbic acid) in a dose-dependent manner. Higher concentrations of acids and sweeteners displayed stronger antioxidant effects, with no observed variation in SG concentration.

(Wo´zniak*et al.,* 2014).Likewise, preservation of fruit beverages with stevia exhibited enhanced antioxidant indexes and augmented sweetness. (Žlabur et al., 2019).

Blood pressure-lowering effects.

Worldwide, around 8.5 million deaths have been linked to systolic blood pressure surpassing 115 mmHg, with nearly 88% of these instances taking place in low- and middle-income nations.(Zhou*et al.,* 2021). As a result, the prevalence of hypertension is greater in low- and middle-income countries (1.04 billion) compared to high-income nations (349 million). (Mills*et al.,* 2020).Hypertension risk factors encompass obesity, alcohol intake, sedentary lifestyle, high sodium consumption, and unhealthy dietary habits. Uncontrolled hypertension can precipitate cardiovascular and renal complications. Owing to hypertension's chronic treatment requirement, substantial interest exists in identifying efficacious therapies with minimal or no adverse effects. Evidence suggests stevioside and rebaudioside A induce vasodilation, diuresis, and natriuresis, decreasing plasma volume and ultimately lowering arterial pressure in both preclinical and clinical studies. (Melis*et al.,* 1992; Chan*et al.,* 2000).

The blood pressure-lowering effect noticed in rats after chronic oral administration of 2.67 g stevia leaves daily for 30 days was validated in spontaneously hypertensive rats. In this animal model, stevioside (100 mg/kg; intravenous) decreased blood pressure without impacting serum levels of epinephrine, norepinephrine, or dopamine. (Chan *et al.,* 1998).These findings corroborate observations in human patients with mild to moderate hypertension. Significant reductions in systolic and diastolic blood pressure were observed after one year of consuming 750 mg/day of stevioside and after two years of daily ingestion of 1500 mg/day of stevioside, with no alterations in blood biochemistry values or left ventricular mass index. (Chan *et al.,* 2000).

Additionally, intraperitoneal administration of stevioside prompted dose-dependent relaxation of vasopressin-induced vasoconstriction in isolated aortic rings, without inhibiting it in a calcium-free medium. This implies that stevioside induces vasorelaxation by inhibiting calcium influx into blood vessels. (Lee*et al.,* 2001).It's important to mention that stevioside's ability to lower blood pressure requires doses higher than the recommended daily intake. There's no indication of it causing low blood pressure in people with normal blood pressure levels. Therefore, stevioside is an interesting candidate for more research because of its specific effect on lowering blood pressure.(Geuns*et al.,* 2007).

Activity Against Diarrhea

Bacterial enterotoxins trigger the release of fluid and chloride ions in the intestine, leading to dehydration and disruptions in electrolyte levels. This release of negatively charged ions is made possible by the cystic fibrosis

transmembrane conductance regulator (CFTR), a vital chloride channel activated by cAMP. Steviol and dyhidrosteviol have been recognized as compounds that inhibit CFTR.(Chatsudthipong*et al.,* 2009). Additionally, stevioside regulates the contraction of intestinal smooth muscles. (Shiozaki,*et al.,* 2006).

These traits, combined with the possible antibacterial and antiviral capabilities of steviol glycosides (SGs), suggest their potential in diarrhea treatment. SGs have shown antibacterial activity against different foodborne pathogens, such as Escherichia coli, which is widely recognized as a major cause of intense diarrhea.(Tomita*et al.*, 1997).Regarding their antiviral properties, SGs seem to interfere with the attachment of rotavirus to host cells. Rotavirus infections are frequently linked with gastroenteritis in children.(Takahashi*et al.,* 2001).

Anti-inflammatory Capability.

Chronic inflammation involves the ongoing recruitment of lymphocytes and monocytes, along with tissue injured caused by sustained stimuli. Numerous chronic conditions, including autoimmune disorders and metabolic issues like obesity, cancer, fibrosis, and atherosclerosis, are primarily obtain by chronic inflammation. (Fleit,*et al.,*2014).

Proinflammatory cytokines, mainly produced by activated macrophages, play a crucial role in triggering inflammatory reaction. Fascinating results came from investigations assessing the release of proinflammatory cytokines (TNF-α and IL-1β) and nitric oxide in a human monocytic THP1 cell line. When THP1 cells were stimulated with lipopolysaccharide (LPS), stevioside at a concentration of 1mM suppressed NF-κB, a key transcription factor that regulates the expression of inflammatory cytokines. Conversely, in THP1 cells not stimulated with LPS, the same concentration of stevioside led to a moderate increase in their release.(Boonkaewwan*et al.,* 2006).After a week-long examination of the effects of stevioside (at a dose of 10 mg/kg/day) on muscle tissue recovery from cardiotoxin-induced damage in Wistar rats, it was observed that stevioside did not directly improve muscle regeneration. However, it did stimulate the activation of satellite cells by altering the NF-κB signaling pathway, resulting in an elevation in the quantity of myonuclei.(Bunprajun*et al.,* 2012).

Furthermore, steviol was found to be accountable for blocking inflammation induced by TPA. Therefore, both steviol and stevioside could offer advantages as dietary additions to aid in muscle recuperation and might hold potential as prospective options for advancing into new medications targeting inflammation.(Mizushina*et al.,* 2005)

Actionagainst cancer

According to the American Cancer Society, it's projected that around 19 million people will be survivors of cancer by 2024. The most common types of cancer

among men are prostate (43%), colon (9%), and melanoma (8%), while among women they are breast (41%), uterine (8%), and colon cancer (8%) (DeSantis et al., 2014). Globally, the three most frequently diagnosed cancers are lung (1.35 million cases), breast (1.15 million), and colorectal (1 million) cancers. The deadliest types include lung (1.18 million cases), stomach (700,000 cases), and liver cancers (598,000 deaths).(Parkin *et al*.,2005).Key limitations in cancer therapy encompass toxicity, poor tolerability, and adherence. Therefore, there is a pressing requirement for new drug therapies that have minimal side effects.(Mun*et al.,* 2018).This discovery was validated in live animal studies, where stevioside effectively suppressed the activity of the recognized tumor promoter, 12-O-tetradecanoylphorbol-13-acetate (TPA), in a mouse model of skin cancer.(Yasukawa et al., 2002).Moreover, stevioside decreased the occurrence of mammary adenomas in F344 rats. (Toyoda *et al.,* 1997).Both steviol and stevioside reduced the survival of human colon carcinoma cells. Steviol specifically hindered DNA synthesis and prompted mitochondrial apoptosis. In laboratory tests, there were indications of possible effectiveness of steviol glycosides against breast cancer cells. (Boonkaewwan et al., 2008).Moreover, steviol hindered the growth of human gastrointestinal cancer cells by activating caspase-3 and initiating the mitochondrial apoptotic pathway. It elevated the Bax/Bcl-2 ratio and promoted the expression of p21 and p53. Its pharmacological effectiveness resembled that of 5-fluorouracil. Remarkably, steviol's toxicity against cancer cells surpassed its impact on normal cells. (Velesiotis et al., 2022).In terms of mechanisms, both stevioside and steviol could inhibit two targets commonly used in cancer treatment: human DNA topoisomerase II and DNA polymerases. (Chen et al., 2018).

Activity against obesity.

Obesity has reached epidemic proportions globally, with a high prevalence and links to cardiovascular, respiratory disorders, musculoskeletal, and numerous metabolic, such as Certain sleep problem. (Mashaal*et al.,* 2018).The consumption of low-calorie sugar substitutes may contribute to weight loss as they do not stimulate appetite, thereby avoiding an increase in calorie supply. This notion is helped by various research, where hyperlipidemic rats administered a certain dose of stevia extract exhibited reduced body weight compared to those with increased weight previously. Stevioside's ability to decrease rat food intake contributes to the inhibition of weight gain. Additionally, stevioside has the potential to decrease weight gain through several mechanisms: by reducing glucose levels, inhibiting the absorption of fat and improving insulin sensitivity, lipogenic enzymes, and facilitating the excretion of fat. (Assaei et al., 2016; Rains *et al.,* 2011).

Activity againstAntiviral

Several research have highlighted the antiviral properties of polysaccharides, termed primary metabolites, extracted from stevia against Herpes Simplex Virus-1 (HSV-1). The effectiveness against HSV-1 was confirmed in two fractions containing arabinogalactans with unique main chains (1 → 6) -d-galactan, isolated from stevia leaves. These fractions, referred to as the homogeneous alkaline fraction (SSFK) and the crude fraction (SFW), have shown the capacity to hinder HSV-1 infection in Vero cells during in vitro testing. (Oliveiraa et al., 2013).

The antiviral mechanism of the two fractions derived from stevia involves inhibiting the adsorption, penetration, and lateral spread of the virus. The virucidal effect demonstrates that this activity is directly linked to the interactions between Stevia polysaccharides and viral glycoproteins, rather than cellular receptors.

The antiviral action of the two fragment (SFW and SSFK) from stevia entails blocking the entry, attachment, and spread of the virus. The sporicidal impact indicates that this function is directly associated with the activity between viral glycoproteins and Stevia polysaccharides, rather than cellular receptors. (Ceole*et al.,* 2018).

Additional research has indicated that stevioside and extracts from Sophora flavescens (SV) exhibit antiviral effects against rotavirus in pigs. When given by mouth, some SV helps increase the absorption of stevioside in the intestines, which then inhibits rotavirus replication and stops it from infecting new epithelial cells. Stevioside shows effectiveness in laboratory conditions by blocking the attachment of rotavirus VP7 to receptors on cells. (Alfajaro*et al.,* 2014).

Activity against high lipid levels

Studies have shown that stevioside can significantly lower levels of total triglycerides, cholesterol, VLDL and LDL, while increasing HDL levels. This reduction in total cholesterol is thought to occur because stevioside enhances the excretion of bile acids by preventing their reabsorption in the small intestine, which disrupts the formation of micelles. The increased excretion of bile acids activates the enzyme 7α hydroxylase cholesterol, promoting the conversion of cholesterol in the liver to bile acids, thereby reducing cholesterol levels. (Hossain*et al.,* 2011; Brijesh*et al.,* 2016).Stevioside lowers triglyceride levels by boosting the activity of liver-produced lipase enzymes, which break down lipids and increase triglyceride excretion through feces. Its impact on reducing lipid levels is further explained by its activation of PPAR receptors. PPAR, a regulator in fat production, stimulates the expression of lipoprotein lipase (LPL) and the C-II apo gene, promoting the absorption of lipids by the liver and the formation of fatty acids. This process also enhances the oxidation of fatty acids in mitochondria. Stevia also reduces the activity of acetyl-coenzyme A carboxylase and fatty acid synthase. (Assaei et al., 2016; Brijesh*et al.,* 2016). Stevioside lowers

LDL levels by increasing LDL receptors and regulating cholesterol metabolism. This boost in LDL receptors improves the uptake of LDL cholesterol from the blood. Furthermore, several studies have shown that stevioside, as well as methanol leaf extract and water extract of stevia, also decrease VLDL levels. (Sing*et al.,* 2014; Sharma *et al.,*2012).In a separate study, researchers found that the water extract of stevia increased HDL levels in albino rats by boosting the activity of acetyl cholesterol transfer lecithin (LCAT), potentially aiding in the control of blood lipid levels.(Akbarzadeh*et al.,* 2015).

Impact on Gut Microorganisms

The human digestive system is occupied by around 1014 bacteria. Studies show that the composition of gut microbiota plays a crucial role in the development of the immune system, neurological functions, and overall human health. When there's an imbalance in gut microbiota, referred to as dysbiosis, it can result in gastrointestinal problems, allergies, obesity, cardiovascular issues, and diseases of the central nervous system. This suggests that different health conditions may have unique profiles of gut microbiota, indicating the potential significance of these microorganisms as both markers and targets for medical treatment. (Wang*et al.,* 2018).Studies have indicated that sweeteners can influence the population of gut microbiota. Saccharin and sucralose induce modifications without any impact on health. Furthermore, acesulfame-K reduces the presence of *Akkermansiamuciniphila* while encouraging the proliferation of *Firmicutes*. Because low-calorie sweeteners are metabolized by gut microbiota, there is a suggestion that they could potentially alter the composition of the microbial community in the gut. (Plaza*et al.*, 2020). However, both in vitro and in vivo research have demonstrated that SGs do not affect the growth of gut microbiota. (Mahalak*et al.,* 2020).

Therapeutic Applications.

According to findings from the World Health Organization (WHO), stevia assists in regulating blood pressure, preventing dental cavities, boosting insulin production in the pancreas, and acting as a bactericidal agent.(Bhosle 2004).No adverse clinical incidents have been recorded in countries where stevia is readily available (Mahmud et al., 2014). The global interest in medicinal plants for managing diverse ailments is on the rise. (Mostofa*et al.*, 2014). Stevia is suitable for individuals with diabetes and obesity, and it may also offer benefits in preventing type 2 diabetes.further, it exhibits antiseptic, antibacterial, anti-fertility, anti-inflammatory, diuretic, cardiotonic, and hypotensive properties. Stevia has demonstrated effectiveness in alleviating skin issues such as eczema, dermatitis,wrinkles,acne, blemishes, rashes, itchiness and scarring. Steviol aids in controlling blood sugar levels by enhancing both insulin secretion and utilization in animals deficient in insulin, while also acting as a digestive tonic. This offers hope for diabetic individuals who crave sweet foods. (Ranjan*et al.,*

2011).Stevia leaves contain approximately 10per cent steviosides, which are intensely sweet compounds with distinct benefits for people with diabetes. (Midmore *et al*., 2002).Stevia in its raw form acts as a catalyst for oral contraceptives, cholesterol-lowering medications, anti-tumor agents targeting prostate tumors, and treatments for rheumatism. The medicinal uses of stevia include controlling blood sugar, preventing hypertension, managing skin conditions, and averting tooth decay. The derivative extracted from stevia is considered the best alternative sweetener for people with diabetes, indicating substantial potential value for this growing crop. Data suggests that in certain countries, up to 30per cent of their sugar requirements are substituted with products that offer sweetness akin to stevioside.(Accessed on 10 April, 2016).The derivative extracted from stevia is regarded as the most optimal substitute sweetener for individuals with diabetes. The potential added value for this emerging crop can increase significantly. Data suggests that in certain countries, up to 30per cent of their sugar requirements are substituted with products that offer sweetness akin to stevioside.(Soejarto., 2002; Rameshet *al*., 2006).Stevia supports pancreatic health, aiding in the restoration of its regular function. Moreover, stevia boasts a notable concentration of phenols and flavonoids, contributing to its strong antioxidant properties. Tadhanie*t al*., 2007; Shuklae*t al*., 2009).Phenols, as secondary metabolites, play a role in reducing the occurrence of cancer and cardiac diseases.(Dragovie*t al*., 2010). Plant potentially exhibits cardio tonic properties, aiding in the normalization of blood pressure and the regulation of heart rhythm. It demonstrates vasodilator effects in animals with both normal and high blood pressure. Stevia has also been observed to decrease instances of enhance diuretic and high blood pressure as well as natriuretic effects in rat experiments. (Jaiswale*t al.,* 2011).Dietary sucrose is associated with the development of dental caries. Sugar substitutes are thought to decrease the occurrence of dental caries. Stevioside has been found to reduce dental cavities through three methods: its antibacterial properties, ability to create a less acidic environment, and anti-plaque activity. (Basu., 2014).The World Health Organization and The Food and Agriculture Organization of the United Nations as well as Food & Drug Administration (FDA) have determined that consuming high purity stevia extract in recommended amounts is safe for most people.(Accessed on 10 April, 2016).

Conclution.

Stevia rebaudiana, known for its sweet leaves containing steviol glycosides, serves as aorganic sugar substitute, particularly beneficial for individuals with hyperglycemia. Cultivated widely due to its economic and medicinal value, it offers various health benefits including antidiabetic, antimicrobial, and antioxidant properties. Stevia leaves contain compounds like steviol glycosides, flavonoid glycosides, and antioxidants. Among these, stevioside and rebaudioside A are prominent. Pharmacokinetic studies reveal steviol's

absorption in the lower intestine and excretion primarily through urine, while stevioside shows limited absorption. Steviol glycosides, especially stevioside and rebaudioside A, exhibit promising pharmacological properties. They enhance insulin secretion, improve glucose metabolism, and possess antioxidant properties, making them potential candidates for diabetes and antioxidant therapy. Their blood pressure-lowering effects through vasodilation and diuresis suggest applications in hypertension management. Steviol glycosides also show antidiarrheal activity by inhibiting CFTR and anti-inflammatory effects by modulating NF-κBsignaling. Moreover, they demonstrate promise in cancer therapy by inhibiting carcinogenesis and inducing apoptosis in cancer cells. Additionally, they offer benefits against obesity, display antiviral activity against HSV-1 and rotavirus, and modulate lipid levels and gut microbiota. With minimal adverse effects, steviol glycosides emerge as valuable candidates for medicinal and dietary supplementation across various health conditions.

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