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Review Article

Antihyperlipidemic Effects of *Stevia rebaudiana* Bertoni: A Mini Review

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ABSTRACT

Stevia rebaudiana, a natural sweetener, has attracted significant attention for its potential antihyperlipidemic effects. This review aims to assess the effectiveness of Stevia in managing hyperlipidaemia with special emphasis on its effect on total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol levels. A literature review of multiple studies was conducted to explore the antihyperlipidemic properties of Stevia. The findings indicated that Stevia possesses significant antihyperlipidemic properties, largely due to its substantial amount of steviol glycosides, such as stevioside, and rebaudioside A. Studies have shown that Stevia consumption significantly reduces TC, TG, and LDL levels while maintaining or potentially increasing HDL levels. Stevia inhibits the activity of HMG-CoA reductase, leading to reduced cholesterol synthesis in Hep-G2 cells, enhances cholesterol internalization, and also promotes cholesterol storage in lipid droplets. Moreover, it upregulates bile acid excretion and prevents bile acids from being reabsorbed in the small intestine, further lowering cholesterol levels. Furthermore, the expression of adipogenic transcription factors and lipogenic genes are also down-regulated, resulting in decreased lipid accumulation and triglyceride contents. Although, initial results are promising, more in-depth clinical investigations are essential to determine the long-term efficacy and safety of Stevia as an antihyperlipidemic agent. These studies would need to consider various dosages, treatment durations, and individual differences regarding Stevia consumption.

Keywords: *Stevia rebaudiana* Bertoni, Antihyperlipidemia, Antihypercholesterolemia, Steviol glycosides, Stevioside, Rebaudioside.

Introduction

Hyperlipidemia is a term used to describe elevated concentrations of lipids, including cholesterol, cholesterol esters, triglycerides, and phospholipids in the plasma. Alternatively, plasma lipoprotein levels may increase, particularly low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL), while high-density lipoprotein (HDL) levels may decrease.[1] Hyperlipidemia is a significant health problem, particularly when associated with diabetes mellitus, which increases morbidity and mortality rates.[2] Hyperlipidemia is a major predisposing factor for atherosclerosis, potentially resulting in various cardiovascular and cerebrovascular diseases.[1–4] According to the WHO Global Health Observatory figures, in 2008, the highest occurrence of total cholesterol levels ≥4.9 mmol/L (≥190 mg/dL) was in Europe, with 54% of both sexes affected. In contrast, Southeast Asia had prevalence rates of 29%.[5] A balanced diet low in fat, regular exercise, and appropriate medication are important factors in preventing and treating elevated lipid levels.[6] Statins are considered as the main and widely used therapy for hyperlipidemia. However, their efficacy can be compromised by several factors. Treatment resistance may occur in some patients due to genetic variations or other health conditions. Poor compliance is also another issue, often stemming from side effects or lack of patient education.

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Adverse events such as diarrhea, hyperuricemia, myositis, and hepatotoxicity can also limit their use or lead to discontinuation. As enzyme inhibitors, statins may also impede other vital enzymes in the body.[2,7] For emerging lipid-lowering medications, the main challenges lie in their accessibility, and high cost.[8] As a result, there is increasing enthusiasm for employing traditional herbal remedies because of their natural origin, safety, and non-toxic properties.[6]

Stevia rebaudiana Bertoni, a wild herbal plant of the Asteraceae family, is commonly known as Stevia. It is a perennial plant indigenous to South America and still exists in its wild state in Paraguay,[9] where it is referred to as a "sweet leaf."[10] Stevia has exhibited significant antihyperlipidemic effects in several earlier studies.[11–13] These hypolipidemic effects are attributed to steviol glycosides, which include stevioside, rebaudioside (A, B, C, D, E), steviolbioside, and dulcoside A.[6] Additionally, Stevia also exhibits a range of other beneficial medicinal properties, including antihyperglycemic, antihypertensive, antiobesity, antioxidant, anti-inflammatory, anticancer, antimicrobial, anticaries, antiviral, renoprotective, and hepatoprotective effect.[10,14,15] Given that Stevia is a safe, non-caloric, and non-toxic natural herb, it presents as a promising alternative medication for hyperlipidemia treatment.[6] Meanwhile, numerous studies have investigated the efficacy of Stevia as pharmaceutical treatment for hyperlipidemia,[8] there is limited investigations of the specific mechanisms behind Stevia's lipid-reducing potential. This review is aimed at bridging that gap by consolidating current findings on Stevia as a natural, non-toxic alternative to conventional lipid-lowering medications, with a particular focus on its mechanisms for reducing lipid levels. The objective is to summarize existing literature on Stevia's antihyperlipidemic properties, particularly the active components, such as steviol glycosides, that aid in its lipid lowering effect, especially for patients who exhibit poor responsiveness to statins, the review also explores Stevia's broader medicinal benefits and identify gaps in the existing literature, offering suggestions for future research directions for managing hyperlipidemia.

Methodology

A comprehensive search was conducted from different search engines, including Google Scholar, PubMed, and ScienceDirect using keywords such as "antihyperlipidemic" and "*Stevia rebaudiana.*" Primary data were sourced from research articles written in English from 2014-2024, which were published in national and international journals. The relevance of each article's title to the research sub-topic was reviewed to ensure that the appropriate context was obtained.

Results and Discussion

Characteristics of Stevia rebaudiana

Stevia rebaudiana can grow up to 65 cm, reaching up to 80 cm at maturity.[16,17] Its leaves are sessile, opposite, lanceolate to oblanceolate on upright, woody stems. There are two sizes of trichomes on the leaf surfaces, and the surfaces are slightly glandular. The inflorescence consists of corycombs, each containing five white tubular blooms (Figure 1). It produces an achene as its fruit, which contains one seed equipped with a feathery pappus.[16] Stevia leaves owe their sweet taste to their steviol glycosides content, mainly stevioside and rebaudioside A (Figure 2), both of which are estimated to be 250–300 times sweeter than sucrose.[10,18,19] This richness in sweet glycosides makes Stevia a notable source of natural sweetener, meeting up with the burgeoning demands of the food market.[19]

Steviol (Figure 3) is a unique compound present in Stevia leaves and is the only metabolite of steviol glycosides formed through metabolic processes in the colon. As steviol glycosides pass through the upper gastrointestinal tract without being digested, they get to the colon, where they are converted to steviol. Once hydrolyzed, steviol enters the enterohepatic circulation where it is partly absorbed, and transformed in the liver through glucuronidation, while the rest of it is excreted in the feces.[20]

Figure 1: Leaves (left) and flowers (right) of *Stevia rebaudiana*

Phytochemical analysis of Stevia rebaudiana

The primary phytochemical analysis of Stevia leaves has unveiled a plethora of bioactive compounds, shedding light on its potential health benefits and therapeutic properties. Among these compounds are alkaloids and steroids, along with flavonoids, tannins, glycosides, triterpenes, saponins, phenolic compounds, and anthraquinones (Table 1). Additionally, the leaves contain all indispensable amino acids, such as alanine, glutamic acid, proline, lysine, serine, aspartic acid, methionine, isoleucine, and tyrosine.[21] They also contain several vitamins, such as vitamin C, folic acid, and vitamin B2.[22] Furthermore, the leaves are rich in various nutrients and minerals, including iron, zinc, selenium, magnesium, manganese, chromium, sodium, potassium, chloride, and other minor elements.[23–28] Currently, Stevia is widely cultivated in many countries, including Paraguay, Spain, Brazil, the United States of America, Germany, Belgium, Argentina, the United Kingdom, Canada, Mexico, China, Japan, South Korea, Australia, Israel, Tanzania, India, Taiwan, Thailand, Vietnam, Malaysia, and Indonesia.[16, 21,29]

Antihyperlipidemic effects of Stevia rebaudiana

The effect of Stevia as an antihyperlipidemic agent is attributed to the existence of steviol glycosides, with the most common being rebaudioside A and stevioside.[6] Research has revealed the potential of Stevia as an anti-hyperlipidemic agent by reducing new cholesterol synthesis in Hep-G2 cells, decreasing cell viability, and enhancing cholesterol internalization. The suggested mechanism of action of Stevia and its glycoside, rebaudiana A (RA), involves the inhibition of the mevalonate pathway. Stevia inhibits 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase enzyme, preventing HMG-CoA conversion to mevalonate (Figure 4), thereby lowering endogenous cholesterol synthesis by increasing cholesterol storage in the form of lipid droplets.[30,31] Then, inhibition of the HMG-CoA reductase enzyme lowers the cholesterol levels intracellularly, triggering the sterol regulatory element-binding protein 2 (SREBP2) proteolytic activation. This activation boosts the transcription of the low-density lipoprotein receptors (LDLR) gene, leading to upregulated LDLR expression on the cell surface.[32] Furthermore, RA enhances the expression of the acyl-CoA: cholesterol acyltransferase (ACAT2) gene.[31]

Statins primarily work by inhibiting the HMG-CoA reductase enzyme to lower cholesterol synthesis.[8] Stevia, which contains stevioside, also inhibits this enzyme, and in addition enhances bile acid excretion, effectively lowering total cholesterol levels. This process involves blocking the bile acids from being reabsorbed from the small intestine, which in turn interferes with the formation of bile acid micelles, leading to the enhanced excretion of bile acids and cholesterol, triggering cholesterol 7α-hydroxylase activity, encouraging the liver to convert cholesterol into bile acids. Consequently, this leads to decreased cholesterol levels.[6]

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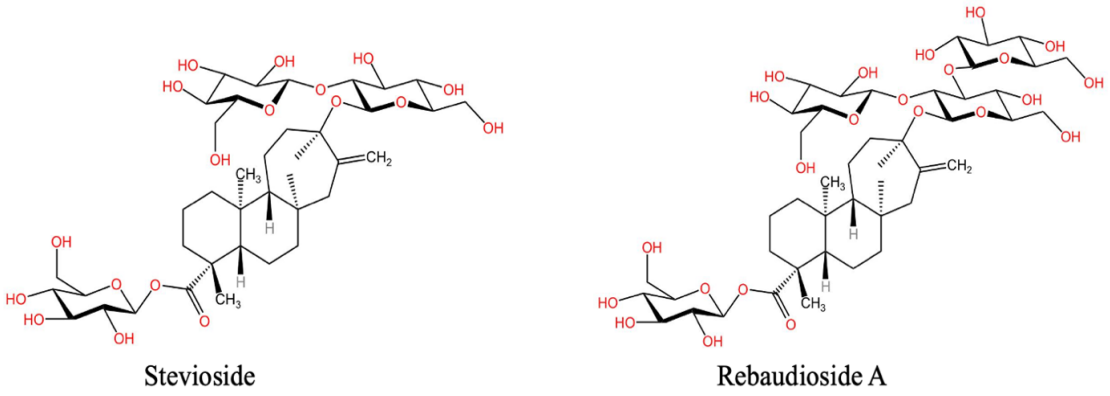

Figure 2: Chemical structure of stevioside and rebaudioside A

In a study conducted by Hou *et al*., it was found that stevioside could decrease TC and TG in the serum and liver of mice on a high-fat diet. Moreover, the study revealed that stevioside improved the swimming endurance of mice in a forced swimming test (FST) compared to a control group. This indicates that stevioside might also inhibit cholesterol production in the liver.[33]

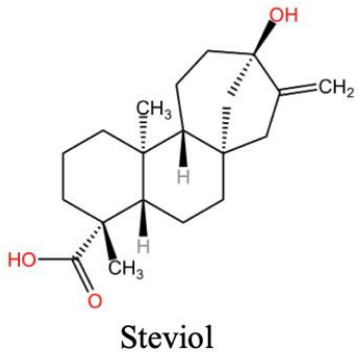

Figure 3: Chemical structure of steviol

The antihyperlipidemic effects of Stevia leaf extracts can also be attributed to their interaction with peroxisome proliferator-activated receptors. These receptors promote lipogenesis by increasing apo C-II and lipoprotein lipase (LPL) gene expression, which aid in the free fatty acids being absorbed and esterified in the liver. This relationship is associated with increased mitochondrial oxidation of free fatty acids.[34] Kurek *et al*. provided further evidence by showing that steviol reduced the TG and lipid accumulation in adipocytes, which was associated with the down-regulation of adipogenic transcription factors, such as CCAAT/enhancer-binding protein α (C/EBPα), peroxisome proliferator-activated receptor gamma (PPAR*γ*), sterol regulatory element-binding protein 1 (SREBP1). These factors play a crucial role in the differentiation and proliferation of adipocytes. Additionally, rebaudioside A and stevioside reduced the expression of the lipogenic genes that are involved in intracellular lipid metabolism, such as adipocyte protein 2 (aP2), fatty acid synthase (FAS), and lipoprotein lipase (LPL).[35] Maintaining low levels of LDL-C is crucial even though there are no universally ideal target LDL levels. This is because adults with LDL-C levels ≤100 mg/dL have a lower risk of cardiovascular and cerebrovascular disease.[36] Selected studies on the antihyperlipidemic effects of *Stevia rebaudiana* are listed in Table 2, which summarizes the subjects, intervention, duration, and results of each study.

Several studies were conducted on rats[37–42] and rabbits[43] which showed that the administration of Stevia significantly reduced TC, TG, and LDL levels while increasing HDL levels. Notably, many drugs used to manage hypercholesterolemia often reduce both TC and HDL-cholesterol levels.[44] However, Stevia extract has potential benefits in managing hypercholesterolemia because it can decrease TC levels and increase HDL-cholesterol levels.[37–43] The increase in HDL levels was attributed to the enhanced activity of lecithin cholesterol acyl transferase (LCAT), suggesting a potential mechanism for the regulation of blood lipids.[37] Besides, HDL is commonly known as "good cholesterol," It helps to transport excess cholesterol from peripheral tissues to the plasma and subsequently delivers it to the liver for catabolism. This process is crucial as it plays a significant role in preventing atherosclerosis.[4]

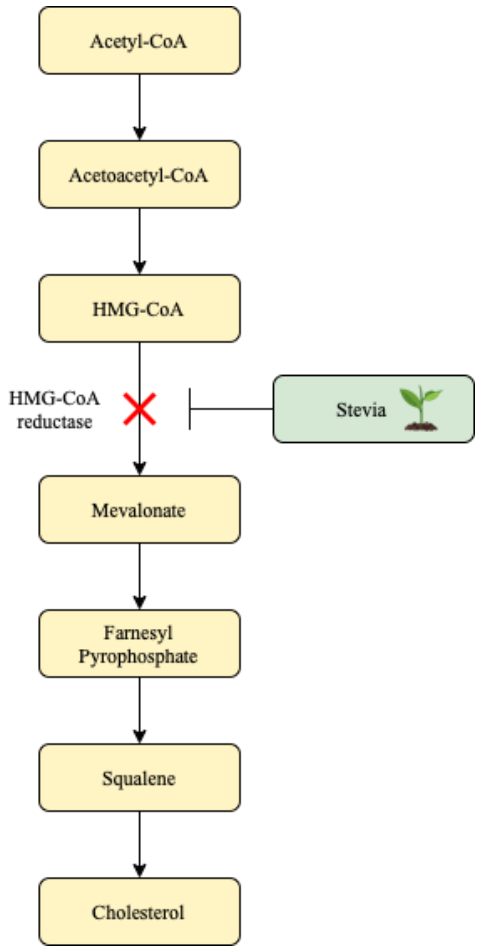

Figure 4: Antihyperlipidemic mechanism of action of Stevia

Although not all studies demonstrated an increase in HDL levels, the most compelling data emerged from a lipid profile study in the stevia-

treated animals, showing significant decreases in TC, TG, and LDL levels despite HDL levels remaining unchanged. Histological examination of the liver using hematoxylin and eosin staining revealed that the treated animals had fewer fat droplets compared to the control group, likely due to the reduced TG levels in the treated group.[45] In a human study conducted by Ritu and Nandini, consumption of Stevia significantly lowered TC, TG, VLDL-C levels, and also blood glucose levels.[46] Holvoet *et al*. also discovered that several compounds, such as stevioside, rebaudioside A, and steviol, help mitigate fatty liver by enhancing the metabolism of glucose, bile acid metabolism, fat breakdown, as well as transportation mechanisms, and lipid storage.[47] In 2018, Rotimi *et al*. explained that the advantages of stevioside on lipid profiles were correlated to its inhibition of the increasing G-protein-coupled receptor kinase.[48]

Table 1: Phytochemical Constituents of *Stevia rebaudiana*

Phytochemical Compound	Reference
Glycosides	23,26,27
Alkaloids	23,24,27
Phenolic compounds	23,27
Flavonoid	23,24,27
Tannins	23,24,27
Triterpenes	23,26
Steroids	23,24,26,27
Saponins	23,24,26,27
Anthraquinones	26

Diabetes causes disruptions in lipid profiles, particularly increasing sensitivity to lipid peroxidation, an oxidative stress biomarker caused by free radicals. In diabetic rats, stevioside treatment significantly reduced hypercholesterolemia and hypertriglyceridemia. This hypolipidemic effect is likely due to decreased synthesis of cholesterol and fatty acids.[38] Pure steviol glycosides (SGs) at both low and high doses have significant lipid-regulating properties in hyperlipidemia associated with diabetes, with the strongest effect observed at high doses of supplementary rebaudioside A (RA). The supplementary SGs showed a dose-dependent effect on serum TG. Stevioside, a free radical scavenger, demonstrates potency that was more effective than standard ascorbic acid. It is known for its inhibitory activity on α-amylase, α-glucosidase, and lipase enzymes, suggesting a mechanism to manage hyperglycemia and hyperlipidemia associated with metabolic syndrome.[49]

The rising consumption of sucrose- and fructose-sweetened beverages has globally increased medical and nutritional concerns related to the increased rates of diabetes mellitus type 2, obesity, and metabolic syndrome.[50] Galindo *et al*. found that individuals consuming Stevia had decreased levels of glucose, insulin, and TG compared to those consuming fructose. Moreover, Stevia consumers had lower TC levels than other groups.[51] Bagiana *et al*. aim to improve the formulation of Stevia leaves to maintain flavonoid stability through the encapsulation process. Stevia contains various substances, including alkaloids, tannins, and flavonoids. Flavonoids are particularly prone to oxidation by light, air, and heat, making them unstable during storage. Besides, encapsulation involves incorporating these substances into a matrix to improve their stability and usability.[52] Suryadinata *et al*. suggested that the antihyperlipidemic activity of Stevia is attributed to its components, such as glycosides and various antioxidants. Compounds in Stevia leaves, such as stevioside, isosteviol, flavonoids, phenolic acid, tannins, and saponins, help lower cholesterol levels and prevent dyslipidemia.[41] Flavonoids, in particular, can enhance the body's resistance to LDL cholesterol oxidation, inhibiting atherosclerosis. Additionally, they improve the HDL/LDL cholesterol ratio, which facilitates cholesterol transport to the liver from peripheral tissues for breakdown and excretion.[53]

Medicinal applications of Stevia rebaudiana

Antihyperglycemic activity

The treatment of diabetic rats with Stevia at 100 mg/kg BW resulted in approximately 40% reduction in blood sugar levels compared to the untreated control group, highlighting the significant protective effect of Stevia leaves against diabetes.[54] Stevia's action involves stimulating pancreatic tissue to increase insulin levels and providing antihyperglycemic benefits through a PPARγ-dependent mechanism and its antioxidant properties.[55] Steviol glycosides, such as stevioside, are noted for their potent antihyperglycemic effects, primarily by enhancing insulin secretion directly from β-cells without affecting the cAMP levels or K^+-ATP channel activity in the pancreatic islets[56] and by suppressing pancreatic glucagon.[17] Philippaert *et al*. found a correlation between the biological activity of steviol glycosides and transient receptor potential cation channel subfamily M member 5 (TRPM5). It is expressed in pancreatic β-cells and type II receptor cells. Steviol glycosides boost TRPM5 activity, preventing diabetic hyperglycemia in high-fat diet mice by increasing glucose-induced insulin secretion.[57] Furthermore, Stevia extracts decreased food and water consumption, reduced body weight, lowered blood glucose levels, and also decreased glycosylated hemoglobin (HbA1c) levels in diabetic albino rats. After eight weeks of treatment, there was also an improvement in liver glycogen and serum insulin levels.[58] Stevia consumption also was found to more effectively regulate glucose and insulin levels than fructose intake.[51] This improved regulation may be correlated to a reduction in the hepatic expression of phosphoenolpyruvate carboxykinase (PEPCK), an enzyme essential for insulin secretion and gluconeogenesis, which are both important for maintaining glycemic control and insulin sensitivity.[37,58]

Antihypertensive activity

Stevia extract also has antihypertensive properties due to its stevioside content. Stevioside acts as a vasoactive drug, similar to verapamil, which is a specific calcium (Ca2+) channel blocker in cardiac and vascular muscles. Stevioside induces vasodilation, which lowers mean arterial pressure (MAP) and promotes renal blood flow by reducing resistance in the renal vasculature.[59] It also lowers MAP via prostaglandin activity, evidenced by the fact that indomethacin (a prostaglandin synthesis inhibitor) counteracts stevioside's antihypertensive effect. Furthermore, stevioside increases the excretion of water, sodium, and potassium in the kidneys.[60] In spontaneously hypertensive rats, the administration of intravenous stevioside significantly lowered blood pressure, with the greatest reduction at a dose of 200 mg/kg.[61] Clinical trials on individuals with mild to moderate primary hypertension showed that consuming stevioside at 250 mg three times daily for three months effectively reduced blood pressure, both systolic and diastolic.[62] Furthermore, another study found that in patients with mild hypertension, consuming stevioside at 500 mg three times a day for two years significantly reduced blood pressure.[63]

Antiobesity activity

Stevia supplementation do not only lowers lipid levels but also reduces body weight gain and feed intake in high-fat diet rats, supporting its potential as an antiobesity agent. The reduction in body weight may result from either the lack of a rapid glucose-releasing source or a reduction in the rats' caloric intake.[37] Decreased body weight was observed among the group of rats given 5.0 mg/kg of stevioside compared to those in the control group. This effect was likely attributed to the reduced food tastiness due to the substantial stevioside concentration.[64] Additionally, in the research conducted by Galindo *et al*., rats that consumed Stevia exhibited lower body weight compared to those that consumed fructose.[51] In a clinical study, the difference in calorie intake between those consuming Stevia extract and the control group could be attributed solely to variations in caloric consumption. Consequently, the consumption of Stevia extract did not appear to influence feelings of hunger or appetite.[65] Stevia serves as a non-caloric sweetener that can help control weight while providing antihyperlipidemic benefits.[37] In contrast, many traditional sweeteners, such as fructose, contribute to increased caloric intake and are correlated to the prevalence of obesity and associated metabolic issues.[51]

Table 2: Antihyperlipidemic Effects of *Stevia rebaudiana*

Subject	Intervention	Duration	Results	Reference
Overweight female Wistar rats	Stevia sweetener at various dose levels of 25, 250, 500, and 1000 mg/kg BW/day	12 weeks	Decreased in TC, TG, LDL, and increased in HDL levels with an effective dose of 500 mg/kg BW/day	[37]
Twenty males and females suffering DM Type 2	Stevia leaf powder 1 g/day	60 days	Decreased in TC, TG, and VLDL levels	[46]
Hyperglycemic rabbits	Stevia leaves aqueous extract of 100 mg/kg BW/day	15 days	Decreased in fasting glucose, TG, LDL, increased in HDL levels	[43]
Alloxan-induced diabetic nephropathy rats	Stevioside of 250 mg/kg BW/day	28 days	Decreased in TC, TG and increased in HDL levels	[38]
Streptozotocin and nicotinamide - induced diabetic rats	Stevia leaves aqueous extract of 400 mg/kg BW/day	3 weeks	Decreased in TC, TG, LDL and increased in HDL levels	[39]
Steptozotocin-induced diabetic rats given a high fat diet	Stevioside 0.5% (500 mg/kg BW/day) and 2.5% (2500 mg/kg BW/day)	5 weeks	Decreased in TC, TG, and LDL levels.	[40]
	Rebaudioside A 0.5% (500 mg/kg BW/day) and 2.5% (2500 mg/kg BW/day)		The most significant decrease in TG levels was achieved with high dosage of SGs	
Healthy male Sprague-Dawley rats	Stevia leaf crude extract at various dose levels of 125, 500, 2000 mg/kg BW/day	28 days	Decreased in TC, TG, and LDL levels	[45]
Steptozotocin-induced diabetic rats with a high fat diet	Stevia leaves aqueous extract of 300 mg/kg BW/day and 500 mg/kg BW/day	4 weeks	Decreased in TC and TG levels	[49]
Alloxan-induced diabetic hypercholesterolemic male Wistar rats	Microencapsulated Stevia leaves extract at various dose levels of 100, 300, 700, and 1000 mg/kg BW/day	8 weeks	TC levels decreased using the dose of 100mg/kg BW/day	[52]
Female Wistar rats with a high-fat diet	Stevia leaves ethanol extract of 40 mg/200 gram BW/day	28 days	Decreased in TC, LDL and increased in HDL levels	[41]
Alloxan-induced diabetic Wistar rats	Stevia leaves ethanol extract of 400 mg/kg BW/ day	28 days	Decreased in TC,TG, and increased in HDL levels	[42]

Abbreviations: TC: Total Cholesterol; TG: Triglycerides; LDL: Low Density Lipoprotein; VLDL: Very Low Density Lipoprotein; HDL: High Density Lipoprotein; DM: Diabetes Mellitus; SG: Steviol Glycoside; BW: body weight

Antioxidant activity

Stevia also offers antioxidant benefits, potentially reducing oxidative stress associated with cardiovascular diseases.[49] Many synthetic lipid-lowering agents do not provide this additional protective effect.[8,44] Antioxidant activities of Stevia were studied using a mixture of steviol glycosides (rebaudioside A, rebaudioside C, stevioside, and dulcoside A) which proved to give protective effects on rat cardiac fibroblasts exposed to hydrogen peroxide. This mixture also increased catalase (CAT), reduced glutathione (GSH) levels, and superoxide dismutase (SOD) level.[66] Stevioside and rebaudioside A exhibit antioxidant properties by reducing lipoperoxidation and protein carbonylation in a fish model.[67] Stevioside has demonstrated a capacity to reduce oxidative damage in the livers and kidneys of rats with high-fat diets and low-dose streptozocin-induced type 2 diabetes. The potential mechanism involves the inhibition of G-protein-coupled receptor kinase and the inhibition of beta-adrenergic receptor kinase.[48] The Stevia extract showed phenolic and flavonoid content, quantified as 9.4 ± 0.2 mg GAE per mL of extract and 8.1 ± 0.1 mg QE per mL of extract, respectively. The antioxidant activity of Stevia was found to be on par with that of ascorbic acid, a potent antioxidant used globally in various cosmetic

products for its radical scavenging and reducing properties. The primary chemical constituents contributing to Stevia's antioxidant activities were identified as its phenolic compounds and flavonoids.[68] Determination of the antioxidant activity of Stevia methanol extract was done using the DPPH (2,2-Diphenyl-1-picrylhydrazyl) assay. The results revealed an IC_{50} value of 32.765 µg/mL for the extract, whereas, the standard antioxidant ascorbic acid had an IC_{50} value of 6.474 µg/mL. This indicates that the methanol extract of Stevia possesses antioxidant properties, although less potent than ascorbic acid in this assay.[69]

Anti-inflammatory activity

The intraperitoneal injection of stevioside effectively decreased the inflammation in the mastitis caused by *Staphylococcus aureus*. It acted by inhibiting the secretions of interleukin (IL)-1β, IL-6, and tumor necrosis factor-alpha (TNF-α). It blocked the pathway of nuclear factor kappa B (NF-κB) in the *S. aureus*-infected mammary gland of the mouse by preventing the phosphorylation of IκBα and p65 protein. It also inhibited the mitogen-activated protein kinase (MAPK) pathway by reducing the phosphorylation activity of p38, extracellular signal-regulated kinase (ERK), and Jun Kinase (JNK) in a dose-dependent manner. Additionally, stevioside was effective in inhibiting the activity of Toll-like receptors (TLRs), which is an immune receptor involved in apoptosis and inflammatory regulation.[70] Stevia aqueous extract demonstrated protective effects against ulcerative colitis induced by acetic acid. It provided not only histopathological protection but also significantly lowered the levels of TNF-α, IL-1β, thiobarbituric acid reactive substances (TBARS), myeloperoxidase (MPO), and the expression of NF-κB, which were significantly increased in the acetic acid group. Furthermore, Stevia significantly boosted the concentrations of GSH, SOD, CAT, and the expression of nuclear erythroid factor 2 (Nrf2) and PPARγ.[71]

Anticancer activity

Stevia serves as a non-caloric sweetener because it is metabolized into a type of sugar that does not enter the bloodstream. This characteristic may contribute to cancer prevention by lowering blood sugar levels, thereby reducing the risks associated with obesity, inflammation, and oxidative stress. Stevia and its derivatives can combat cancer directly by destroying cancer cells. It could also combat cancer indirectly through the lipid regulation properties and the use of antioxidants. The polyphenols and flavonoids in Stevia provide cellular protection against oxidative damage, thereby decreasing the risk of tumor development due to oxidative stress.[72] In a study by Gupta *et al*., steviol induced apoptosis and disrupted the cell cycle by causing an arrest at the transition of the G2/M phase, significantly reducing the number of human MCF-7 breast cancer cell lines.[73] Furthermore, an experiment demonstrated that steviol could suppress six types of human gastrointestinal cancer cell proliferation at concentrations of 100-200 µg/mL with efficacy comparable to anti-cancer drug 5-fluorouracil (5-FU). It even exhibited stronger inhibitory effects than 5-FU at a concentration of 250 µg/mL. The mechanism of inhibition is through the mitochondrial apoptotic pathway, which involves the up-regulation of the Bax/Bcl-2 ratio, the Caspase 3-independent mechanism, and the up-regulation of p21 and p53 expression.[20]

Antibacterial activity

The aqueous, ethanol, hexane, and carbon tetrachloride extracts of Stevia revealed their antimicrobial activity against bacteria such as *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Pseudomonas aeruginosa*. Among all the preparations, the aqueous Stevia extract showed the highest inhibitory effect against *Staphylococcus epidermidis*, achieving 84.4% inhibition.[74] The methanol extract of Stevia has demonstrated significant antimicrobial activity against antibiotic resistance extended spectrum β-lactamase (ESBL) producing uropathogens, which are responsible for urinary tract infections (UTIs). The Minimum Bactericidal Concentration (MBC) for the methanol extract was found to be between 10 mg/mL and 20 mg/mL. Furthermore, the methanol extract displayed a synergistic effect when combined with ampicillin.[69]

Anticaries activity

The use of oral rinses containing the two primary Stevia compounds, rebaudioside A and stevioside, has been considered effective in reducing the formation of *Streptococcus mutans* biofilms, thereby preventing dental caries.[75] In high-risk dental caries patients, the application of microwave-assisted 0.5% Stevia extract as a mouthwash has been observed to enhance both the buffering capacity and pH of the saliva. Additionally, it has demonstrated antimicrobial effectiveness against *Streptococcus mutans* and *Lactobacilli*.[76]

Antiviral activity

The hot aqueous extracts of Stevia effectively inhibited Human Rotavirus (HRV) by suppressing the viral replication of its four serotypes.[77] Two polysaccharide fractions of Stevia, namely SSFK (a homogeneous alkaline fraction) and SFW (a crude fraction), exhibited antiviral activity against Herpes Simplex Virus Type 1 (HSV-1). These fractions inhibited viral adsorption, viral penetration, and viral spread. These antiviral effects are attributed to the direct interaction between viral glycoproteins and Stevia polysaccharides.[78]

Hepatoprotective activity

Stevia can prevent liver damage through the upregulation of Nrf2, which mitigates oxidative stress and prevents further liver damage due to hepatotoxic agents. It also modulates proinflammatory cytokines by inhibiting the NF-κB pathway.[79] Stevia also inhibits the activation of ERK and JNK kinases, part of the cell signaling pathways, resulting in decreased phosphorylation of pSmad3L, which promotes fibrosis when activated.[80] Treatment with Stevia also showed significant improvement in histological liver damage caused by gentamicin-induced nephrotoxicity in rats, reducing inflammation, portal expansion, ductular cell proliferation, fibrosis, and vascular congestion.[81]

Renoprotective activity

In rats with gentamicin-induced nephrotoxicity, Stevia exhibited renal failure prevention effect by lowering serum creatinine and blood urea nitrogen levels, reducing chronic inflammation, decreasing inflammatory cell presence, and mitigating tubular injury in the kidneys.[81] In chronic kidney disease (CKD) patients, taking 250 mg of stevioside capsules twice daily for three months demonstrated beneficial effects, including improved microalbuminuria and reduced serum uric acid levels.[82]

Conclusion

Stevia rebaudiana could serve as a valuable and effective option for managing hyperlipidemia, as several studies have highlighted its potential as a functional food ingredient with health-promoting properties. The presence of stevioside and rebaudioside A contributes to its ability to lower TC, TG, and LDL levels while also enhancing bile acid excretion and maintaining or potentially increasing HDL levels. These effects are largely attributed to the inhibition of the HMG-CoA reductase enzyme and reduced fat accumulation in the liver. However, further study, including well-structured clinical trials, is important to fully validate the efficacy and safety of Stevia and its glycosides in managing hyperlipidemia across various populations. Additional studies are required to clarify the specific biochemical pathways involved. Comparative studies with conventional lipid-lowering medications like statins could help establish Stevia's potential role in complementing current treatments. Furthermore, it is important to consider several factors, such as dosage, treatment duration, and individual variations in response to effectively tailor therapeutic interventions. Public awareness and education are also crucial in promoting the health benefits of incorporating Stevia into diets, helping individuals make informed choices for better health outcomes.

Conflict of Interest

The authors declare no conflict of interest.

Author's Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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