JOURNAL OF NATURAL REMEDIES
DOI: 10.18311/jnr/2024/36196

SHORT REVIEW

Exploring Stevia: A Natural Sweetener with Multifaceted Health Benefits

Piyushkumar Sadhu[1], Falguni Rathod[2], Mamta Kumari[1*], Niyati Shah[1], Chitrali Talele[1] and Chintan Aundhia[1]

[1]Department of Pharmacy, Sumandeep Vidyapeeth Deemed to be University, Piparia, Vadodara - 391760, Gujarat, India; mamtastar36@gmail.com

[2]Sumandeep Nursing College, Sumandeep Vidyapeeth Deemed to be University, Piparia, Vadodara-391760, Gujarat, India

Abstract

Natural sweeteners, especially those derived from plants, have become popular as low-calorie options compared to traditional sweeteners. Such discussion explores the world of natural sweeteners, emphasizing the growing demand for alternatives to artificial ones like saccharin and cyclamates. These sweeteners, sourced from plants, fruits, and honey, provide a healthier choice with fewer calories. Stevia, extracted from the *Stevia rebaudiana* plant, is a notable natural sweetener due to its zero-calorie content and strong sweetness. The review explores the background of Stevia, its glycoside compounds, and how it attains its sweetness. The pharmacological aspects of Stevia are also explored, highlighting its potential benefits in managing Type 2 diabetes, reducing blood pressure, alleviating inflammation, acting as an antioxidant, and showing anticancer properties. Studies suggested that Stevia's active ingredients, are primarily Stevioside and Rebaudioside A, contribute to its sweetness. The chemical composition of these active ingredients is influenced by factors like geographical location, cultivars, and processing methods. Stevia offers advantages such as low caloric content, suitability for diabetics, and benefits for dental health, making it an appealing sugar substitute for those focused on weight management and a health-conscious lifestyle. However, it is important to note potential drawbacks, including a bitter aftertaste, individual sensitivities, and regulatory considerations. Some commercial Stevia products may contain additives that impact their nutritional profile. Despite these factors, high-purity Stevia extracts have received safety approvals from global food safety authorities. In summary, Stevia emerges as a natural sweetener with the potential to address health-related concerns linked to traditional sugar consumption.

Keywords: Anti-diabetic, Artificial Sweeteners, Natural Sweeteners, Stevia, Zero Glycemic Index

1. Introduction

A sugar substitute is a food additive that has low food energy content (less than that of sugar-based sweeteners) and tastes as sweet as sugar, making it low or zero-calorie (non-nutritive). For humans, sweetness is an essential sense of taste. Natural sweeteners are becoming more and more popular due to the lack of acceptable substitutes for saccharin and cyclamates. Natural sweeteners are substances that impart sweetness to food and beverages without the use of artificial or refined sugars[1]. These sweeteners are derived from natural sources such as plants, fruits, and honey, offering an alternative to traditional sugar for those seeking a healthier option with fewer calories. There are various natural sweeteners widely used in the market such as Stevia, honey, maple syrup, agave nectar, monk fruit sweetener etc. Where Stevia is derived from the *Stevia rebaudiana* plant, Stevia is a zero-calorie sweetener with intense sweetness, making it a popular sugar substitute. Honey is a natural sweetener produced by bees from flower nectar. It contains various vitamins, minerals, and antioxidants, providing both sweetness and potential health benefits. Maple syrup extracted

*Author for correspondence

Article Received on: 12.01.2024 Revised on: 26.02.2024 Accepted on: 29.02.2024

from the sap of maple trees, is a natural sweetener with a unique flavour profile and contains some minerals and antioxidants. Agave nectar is obtained from the agave plant, it is a sweetener with a low glycemic index. It is often used as an alternative to traditional sugars. Monk fruit contains compounds called Mogrosides that provide sweetness without calories. Natural sweeteners also have several pharmacological qualities, including minimal calorie impact, blood-sugar control, antioxidant, and anti-inflammatory effects[2].

Stevia is a natural sweetener that is derived from the leaves of the *S. rebaudiana* plant, which belongs to the family Asteraceae also known as the 'sunflower family' (Figure 1). The plant has been used by indigenous people to sweeten medicines and foods before the 16th century[3]. Dr. Moisés S. Bertoni, an Italian-Swiss botanist, was credited with discovering the Stevia plant's sweetness in 1901. The sweetness of the Stevia plant is achieved through the formation of sweet chemicals in the plant's leaves known as Steviol glycosides. M. Bridel and R. Lavielle, two French researchers, originally isolated the particular glycosides in 1931, highlighting their sweetening activity, which is 50 – 450 times that of sucrose[4]. It is known for its intense sweetness and is widely used as a sugar substitute in various food and beverage products. Stevia has gained popularity as a natural alternative to traditional sweeteners due to its zero-calorie content and potential health benefits[5]. *Stevia rebaudiana* is a small perennial shrub native to the region of South America, particularly to regions of Paraguay and Brazil. It is characterized by its green, serrated leaves. The sweetness of Stevia is attributed to certain glycosides present in the leaves, with the most notable ones being Stevioside and Rebaudioside. Stevia leaves are sweetened by immersing their leaves that have dried in water, filtering and extracting the liquid from the leaves and stems, and then subsequently filtering the extracted plant using either water or food-grade alcohol. For decades, extremely pure Stevia derivatives have been allowed for use in foods and drinks in Japan. Positive safety opinions from global food safety authorities such as the World Health Organization/ Joint Expert Committee on Food Additives, the European Food Safety Authority, and the United States Food and Drug Administration have opened the market for this novel and exciting sweetener over the last 10-15 years[6].

Figure 1. Stevia (*Stevia rebaudiana*) leaf (*Source:* http://www.info-Stevia.com/).

1.1 Mechanism of Action of Stevia

The sweetness of Stevia arises from the production of sweet chemicals called Steviol glycosides in the leaves of the plant. Two significant non-nutritive compounds, Stevioside and Rebaudioside A, contribute to this sweetness. Once consumed, these glycosides undergo enzymatic hydrolysis in the gastrointestinal tract, releasing the Aglycone Steviol. Steviol is absorbed in the intestine and undergoes further metabolism, leading to the excretion of water-soluble metabolites. The lack of caloric content makes Steviol glycosides appealing to those seeking alternatives to caloric sweeteners. These glycosides consist of a Steviol molecule bound to one or more glucose molecules. The primary way in which Steviol glycosides produce sweetness is by interacting with taste receptors on the tongue. Activating the sweet taste receptor T1R2/T1R3, a heterodimeric G-protein coupled receptor, these glycosides initiate a signal cascade resulting in the perception of sweetness. Unlike sugar, which provides energy through metabolism, Steviol glycosides undergo minimal caloric breakdown, making them suitable for individuals concerned about caloric intake[7]. The sweetness of Steviol glycosides varies depending on the specific glycoside, generally ranging from 50 – 450 times the sweetness of sucrose. This high sweetness potency allows for the use of significantly smaller quantities of Stevia to achieve the same level of sweetness as sugar. Factors such as the specific Steviol glycoside present and individual taste perception influence this comparative sweetness.

1.2 Active Ingredients of Stevia Leaf

The geographical location and cultivars of Stevia affect the chemical constitution of the leaves. The way that

Stevia is dried and processed has an impact on the chemical constituents of its active ingredients. The diterpene glycoside ent-kaurene, which is present in Stevia leaves, constitutes the ingredient that gives them their extreme sweetness. There are now nine such chemicals that have been identified; their concentration varies according to the corresponding part of the plant; the leaves possess the highest level of concentration, after flowers, stems, and seeds[8]. Stevioside has a persistently bitter taste and possesses exceptional stability in aqueous solutions throughout a wide pH range of 1 – 10 and temperatures up to 98°C. Its sweetness exceeds that of sucrose by 150 – 300 times, depending on the concentration. Out of all the rebaudiosides, Rebaudioside A is the most significant since it exhibits 250 – 450 times greater sweetening properties than sucrose. Although it lacks the unpleasant flavour of Stevioside, it is the most stable glycoside. Furthermore, triterpenes and labdane diterpenes are also present in Stevia. Additionally, Stevia leaves are a wonderful source of fats, proteins, amino acids, vitamins, and minerals. The two main glycosides found in Stevia plants, Stevioside and rebaudioside A, account for 90% of the total weight of sweet glycosides in the leaves[9]. Steviolbioside and rebaudiosides B, D, E, and F are also present, but in smaller amounts. Rebaudioside M, is a novel molecule that is 200 – 350 times sweeter than sucrose. Except for a few minor variations in the number of carbohydrate residues, such as mono-, di-, and tri-saccharides containing glucose and/or rhamnose at positions C13 or C19, all diterpenoid glycosides extracted from *S. rebaudiana* have comparable Steviol (chemical backbone structures)[10].

2. Pharmacological Aspects of Stevia

2.1 Antidiabetic Action

Diabetes is a long-term metabolic condition marked by low insulin levels (Type 1 diabetes) from pancreatic beta cell death or high insulin levels (Type 2 diabetes) from decreased cell responsiveness. For a better understanding of Stevioside's hypoglycemic action, research was conducted in Type 2 diabetic Goto-Kakizaki (GK) and normal Wistar rats with and without Stevioside. Additionally, Rebaudioside-enhanced synthesis of insulin in isolated mouse islets of Langerhans is contingent upon the quantity of extracellular Ca^{2+}. Rebaudioside A and Stevioside functioned as receptor ligands, simulating the action of insulin[11]. In contrast, Stevioside increased insulin levels in normal rats during the IVGT above basal levels without changing the blood glucose response. According to this study, Stevioside may be a viable medication option for the treatment of Type 2 diabetes. Stevia leaf extracts have been demonstrated in several clinical experiments with healthy, normal volunteers to improve glucose tolerance in people. Stevia may thus be beneficial in the management of Type 2 diabetes[12]. Numerous studies discovered that these glycosides aid in lowering blood sugar levels and shielding the body against diabetes and obesity by improving insulin production and utilisation in those with insulin deficit[13].

2.2 Antihypertensive Activity

The most significant risk factor for the development of myocardial infarction and ischemic stroke is high blood pressure, often known as hypertension. Several factors can contribute to hypertension, including obesity, alcoholism, insufficient physical exercise, excessive salt intake, and unhealthful eating patterns. Kidney problems and cardiovascular problems might result from uncontrolled hypertension. The quest for efficient therapeutic solutions with few or no side effects is especially important because the treatment of hypertension is a long-term process. According to preclinical and clinical evaluations, Stevioside and Rebaudioside A have been shown to cause vasodilation, diuresis, and natriuresis along with a decrease in plasma volume, which results in overall drops in arterial pressure[14]. The research reports on the outcomes seen among individuals with mild to moderate hypertension. Without alterations in blood biochemistry values or the left ventricular mass index, a remarkable reduction in systolic and diastolic blood pressure was noted following a year of continuous 750 mg/day and two years of daily 1500 mg/day Stevioside ingestion. Furthermore, in a Ca^{2+} free media, intraperitoneal Stevioside failed to suppress vasopressin-induced vasoconstriction but instead generated a dose-dependent relaxing of it in isolated aortic rings. This finding implies that Stevioside causes vasorelaxation by preventing Ca^{2+} from refluxing into the blood vessel[15]. Consequently, because of its selective

antihypertensive action, Stevioside is a compelling option for more research.

2.3 Anti-inflammatory Property

The characteristic features of chronic inflammation are tissue damage brought on by persistent stimulation and continuous activation of monocytes and lymphocytes. Chronic inflammation is a major contributing factor to several chronic diseases, including autoimmune problems and metabolic disorders such as atherosclerosis, obesity, fibrosis, and cancer. Activated macrophages are the primary source of proinflammatory cytokines, which are responsible for initiating inflammatory reactions. Stevioside inhibited the upregulation of liver-inflammation-related genes *in vitro*[16]. Tumour Necrosis Factor Receptor (TNFR)-1 and Toll-like Receptor (TLR)-4-MD2 were the two proinflammatory receptors in which their antagonistic activity was shown by *in silico* experiments. Since Stevioside strengthens the innate immune system, it may also be advantageous for healthy individuals. Steviol was discovered to be accountable for preventing TPA-induced inflammation in addition to Stevioside[17]. Therefore, it may be beneficial to use Steviol and Stevioside as dietary supplements to aid in muscle rehabilitation. They may also be strong candidates for further development as novel medications to treat inflammation.

2.4 Antioxidant Activity

Oxidative stress overwhelms the body's antioxidative defences when reactive oxygen/nitrogen species production increases. This leads to oxidative alteration of biological macromolecules, rapid cell death, and tissue damage. When exposed to hydrogen peroxide, a combination of Stevioside, Rebaudioside A, Rebaudioside C, and dulcoside A increased the viability of rat cardiac fibroblasts and increased the amount and activity of catalase and superoxide dismutase[18]. A fish model was utilised to validate the antioxidative impact of Stevioside and Rebaudioside A. Lipoperoxidation and protein carbonylation were both efficiently regulated. In addition, Stevioside shielded the liver and kidneys of a mouse model of Type 2 diabetes against oxidative DNA damage. Its *in silico* findings demonstrated the possible mode of action of the Stevioside, which is linked to its suppression of G-protein-coupled and beta-adrenergic receptor kinases[19].

2.5 Antidiarrheal Activity

The crucial cAMP-activated chloride channel known as the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) mediates this anion secretion and this CFTR is inhibited by Steviol and Dihydrosteviol. Additionally, Stevioside regulates the contraction of colonic smooth muscles[20]. Due to these characteristics as well as the possibility of their antiviral and antibacterial activities, Steviol glycosides may be used to treat diarrhoea. Steviol glycosides are proven to exhibit antibacterial activity against a range of foodborne pathogenic microbes, such as *Escherichia coli*, which is widely recognised as the causative cause of severe diarrhoea. In terms of their antiviral qualities, Steviol glycosides appear to prevent rotavirus from attaching themselves to host cells[21]. Paediatric gastroenteritis is often linked to rotavirus.

2.6 Anticancer Activity

The main drawbacks of cancer therapy include toxicology, poor acceptance, and resistance. Novel medication therapies that have minimal side effects are therefore desperately needed. According to the research studies the viability of human colon cancer cells was reduced by Stevioside and Steviol. Steviol reduced the synthesis of DNA and caused mitochondrial mortality[22,23]. Steviol glycosides also exhibited potential efficacy against breast cancer cells *in vitro*. Furthermore, Steviol suppressed human gastrointestinal cancer cell proliferation by activating caspase-3 and activating the mitochondrial apoptotic pathway, as well as increasing the Bax/Bcl-2 ratio and stimulating p21 and p53 expression. It has equal pharmacological efficacy to 5-fluorouracil. Steviol's cytotoxicity against cancer cells was significantly greater than its activity on normal cells[24]. In terms of mechanism of action, Stevioside and Steviol were shown to inhibit two cancer therapeutic targets: DNA polymerases and human DNA topoisomerase II. In general, these findings point to Stevioside, Steviol, and isosteviol as promising chemotherapeutic possibilities for cancer treatment.

3. Advantages of Stevia

Stevia has become a popular choice as a natural sweetener, offering various advantages for those

pursuing a health-conscious lifestyle. Notably, it stands out for its low caloric content, making it a great option for individuals focused on weight management. By replacing sugar with Stevia in recipes or drinks, people can enjoy sweetness without adding extra calories, supporting weight loss efforts[25]. Additionally, Stevia is suitable for diabetics, as it does not significantly affect blood glucose levels. Compounds like Stevioside and Rebaudioside A provide sweetness without causing spikes in blood sugar, offering a safe alternative for those managing diabetes[26]. Stevia also brings dental health benefits, being non-cariogenic and not contributing to tooth decay. It can be part of dental-friendly diets, providing a sweet taste without the adverse effects on oral health associated with sugar consumption[27]. As a natural sweetener, Stevia is easily incorporated into various foods and drinks, such as tea, coffee, desserts, and baked goods, making it a versatile choice for maintaining a health-conscious diet without sacrificing sweetness[27]. Moreover, Stevia boasts a zero glycemic index, making it advantageous for individuals following low-carbohydrate or low-glycemic diets.

4. Disadvantages of Stevia

While generally considered safe for consumption, it is important to be aware of potential drawbacks and considerations associated with using Stevia. It is crucial to understand these factors before consuming Stevia as a diet. Some drawbacks include a possible bitter aftertaste, especially in larger quantities, with taste variations among different brands and forms. Individuals might find the bitterness unpleasant initially and may need time to get used to it[28]. As with any food product, some people may have sensitivities or allergies to Stevia, leading to rare instances of gastrointestinal discomfort or allergic reactions. Starting with small amounts and monitoring the body's response is advisable, particularly for those with a history of allergies or sensitivities[28]. The regulatory status of Stevia varies by country, with approvals as a food additive in some regions and more restrictive regulations in others. Concerns have been raised about extraction and purification processes involving chemicals, but high-purity Stevia extracts are generally recognized as safe by regulatory authorities[29]. Commercial products labelled as 'Stevia' may include additional ingredients like fillers, bulking agents, or other sweeteners, potentially altering the overall nutritional profile. Some blends may aim to improve taste and reduce the bitter aftertaste but may not offer the same benefits as pure Stevia[30].

5. Marketed Stevia Products

Stevia is available as fresh and dried leaves, leaf powder, extracts, and liquid concentrates, among other forms. The market is divided into two categories: powder and liquid. Stevia may be found in a variety of food and beverage products, including bakery, confectionery, drinks, dairy, tabletop sweeteners, and others. Stevia is also utilised as a natural, low-calorie substitute for sugar-based components in several personal care products. Various forms of Stevia products available in the market are listed in Table 1.

6. Future Research and Developments

Stevia has been gaining popularity as a natural sweetener, and research is being conducted to explore its potential benefits; some of the areas of research are listed in Table 2.

Table 1. Various Stevia products available in the market

Product name	Brand name	Product type	Dosage form	Additional features
Stevia sweet drops	SweetLeaf	Liquid sweetener/drops	Liquid	Available in different flavors
Truvia	Truvia	Sweetener blend	Powder, Packets	Erythritol-Stevia blend
Stevia in the raw	Stevia (Raw)	Granulated sweetener	Granules	Granulated form
Pyure organic Stevia	Pyure	Sweetener blend	Powder, Liquid	Organic blend
Pure Via	Pure Via	Sweetener blend	Packets, Liquid	Stevia and dextrose blend

Table 2. Description of several area of research related to Stevia

Area of Research	Description	References
Health Benefits	Investigating additional health benefits of Stevia beyond sweetness, such as potential anti-inflammatory, antioxidant, or antimicrobial properties.	31
Clinical trials	Conducting well-designed clinical trials to further evaluate the impact of Stevia on specific health conditions, including diabetes, hypertension, and weight management.	32
Taste Improvement	Research on enhancing the taste profile of Stevia-based products to minimize bitter aftertastes and improve overall palatability.	33
New Product Formulations	Developing innovative ways to incorporate Stevia into various food and beverage products while maintaining taste and texture characteristics.	34
Extraction Methods	Exploring alternative extraction methods to produce Stevia extracts with improved purity and reduced environmental impact.	35
Genetic Engineering	Investigating the potential for genetic engineering to enhance Stevia plants, optimizing sweetness levels and reducing undesirable compounds.	36
Regulatory Approvals	Monitoring regulatory developments globally and working towards achieving standardized approvals for Stevia-based products in different regions.	37

7. Conclusion

The emergence of natural sweeteners, especially Stevia, represents a notable shift towards healthier options compared to conventional sugars. Extracted from the *S. rebaudiana* plant, Stevia is a popular zero-calorie sweetener known for its intense sweetness, making it a preferred choice for those aiming for a healthier lifestyle. The glycosides in Stevia, like Stevioside and Rebaudioside A, contribute to its sweetness without adding calories, making it beneficial for weight management and diabetes control. Besides its sweetening role, Stevia offers various health benefits, including antidiabetic, antihypertensive, anti-inflammatory, antioxidant, antidiarrheal, and anticancer properties, positioning it as a promising candidate for health-related applications. Additionally, Stevia promotes dental health by being non-cariogenic and not causing tooth decay. Nevertheless, it's important to recognize potential drawbacks, such as the bitter aftertaste, individual sensitivities, and regulatory considerations associated with Stevia. Users should be mindful of product composition, as some commercial blends may contain additives altering the nutritional profile. In summary, Stevia provides a natural and versatile alternative to traditional sweeteners, aligning with the increasing demand for healthier dietary choices. While ongoing research further explores its benefits and addresses concerns, Stevia remains a compelling option for those seeking sweetness with minimal impact on health.

8. References

1. Ali A, More TA, Shaikh Z. Artificial sweeteners and their health implications: A review. Biosci Biotechnol Res Asia. 2021 A; 18(2):227-37. https://doi.org/10.13005/bbra/2910
2. Sudan P, Kaur R, Sharma S, Jain U K. A critical review on natural and artificial sweeteners. Pharm Chem J. 2016; 3(1):21-29.
3. Sharangi AB, Bhutia PH. Stevia: Medicinal miracles and therapeutic magic. Int J Crop Sci Technol. 2016; 2(2).
4. Carakostas MC, Curry LL, Boileau AC, Brusick DJ. Overview: The history, technical function and safety of Rebaudioside A, a naturally occurring Steviol glycoside, for use in food and beverages. Food Chem Toxicol. 2008; 46(7):S1-0. https://doi.org/10.1016/j.fct.2008.05.003 PMid:18555576
5. Mejia E, Pearlman M. Natural alternative sweeteners and diabetes management. Curr Diabetes Rep. 2019; 19:1-0. https://doi.org/10.1007/s11892-019-1273-8 PMid:31754814
6. Singh DP, Kumari M, Prakash HG, Rao GP, Solomon S. Phytochemical and pharmacological importance of Stevia: A calorie free natural sweetener. Rassa J of Sci For Soc. 2020; 2(3):169-76. https://doi.org/10.1007/s12355-019-00704-1
7. Mayank, Jaitak V. Interaction model of Steviol glycosides from *Stevia rebaudiana* (Bertoni) with sweet taste receptors: A computational approach. Phytochem. 2015; 116:12-20. https://doi.org/10.1016/j.phytochem.2015.05.006 PMid:26021732
8. Khiraoui A, Bakha M, Amchra F, Ourouadi S, Boulli A, Al-Faiz C, Hasib A. Nutritional and biochemical properties of natural sweeteners of six cultivars of *Stevia rebaudiana* Bertoni leaves grown in Morocco. J Mater Environ Sci. 2017; 8(3):1015-22.

9. Gasmalla MA, Yang R, Amadou I, Hua X. Nutritional composition of *Stevia rebaudiana* Bertoni leaf: Effect of drying method. Trop J Pharm Res. 2014; 13(1):61-5. https://doi.org/10.4314/tjpr.v13i1.9
10. Kobus-Moryson M, Grazma-Michałowska A, Kobus-Cisowska J, Korczak J. Zawartośćwybranychpierwiastków w ekstraktachstewii (*Stevia rebaudiana* Bertoni). Probl Hig Epidemiol. 2014; 95(2):445-8.
11. Abudula R, Jeppesen PB, Rolfsen SE, Xiao J, Hermansen K. Rebaudioside A potently stimulates insulin secretion from isolated mouse islets: Studies on the dose-, glucose-, and calcium-dependency. Metabolism. 2004; 53(10):1378-81. https://doi.org/10.1016/j.metabol.2004.04.014 PMid:15375798
12. Chen TH, Chen SC, Chan P, Chu YL, Yang HY, Cheng JT. Mechanism of the hypoglycemic effect of Stevioside, a glycoside of *Stevia rebaudiana*. Planta Medica. 2005; 71(02):108-13. https://doi.org/10.1055/s-2005-837775 PMid:15729617
13. Anton SD, Martin CK, Han H, Coulon S, Cefalu WT, Geiselman P, Williamson DA. Effects of Stevia, aspartame, and sucrose on food intake, satiety, and postprandial glucose and insulin levels. Appetite. 2010; 55(1):37-43. https://doi.org/10.1016/j.appet.2010.03.009 PMid:20303371 PMCid:PMC2900484
14. Chan P, Tomlinson B, Chen YJ, Liu JC, Hsieh MH, Cheng JT. A double-blind placebo-controlled study of the effectiveness and tolerability of oral Stevioside in human hypertension. Br J Clin Pharmacol. 2000; 50(3):215-20. https://doi.org/10.1046/j.1365-2125.2000.00260.x PMid:10971305 PMCid:PMC2014988
15. Lee CN, Wong KL, Liu JC, Chen YJ, Cheng JT, Chan P. Inhibitory effect of Stevioside on calcium influx to produce antihypertension. Planta Medica. 2001; 67(09):796-9. https://doi.org/10.1055/s-2001-18841 PMid:11745013
16. Boonkaewwan C, Toskulkao C, Vongsakul M. Anti-inflammatory and immunomodulatory activities of Stevioside and its metabolite Steviol on THP-1 cells. J Agric Food Chem. 2006; 54(3):785-9. https://doi.org/10.1021/jf0523465 PMid:16448183
17. Mizushina Y, Akihisa T, Ukiya M, Hamasaki Y, Murakami-Nakai C, Kuriyama I, Takeuchi T, Sugawara F, Yoshida H. Structural analysis of *iso*Steviol and related compounds as DNA polymerase and DNA topoisomerase inhibitors. Life Sci. 2005; 77(17):2127-40. https://doi.org/10.1016/j.lfs.2005.03.022 PMid:15935396
18. Sánchez-Aceves LM, Dublán-García O, López-Martínez LX, Novoa-Luna KA, Islas-Flores H, Galar-Martínez M, García-Medina S, Hernández-Navarro MD, Gómez-Oliván LM. Reduction of the oxidative stress status using Steviol glycosides in a fish model (*Cyprinus carpio*). BioMed Res Int. 2017; 2017. https://doi.org/10.1155/2017/2352594 PMid:28691017 PMCid:PMC5485310
19. Rotimi SO, Rotimi OA, Adelani IB, Onuzulu C, Obi P, Okungbaye R. Stevioside modulates oxidative damage in the liver and kidney of high fat/low streptozocin diabetic rats. Heliyon. 2018; 4(5). https://doi.org/10.1016/j.heliyon.2018.e00640 PMid:29872771 PMCid:PMC5986550
20. Shiozaki K, Fujii A, Nakano T, Yamaguchi T, Sato M. Inhibitory effects of hot water extract of the Stevia stem on the contractile response of the smooth muscle of the guinea pig ileum. Biosci Biotechnol Biochem. 2006; 70(2):489-94. https://doi.org/10.1271/bbb.70.489 PMid:16495667
21. Takahashi K, Matsuda M, Ohashi K, Taniguchi K, Nakagomi O, Abe Y, Mori S, Sato N, Okutani K, Shigeta S. Analysis of anti-rotavirus activity of extract from *Stevia rebaudiana*. Antivir Res. 2001; 49(1):15-24. https://doi.org/10.1016/S0166-3542(00)00134-0 PMid:11166857
22. Chranioti C, Chanioti S, Tzia C. Comparison of spray, freeze and oven drying as a means of reducing bitter aftertaste of Steviol glycosides (derived from *Stevia rebaudiana* Bertoni plant)–Evaluation of the final products. Food Chem. 2016; 190:1151-8. https://doi.org/10.1016/j.foodchem.2015.06.083 PMid:26213089
23. Boonkaewwan C, Burodom A. Anti-inflammatory and immunomodulatory activities of Stevioside and Steviol on colonic epithelial cells. J Sci Food Agric. 2013; 93(15):3820-5. https://doi.org/10.1002/jsfa.6287 PMid:23794454
24. Chen J, Xia Y, Sui X, Peng Q, Zhang T, Li J, Zhang J. Steviol, a natural product inhibits proliferation of the gastrointestinal cancer cells intensively. Oncotarget. 2018; 9(41):26299. https://doi.org/10.18632/oncotarget.25233 PMid:29899860 PMCid:PMC5995179
25. Mathur S, Bulchandani N, Parihar S, Shekhawat GS. Critical review on Steviol glycosides: Pharmacological, toxicological and therapeutic aspects of high potency zero caloric sweetener. Int J Pharmacol. 2017; 13(7):916-28. https://doi.org/10.3923/ijp.2017.916.928
26. Tirapelli CR, Ambrosio SR, de Oliveira AM, Tostes RC. Hypotensive action of naturally occurring diterpenes: A therapeutic promise for the treatment of hypertension. Fitoterapia. 2010; 81(7):690-702. https://doi.org/10.1016/j.fitote.2010.05.018 PMid:20685303
27. de Slavutzky SM. Stevia and sucrose effect on plaque formation. J Verbrauch Lebensm. 2010; 5:213-6. https://doi.org/10.1007/s00003-010-0555-5
28. Purohit V, Mishra S. The truth about artificial sweeteners–Are they good for diabetics? Indian Heart J. 2018; 70(1):197-9. https://doi.org/10.1016/j.ihj.2018.01.020 PMid:29455781 PMCid:PMC5903011
29. Curry LL, Roberts A. Subchronic toxicity of Rebaudioside A. Food Chem Toxicol. 2008; 46(7):S11-20. https://doi.org/10.1016/j.fct.2008.04.042 PMid:18562069
30. Anton SD, Martin CK, Han H, Coulon S, Cefalu WT, Geiselman P, Williamson DA. Effects of Stevia, aspartame,

and sucrose on food intake, satiety, and postprandial glucose and insulin levels. Appetite. 2010; 55(1):37-43. https://doi.org/10.1016/j.appet.2010.03.009 PMid:20303371 PMCid:PMC2900484

31. Prakash I, DuBois GE, Clos JF, Wilkens KL, Fosdick LE. Development of *rebiana*, a natural, non-caloric sweetener. Food Chem Toxicol. 2008; 46(7):S75-82. https://doi.org/10.1016/j.fct.2008.05.004 PMid:18554769
32. Konoshima T, Takasaki M. Cancer-chemopreventive effects of natural sweeteners and related compounds. Pure Appl Chem. 2002; 74(7):1309-16. https://doi.org/10.1351/pac200274071309
33. Wang M, Li H, Xu F, Gao X, Li J, Xu S, Zhang D, Wu X, Xu J, Hua H, Li D. Diterpenoid lead Stevioside and its hydrolysis products Steviol and *iso*Steviol: Biological activity and structural modification. Eur J Med Chem. 2018; 156:885-906. https://doi.org/10.1016/j.ejmech.2018.07.052 PMid:30059803
34. Urban JD, Carakostas MC, Taylor SL. Steviol glycoside safety: Are highly purified Steviol glycoside sweeteners food allergens? Food Chem Toxicol. 2015; 75:71-8. https://doi.org/10.1016/j.fct.2014.11.011 PMid:25449199
35. Silva FV, Bergamasco R, Andrade CM, Pinheiro N, Machado NR, Reis MH, de Araújo ÁA, Rezende SL. Purification process of Stevioside using zeolites and membranes. Int J Chem React Eng. 2007; 5(1). https://doi.org/10.2202/1542-6580.1443
36. Uçar A, Yılmaz S, Yılmaz Ş, Kılıç MS. A research on the genotoxicity of Stevia in human lymphocytes. Drug Chem Toxicol. 2018; 41(2):221-4. https://doi.org/10.1080/01480545.2017.1349135 PMid:28738695
37. Mayasari NR, Susetyowati, Wahyuningsih MS, Probosuseno. Antidiabetic effect of rosella-Stevia tea on prediabetic women in Yogyakarta, Indonesia. J Am Coll Nutr. 2018; 37(5):373-9. https://doi.org/10.1080/07315724.2017.1400927 PMid:29425471