Journal of Clinical and Nursing Research, 2024, Volume 8, Issue 6
http://ojs.bbwpublisher.com/index.php/JCNR
Online ISSN: 2208-3693
Print ISSN: 2208-3685

Advances in Pharmacological Effects of Stevioside

Shiqin Fu, Yanling Huang, Yiting Xie, Jing Zhang*

Jiangxi University of Chinese Medicine, Nanchang 330004, Jiangxi Province, China

***Corresponding author:** Jing Zhang, m827027934@163.com

Abstract: Stevioside is a low-calorie high-power sweetener with a variety of positive pharmacological effects. With the growing attention to health, stevia leaf has garnered widespread interest at home and abroad. This article reviews the main pharmacological effects of stevioside and their mechanisms, in order to provide references for the research on the edible and medicinal value of stevioside.

Keywords: Stevioside; Pharmacological effect; Safety

Online publication: July 17, 2024

1. Introduction

Stevioside is extracted from the dried leaves of *Stevia* (*Asteraceae*). It is a natural sweetener with high sweetness and low calories and does not produce toxic side effects on the human body [1]. The basic structure of stevioside is shown in **Figure 1** and related compounds are presented in **Table 1**. Stevioside and rebaudioside A are the main extracts of stevia leaf, and the average sweetness of the two compounds is about 200 to 300 times that of sucrose (**Table 1**), but the calorie is only about 1/250 times that of sucrose [2]. Therefore, stevioside is the third natural sugar source with commercial value after sucrose and beet sugar. A large number of studies have shown that stevioside possesses a variety of pharmacological effects, with certain therapeutic and auxiliary therapeutic effects on diabetes, obesity, hypertension, and the prevention of dental caries.

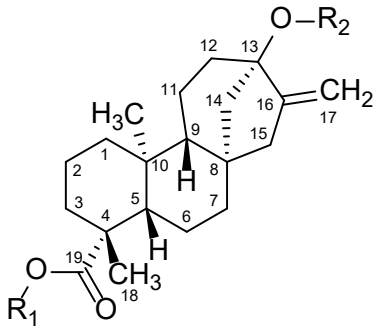

Figure 1. Chemical structure of stevioside

Table 1. Structure and sweetness of stevioside [3]

Serial no.	Compound name	R_1	R_2	Sweetness
1	Steviol	H-	H-	0
2	Stevioside	G-	G-^{2}G-	100~300
3	Steviolbioside	H-	G-^{2}G-	10~15
4	Rebaudioside A	G-	G-^{3}G-^{2}G-	150~300
5	Rebaudioside B	H-	G-^{3}G-^{2}G-	10~15
6	Rebaudioside D	G-^{2}G-	G-^{3}G-^{2}G-	200~250
7	Rebaudioside E	G-^{2}G-	G-^{2}G-	150~200
8	Dulcoside A	G-	G-^{2}Rh-	40~60
9	Dulcoside B	G-	G-^{3}G-^{2}Rh-	40~60
10	Rubusoside	G-	G-	-

Note: Sweetness is based on sucrose, "G" stands for glucose, "Rh" stands for rhamnose

2. Pharmacological effects of stevioside

2.1. Anti-diabetic and obesity effects

Diabetes and obesity are global health concerns that place long-term and complex demands on patients' lives, including strict dietary control and medication. Stevioside has attracted much attention due to its high sweetness and low-calorie characteristics, and it is thought to play a positive role in the treatment of type 2 diabetes and obesity. Gregersen *et al.* [4] found that taking stevioside with meals in patients with type 2 diabetes can reduce postprandial blood glucose, without affecting urine glucose content, and can promote insulin secretion in patients. It is speculated that when stevioside enters the digestive tract, glucosidase cannot decompose and digest stevioside, so it does not cause an increase in blood glucose, and it also promotes the secretion of insulin [5]. Stamataki *et al.* [6] have shown that daily consumption of stevia can affect individual glucose homeostasis, energy intake, and body weight. They found that consumption of stevia reduced energy intake, leading to weight loss, but had no effect on blood glucose levels.

2.2. Blood pressure-lowering effects

Studies have found that isosteviol in stevioside can reduce the concentration of intracellular free calcium ions by indirectly inhibiting calcium channels, which makes blood vessels relax and play a role in lowering blood pressure. This effect is achieved through the activation of ATP-sensitive K^+ channels, voltage-dependent K^+ channels, and conductance calcium-activated K^+ channels [7].

Chan *et al.* [8] conducted a study that followed 106 hypertensive patients for one year and found that after 3 months of oral administration of stevioside (250 mg/day), systolic and diastolic blood pressure significantly decreased without significant changes in blood biochemical parameters, suggesting that stevioside can be used as an adjuvant therapy for hypertensive patients. Another study found that intravenous injection of stevioside (200 mg/kg) in spontaneously hypertensive rats significantly reduced blood pressure within 10 minutes and lasted for more than one hour, without affecting blood dopamine, norepinephrine, and catecholamine levels [9].

2.3. Anti-tumor effects

Many traditional herbs are used to treat cancer or relieve related symptoms, and natural ingredients such as *As-*

teraceae plants have been found to have anti-tumor effects. One of the plants is stevia leaves, which have been found to have anti-tumor potential. Paul *et al.* [10] found in their study that stevioside can induce apoptosis and inhibit cell proliferation in human breast cancer cells, and its mechanism may be increasing the expression of apoptotic protein Bax through reactive oxygen species (ROS) signaling. In addition, steviol and isosteviol derivatives have certain anti-tumor activities, and their main mechanism of action is to induce apoptosis of tumor cells through Ras/Raf/ERK, Akt, or NF-κB signaling pathways [11].

2.4. Anti-caries effects

Some animal experiments have used plaque to produce acid *in vitro* to observe the anti-caries effect of stevia and found significant anti-caries effect. A study showed that stevia reduces the production of acid, reduces the formation of plaque, and thus reduces the incidence of dental caries [12]. Another study compared the depth of enamel demineralization induced by glucose, fructose, and stevia extracts and found that the average demineralization depth of stevia extract was 170.66 μm, which was much lower than that induced by glucose and fructose (**Table 2**). The reason for this phenomenon was that stevia extract reduced the amount of microbial acid production and cell surface hydrophobicity, and inhibited the adhesion of streptococci, thereby reducing dental plaque [13].

Table 2. Enamel demineralization depth of different solutions (μm)

Groups	Number of teeth	Average depth of demineralization	Minimum depth of demineralization	Maximum depth of demineralization
A 20% glucose solution	12	237.08	198	281
A 20% fructose solution	12	216.08	173	251
A solution of 20% stevia extract	12	170.66	119	211

2.5. Other pharmacological effects

In addition to the above effects, stevioside also has antidiarrheal, immunomodulatory, anti-inflammatory, and other effects. Shiozaki *et al.* [14] found that stevioside can reduce the symptoms of diarrhea by inhibiting the contraction of gastrointestinal smooth muscle. Sehar *et al.* [15] showed that stevioside can promote the proliferation of B cells and T cells, enhance the function of macrophages, and play an immunomodulatory role. Wang *et al.* [16] showed that stevioside could effectively inhibit the expression of key inflammatory mediators TNF-α, IL-1β, and IL-6, and the inhibitory effect was more obvious with the increase of the amount of stevioside (33 mg/kg, 100 mg/kg, and 300 mg/kg).

3. Safety of stevioside

According to relevant survey data, up to now, hundreds of regions or food regulatory agencies (such as the Food and Drug Administration) at home and abroad have agreed that stevioside can be used as a food additive. According to the certification of some authoritative agencies and the current scientific research, stevioside is relatively safe in terms of pharmacological effects [17].

At the same time, the pharmacological effect of stevioside is different from that of most artificial sweeteners. Stevioside cannot be degraded by gastric juice, and its metabolism *in vivo* is mainly phase II metabolism, which occurs in the colon [18]. It was found that the metabolites of stevioside were mainly excreted in the urine, rather than metabolized or deoxidized to metabolites such as sucralose. Undoubtedly, there are also some controversies about its safety. Through a variety of experimental studies, the results found that stevioside shows a dose-dependent effect [19], so further research is necessary for an in-depth study of stevioside.

4. Conclusion

As a new type of low-calorie sweetener, stevioside not only helps to treat cardiovascular and cerebrovascular diseases, obesity, and diabetes, but also plays a positive role in the prevention and treatment of dental caries. Thus, stevioside has a wide range of application value in food and medicine.

Disclosure statement

The authors declare no conflict of interest.

References

[1] Li Y, Li Y, 1983, Extraction of Stevioside from *Stevia*. Yunnan Chemical Technology, (04): 75–77.

[2] Ding N, Hao Z, Chen X, et al., 2005, Research and Development of *Stevia* and Its Glycosides. Shanghai Agricultural Science and Technology, (04): 8–10.

[3] Wang L, Jia J, 2023, Application and Development Trend Analysis of Stevioside in Food. Modern Food, 29(14): 38–42.

[4] Gregersen S, Jeppesen PB, Holst JJ, et al., 2004, Antihyperglycemic Effects of Stevioside in Type 2 Diabetic Subjects. Metabolism, 53(1): 73–76.

[5] Li Z, 2020, Therapeutic Effects of Stevioside Root Polysaccharide on Nonalcoholic Fatty Liver in Rats, dissertation, Wannan Medical College.

[6] Stamataki NS, Crooks B, Ahmed A, et al., 2020, Effects of the Daily Consumption of Stevia on Glucose Homeostasis, Body Weight, and Energy Intake: A Randomised Open-Label 12-Week Trial in Healthy Adults. Nutrients, (12): 3049.

[7] Wong KL, Yang HY, Chan P, et al., 2004, Isosteviol as a Potassium Channel Opener to Lower Intracellular Calcium Concentrations in Cultured Aortic Smooth Muscle Cells. Planta Medica, 70(02): 108–112.

[8] Chan P, Tomlinson B, Chen YJ, et al., 2000, A Double-Blind Placebo-Controlled Study of the Effectiveness and Tolerability of Oral Stevioside in Human Hypertension. Br J Clin Pharmacol, 50(3): 215–220.

[9] Chan P, Xu DY, Liu JC, et al., 1998, The Effect of Stevioside on Blood Pressure and Plasma Catecholamines in Spontaneously Hypertensive Rats. Life Sciences, 63(19): 1679–1684.

[10] Paul S, Sengupta S, Bandyopadhyay TK, et al., 2012, Stevioside Induced ROS-Mediated Apoptosis Through Mitochondrial Pathway in human breast cancer cell Line MCF-7. Nutr Cancer, 64(7): 1087–1094.

[11] Yu S, Zhang D, 2014, Research Progress on Biological Activities of Stevioside and Its Derivatives. Progress in Pharmacy, 38(08): 577–584.

[12] Wang W, Liu D, 1989, Application of Stevia in the Prevention of Dental Caries: Animal and *In Vitro* Experimental Study. J Practical Stomatology, (01): 19–22.

[13] Rezaei-Soufi L, Raedi S, Alikhani MY, et al., 2016, Comparison of the Effect of Stevia Extract with Glucose and Fructose on Dental Enamel Caries Formation. J Chem Pharmac Sci, (9): 685–689.

[14] Shiozaki K, Fujii A, Nakano T, et al., 2006, 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, 70(2): 489–494.

[15] Sehar I, Kaul A, Bani S, et al., 2008, Immune Up-Regulatory Response of a Non-Caloric Natural Sweetener, Stevioside. Chem Biol Interact, 173(2): 115–121.

[16] Wang T, Guo M, Song X, et al., 2014, Stevioside Plays an Anti-Inflammatory Role by Regulating the NF-κB and MAPK Pathways in *S. aureus*-Infected Mouse Mammary Glands. Inflammation, (37): 1837–1846.

[17] Yang Y, Li F, Ju Z, et al. 2011, Application Status and Development Prospect of Stevia. Fermentation Technology

Communication, 40(01): 40–44.

[18] Chen J, 2019, *In Vitro* Metabolism and Biological Activity of Stevioside, dissertation, Jiangnan University.

[19] Yasukawa K, Kitanaka S, Seo S, 2002, Inhibitory Effect of Stevioside on Tumor Promotion by 12-O-Tetradecanoylphorbol-13-Acetate in Two-Stage Carcinogenesis in Mouse Skin. Biol Pharm Bull, 25(11): 1488–1490.