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Review Article

A comprehensive review of *Stevia rebaudiana* Bertoni effects on human health and its mechanism

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ABSTRACT

Stevia rebaudiana Bertoni. is a non-calorie natural sweetener that has been used for hundreds of years. Stevia has 250-300 times the sweetness of sucrose because of the content of steviol glycosides found in stevia leaves. There are many studies on the health benefits of stevia such as antidiabetic, antihypertensive, anti-hyperlipidemia, antiobesity, anticancer, antioxidant, anti-inflammatory, antimicrobial, antiviral, improve liver and kidney function. There have been no reports on the adverse effects of stevia on human health, therefore stevia has the potential to be developed into functional food with many health benefits. The main objective of this review article was to summarize the various benefits of stevia in health and the mechanisms that occur for each effect of Stevia.

Keywords: Stevia leaves, Steviol glycoside, Stevioside, medicinal uses

Introduction

Stevia rebaudiana (*S. rebaudiana*) Bertoni or commonly known as stevia, is a plant of the Asteraceae family; native plants from Paraguay, Brazil, and Argentina. Medicinal plants have been used for centuries as a remedy for various human diseases through having antibacterial, antifungal, or antioxidant activities [1]. The practice of indigenous medicine has time and again focused on herbs for their innate antimicrobial activity against a plethora of bacteria and moulds since ages. [2] Stevia has been used for generations for hundreds of years as a medicinal plant in Paraguay and Brazil.[3] Currently, there are more than 150 species of stevia, but *S. rebaudiana* Bertoni is the only one that has a sweet nature because of the high content of steviol glycosides in its leaves. Stevia contains 11 major steviol glycosides, of which rebaudioside A and stevioside are the most abundant components in stevia. Pure stevia leaf extract can contain one steviol glycoside or several different glycosides and can reach 250-300 times sweeter than sucrose. [4] Stevia leaves also contain several important phytochemical constituents such as alkaloids, flavonoids, chlorophyll, xanthophyll, oligosaccharides, amino acids, essential oils, lipids, proteins, free sugars, trace elements and hydroxycinnamic acids (chlorogenic acid, caffeic acid). [5] Besides having sweetening properties, several studies have shown that stevia has anti-diabetic, antihypertensive, antihyperlipidemic, antiobesity, anticancer, antioxidant, anti-inflammatory, antimicrobial, antiviral properties, improving liver and kidney function. [3] This effect is associated with the content of phenolic compounds present in stevia (most in leaves, and some in stems). Although phenolic compounds do not have known nutritional functions, they are important for human health because of their antioxidant potential. [6]

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Method

The method used is a literature study. The literature study was conducted using a browser and search site with the keywords "Stevia rebaudiana", "Effect of stevia", "Mechanism of stevia

as...". This keyword search is done in English. The findings of the articles and research journals are presented descriptively. The range of journals used in this review article 2010-2020. The number of journals used in this review article is thirty-one journals, and four supporting literature. The total literature used in this review article is thirty-five.

Result and Discussion

Antidiabetic activity

Several studies have revealed that compounds found in stevia can reduce plasma glucose levels. Stevioside, which is the main compound of stevia decreases blood glucose levels through several mechanisms: increasing insulin secretion and sensitivity, reducing glucagon secretion. [7]

Another study showed that stevia extract increasing the expression of peroxisome proliferator-activated receptor-γ (PPARγ) and insulin mRNA. [8] Also, stevioside and steviol compounds have increased activity in gene expression and glucose transporter type 4 proteins (GLUT4). Increased expression of PPARγ and GLUT4, will increase glucose intake into cells so that glucose in the blood is metabolized and blood glucose levels will decrease. [9] Research conducted by Lestari, et al. 2019 also showed that the water extract of stevia leaves at a dose of 3.125 mg/kg BW, 6.25 mg/kg BW, and 12.5 mg/kg BW could reduce blood glucose levels significantly. [10] Natural medicines that can be used to prevent and reduce obesity and type 2 diabetes mellitus are the plants that contain secondary metabolites. [11]

Antihypertensive activity

Natural compounds that have hydrophobic terpenes such as steviol glycosides from stevia can inhibit or block one of the 3 active sides of Angiotensin-Converting Enzyme (ACE). [12] Research conducted by Wang et al., 2019 compared the activity of ACE inhibitors from ethanol extracts, steviol glycosides, and protein hydrolyzate from stevia, and captopril. ACE inhibitory activity from the largest to the smallest is captopril > protein hydrolyzate > steviol glycosides > ethanol extract of stevia. Although the ACE 2 inhibitory activity of protein hydrolyzate and steviol glycosides is lower than captopril, it shows better toxicity results than captopril. [13]

Antihyperlipidemic activity

Studies have shown that stevioside can significantly reduce total cholesterol, triglyceride, LDL, and VLDL levels, and increase HDL levels. The reduction in total cholesterol levels is explained by the mechanism of increasing bile acid excretion by preventing reabsorption of the small intestine through the disruption of micelle formation. Increased bile acid excretion activates 7α-hydroxylase cholesterol which increases the conversion of liver cholesterol to bile acid thereby resulting in a reduction in cholesterol. [14, 15]

Stevioside decreased triglyceride levels through stimulation of lipase enzyme activity produced by the liver which resulted in lipid catabolism as well as increased excretion of triglycerides through feces. [16] The hypolipidemic effect of stevia is also explained by the activation of PPAR receptors. PPAR as a regulating factor in the lipogenesis process activates the expression of lipoprotein lipase (LPL) and the *C-II apo* gene as well as liver absorption and free fatty acid etherification, along with the increased oxidation of mitochondrial free fatty acids. Stevia also reduces the activity of acetyl-coenzyme A carboxylase and fatty acid synthase. [8, 15]

Decreased LDL levels from stevioside are explained through the mechanism of increasing LDL receptors and modulating cholesterol metabolism. An increase in LDL receptors increases the absorption of LDL cholesterol from the blood circulation. Several studies also revealed that stevioside, stevia methanol leaf extract, and stevia water extract reduced VLDL levels. [17, 18] Another study found that stevia water extract increased HDL levels in albino rats due to increased activity of acetyl cholesterol transfer lecithin (LCAT) which could be linked to blood lipid regulation. [19]

Antiobesity activity

Obesity has achieved worldwide plague extents with high prevalence. It is associated with various metabolic, cardiovascular, musculoskeletal, and respiratory disorders like obstructive sleep apnea [20]. Consumption of low-calorie sugar substitutes can play a role in weight loss because it will not stimulate the appetite, so it does not increase calorie intake. This is supported by several studies, when hyperlipidemic rats are given stevia extract with a certain dose can reduce the body weight of rats that previously had increased. The inhibition of weight gain is caused by the ability of stevioside to reduce rat food intake. Also, stevioside can decrease weight gain by reducing glucose levels, fat absorption, and lipogenic enzymes, increasing insulin sensitivity, and fat excretion. [8, 21]

Anticancer activity

Research conducted by Khare et al., 2018 shows that stevioside has anticancer activity and sensitizing effects on breast cancer cells. Caspases 3 and 9 enzymes (responsible for the process of cell death) become active by administering stevioside. Also, stevioside increases pro-apoptotic protein (Bax) and decreases anti-apoptotic protein (Bcl-2). [22] Other anticancer mechanisms of stevioside are inhibition of DNA synthesis, suppression of cell viability, induction of apoptotic cells through the mitochondrial apoptotic pathway. Stevioside also shows activity on stress-related transcription factors such as factor-2 and NF-E2 which are related to Stevia's anticancer activity. [23]

In colon cancer cells (HT29), stevioside exhibits activity by inducing apoptosis through increased levels of MAPK (mitogen-activated protein kinase) expression (ERK and p38), which are involved in apoptosis mediated by ROS. [24] Other studies have shown that steviol has inhibitory activity in six human digestive cancer cells with the same efficiency as 5-FU. Steviol inhibitory

mechanism by increasing the Bax / Bcl-2 ratio, activation of p21, p53; and caspase 3-independent mechanism. [25]

Another mechanism in anticancer stevia is through cyclin-dependent kinases (CDK), the main proteins in the regulation, and the proliferation of the cell cycle. Ethanol extract of stevia showed antiproliferative activity in HeLa, HCT116, and MiaPaCa-2 cells through CDK4 inhibition. [26]

Antioxidant and Antiinflammatory

The incorporation of active ingredients into nanosystems to increase their shelf life, bioactivity, and bioavailability without inducing immune-system reactions has become a research hotspot [27]. The compounds contained in Stevia extracts such as steviol glycosides, flavonoids, quinic acid, caffeic acid, and their derivatives are biologically active molecules and capable to suppress the expression of inflammatory proteins and cytokines through the removal of Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) with antioxidant capacity. [28]

Flavonoids and proanthocyanidins contained in stevia can inhibit the production of Nitric Oxide in macrophages stimulated by lipo-polysaccharides (LPS) / gamma interferon (IFNγ). Natural diterpenoids (austroinulin and 6-O-acetyl austroinulin) in stevia can inhibit the production of nitric oxide synthase (iNOS), proinflammatory cytokines (TNF-α, IL-6, IL-1β, and mast protease-1 cells), and prostaglandin E2. The mechanism that occurs is the inhibition of NF-κB activation and (MAPK) phosphorylation. [29, 30]

Antimicrobial activity

In vitro research showed that absolute chloroform and ethyl alcohol extracts from stevia have antibacterial and antifungal activity. Stevia extract has antibacterial activity against *Ralstonia solanacearum, Pseudomonas syringae* pv.*actinidiae* strains, and *Erwinia amylovora*. Meanwhile, antifungal activity was shown in *Alternaria alternata, Colletotrichum gloeosporioides,* and *Fusarium moniliforma*. This result was shown by the reduced fungus growth compared to control (mycelium is weak or absent). Microscopic examination also showed that the walls of microorganisms became soluble and hyphae were deformed. [31]

Antibacterial and antifungal activity of ethanol and water extracts, sokhlet and column methods were compared in a study conducted by Mali et al., 2017. Ethanol extract had the highest activity against *Staphylococcus albus, Klebsiella aerogenes, Escherichia Coli* and, *Enterobacter aerogenes*. Meanwhile, stevia water extract is the most effective in inhibiting the growth of *Bacillus subtilis* and *Candida albicans. Aspergillus Niger* and *Penicillium chrysogenum* are only effectively inhibited by the column method of stevia extract. Based on these results it can be concluded that stevia extract contains strong antibacterial and antifungal components. [32] The antibacterial and antifungal activity of stevia has been reported by many studies. However, research on the mechanism of stevia in inhibiting the growth of bacteria and fungi is still not known with certainty.

Antiviral activity

Several studies have reported the antiviral activity of polysaccharides (primary metabolites) from stevia in Herpes Simplex Virus-1 (HSV-1). Antiviral activity against HSV-1 was verified from two fractions containing arabinogalactans with unusual main chains (1 → 6) -d-galactan, isolated from stevia leaves. These two fractions (homogeneous alkaline fraction, SSFK, and crude fraction, SFW) can inhibit HSV-1 infection in Vero cells *in vitro*. [33]

The mechanism of the two fractions (SSFK and SFW) in stevia which has antiviral activity by inhibition of adsorption, penetration, and lateral spread of the virus. The virucidal effect shows that this activity is directly related to interactions between polysaccharides from Stevia and viral glycoproteins, not from cellular receptors. [34]

Other studies have reported that stevioside and *Sophora flavescens* (SV) extracts have antiviral activity for rotavirus in pigs. Part of the SV given orally can increase the absorption of stevioside into the intestinal lumen, thereby inhibiting rotavirus replication and preventing rotavirus re-infection into new epithelial cells. Stevioside showed in vitro activity by inhibiting the binding of rotavirus VP7 to cellular receptors. [35]

Effect on Kidney function

Stevia extract in diabetic rats showed a significant decrease in Glomerular Filtration Rate (GFR). [36] Rats given Stevia showed a significant protective effect against kidney failure. Serum creatinine and blood urea levels are reduced after previously given Gentamicin (toxic effects on the kidneys). [37]

Gentamicin increases intracellular Ca^{2+} levels and activates calcium entry from both an external source and internal Ca^{2+} release which causes mesangial cellular contraction of the kidney. Stevia has a hypotensive effect by interfering with the entry of Ca^{2+}, so it can also protect kidney damage. [38]

Effect on Liver Function

Stevia can prevent liver cirrhosis in rats (CCl4-induced) by maintaining markers of serum necrosis (ALT), cholestasis (AP, γ-GTP, and bilirubin), and the normal structure of the liver parenchyma. The mechanism that occurs due to the antioxidant effect of stevia through its ability to prevent increased lipid peroxidation and 4-HNE, (oxidative stress marker in the membrane) and prevent downregulation of liver Glutathione Peroxidase (GSH, oxidative stress marker in the cytosol). [39]

Other studies reported that the effects of stevia on decreasing marker enzymes for impaired liver function, SGOT, and SGPT, after previously being given alloxan. [40]

Conclusion

S. rebaudiana Bertoni is a plant that contains primary and secondary metabolites which have many health benefits for the body. This has been proven by several studies which state that

stevia has benefits as antidiabetic, antihypertensive, antihyperlipidemic, anticancer, antioxidant, anti-inflammatory, antimicrobial, antiviral, as well as benefits to the effects of kidneys and liver. The effects of Stevia in a variety of benefits through different mechanisms. Moreover, the sweet taste in stevia can be used as a sugar substitute sweetener which is healthy and non-calorie. Because Stevia is natural, so this plant is harmless and has a lower toxic effect than the synthetic compound. Stevia is a potential plant for treatment or prevention agents of various diseases.

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