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Ethnopharmacology of Stevia rebaudiana: A Non-Nutritive sweetener

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ABSTRACT

Indigenous tribes of South America were using Stevia rebaudiana Bertoni for centuries for its medicinal value. Stevia is a small perennial shrub that has been used as a natural sweetener. It has many traditional uses including anti glycaemic activity. Ethnopharmacology plays an important role in identifying new templates or lead molecules for various disorders. The traditional medicinal system is getting more and more appreciation nowadays. Hence there is an increasing demand for natural food supplements, herbal remedies, and other products supported by medicinal plants. The aim of this paper is to present the health-promoting value of S. rebaudiana..

Keywords: *Stevia rebaudiana*, traditional uses, ethnopharmacology, herbal remedies, medicinal plants

INTRODUCTION

Stevia is utilized as a non-nutritive sugar and herbal supplement. It is known as sweet leaf, honey leaf, candy leaf, sweet weed or sweet herbs [1]. Stevia not only have the sweet taste but also maintain the normal sugar level. It is used as antioxidant, hepatoprotective, antihypertensive, nephron protective, anti-inflammatory agent etc [2]. The genus Stevia belongs to Asteraceae family, and comprises of 240 species [3]. The sweetness of Stevia is due to diterpenes glycosides (Steviol glycosides): Stevioside (4–13%), rebaudioside A (2–4%), Dulcoside A (0.4–0.7%), rebaudioside C (1–2%) along with other less abundant types like rebaudioside B, rebaudioside F, steviolbioside, steviolmonoside and rubusoside. Food and drug administration (FDA) have given the GRAS (generally recognized as safe status) to Stevia and established the ADI (acceptable daily intake) for Stevia which is 4 mg/kg bw/day [4]. (Figure 1).

The most common species of this genus and family with sweetening property are *Stevia dianthoidea, S. phlebophylla, S. anisostemma, S. bertholdii, S. crenata, S. enigmatica, S. eupatoria, S. lemmonii, S. micrantha, S. plummerae, S. rebaudiana, S. salicifolia, S. serrata and S. viscida* but among these only *S. rebaudiana* exhibits the highest intensity of sweetness(5)(6). Studies shown that Stevia has been used since ancient times for different purposes throughout the world. For centuries, the Guarani populations of Paraguay and Brazil utelised Stevia species, primarily S. rebaudiana, which they called ka'a he'ê (''sweet herb''), as a sweetener in yerba mate and medicinal teas for curing heartburn and other ailments(7). Stevioside is a diterpenoid glycoside having an aglycone(steviol) and three molecules of glucose. Additionally, to stevioside, several other sugary compounds such as steviobioside, rebaudioside A, B, C, D, E and ducoside A were isolated from *S. rebaudiana* Bertoni leaf. All of these isolated diterpenoid glycosides have the same chemical backbone structure (steviol) but differ in the residues of carbohydrate at positions C_{13} and C_{19}(8). (Table 1)

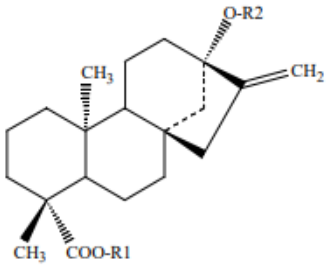

Figure 1: structure of Stevioside and their derivatives

Table 1: Chemical constituents and sweetening power

Chemical constituents	R_1	R_2	Sweetening power(with reference to saccharose)(11)
Stevioside	β-Glc	β-Glc.β-Glc	150–300
Rebaudioside A	β-Glc	β-Glc.β-Glc.β-Glc	250–450
Rebaudioside B	H	β-Glc.β-Glc.β-Glc	300–350
Rebaudioside C	β-Glc	β-Glc.α Rha.β-Glc	120–500
Dulcosid A	β-Glc	β-Glc. α Rha	50–120

Docking studies on stevia leaf extract

Molecular docking has become more and more chief tool for drug discovery [9-12]. In this review, we present a brief introduction of the docking studies on stevia glycosides from leaf extracts and their pharmacological actions. *In silico* analysis of stevia glycosides with PRAD1 is done to check anti-cancer activity [13]. GC-MS analysis of *Stevia rebaudiana* extract identified twenty phytocompounds. Docking results showed Tetradecanoic acid and Stigmastan-3,5-diene as best docked to the PRAD1. Tetradecanoic acid showed docking energy of 26.52K.cal/mol and stigmastan3,5-diene of 28.24K.cal/mol with PRAD1. Docking and molecular dynamics of steviol glycoside on human bitter receptor interactions has been reported [14]. *In vitro* studies in HEK 293 cells revealed that steviol glycoside specifically activate the hT2R4 and hT2R14 bitter taste receptors. Steviol glycoside have only one site for orthosteric binding to these receptors. The binding free energy (ΔG binding) between the receptor steviol glycoside is hT2R4 (r = -0.95) and hT2R14 (r = -0.89).Docking studies were reported on natural sweeteners from *Stevia rebaudiana* by constructing homology models of T1R2 and T1R3 subunits of human sweet taste receptors [15].The binding pattern indicated that Asn 44, Ans 52, Ala 345, Pro 343, Ile 352, Gly 346, Gly 47, Ala 354, Ser 336, Thr 326 and Ser 329 are the main interacting amino acid residues in case of T1R2 and Arg 56, Glu 105, Asp 215, Asp 216, Glu 148, Asp 258, Lys 255, Ser 104, Glu 217, Leu 51, Arg 52 for T1R3, respectively. Amino acids interact with steviol glycoside mainly by forming hydrogen bonds with the hydroxyl group of glucose moieties.

Molecular interaction between the enzyme dipeptidyl peptidase-4 (DPP-4) with stevioside and rebaudioside A is reported. Different molecular modeling tools are used in this study (molecular mechanics, molecular dynamics and molecular docking). The total interaction energy, of Stevioside was 1491.86 kcal / mol and Rebaudioside A is 6623.34.The result indicates that steviosides have more optimized inhibition of dipeptidyl peptidase-4 (DPP-4) than rebaudioside A [16].

The *in vitro* α-amylase inhibitory activity of the extracts of *S. rebaudiana* is investigated along with *in silico* studies. From this study it was found that water extract shows highest α-amylase inhibitory activity as compared to other extracts. Rebaudioside A showed docking score of −14.59 kcal/mol and H-bonding is 76.31% (−11.21 kcal/mol) of the total binding energy with the receptor site [17]. The essential amino acids participating in the interactions were Tyr 163, Asp 197, His 299 and Asp 300.

Pharmacological importance of *Stevia rebaudiana*

Now a day, various medicinal plants are becoming popular for the treatment of different diseases. A number of the pharmaceutical industries are introducing herbal products because of public demand and safety of the therapy. Phytocompounds and also their chemical analogs have provided abundant clinically useful drugs in the treatment of chronic and acute diseases. And still research is continued to search for newer therapeutic agents from medicinal plants [18]. (Table 2)

Table 2: Pharmacological activities and mechanism of action *Stevia rebaudiana* leaf extracts

Pharmacological action	Mechanism of action
Antidiabetic activity The effects of stevioside on the glucose and insulin metabolism in two models of diabetes in rats, STZ-induced diabetic rats and NIDDM diabetic rats induced by feeding with fructose has been reported.	Stevioside was able to regulate blood glucose levels by enhancing not only insulin secretion, but also insulin utilization in insulin-deficient rats; the latter was due to decreased PEPCK gene expression in rat liver by stevioside's action of slowing down gluconeogenesis [19].
Antibacterial Property the inhibitory effect of *Stevia rebaudiana* leaf extracts and its purified bioactive compound 'stevioside' against food-related pathogens has been reported.	Purified stevioside prevented the growth of tested bacterial species, i.e. *B. subtilis, K. pneumoniae and S. typhimurium* etc. Significant zone of inhibition (12 mm) was observed against *B. cereus* which proposes potential application of stevioside in foods to increase their shelf life [20].

Antioxidant Property Antioxidant activity, phenol and flavonoid content, and formulation cream of Stevia rebaudiana has been reported	DPPH radical-scavenging activities [21].
Stevia leaf powder (SLP) and a commercial stevioside powder (CSP) were analyzed for their polyphenol content, isothermal sorption behavior and their antioxidant activity was evaluated by DPPH radical scavenging activity, ferric reducing power and ABTS assay	The antioxidant activity of the methanolic extracts were determined and DPPH radical scavenging and ABTS activity for SLP showed inhibition at slightly higher compared to CSP stevioside. Higher ferric reducing power was seen in CSP than SLP for 100 µg [22].
Antihyperglycemic Property Antihyperglycemic effect of stevia alone and in combination with saxagliptin was evaluated	DPP-4 attenuation, antihyperlipidemic and antioxidant activity as well as improvement of insulin sensitivity may be involved in the antidiabetic action of stevia. Stevia has an antihyperglycemic effect and could enhance the antidiabetic activity of saxagliptin [23].
Hepatoprotective Property The ability of aqueous extract of stevia (AES) to prevent experimental liver cirrhosis in rats has been reported.	The aqueous extract of stevia induced Nrf2 expression, reduce NF-κB expression and block several profibrogenic signaling pathways, subsequently inhibiting HSC activation and preventing fibrosis induced by chronic CCl_4 administration [24].
Anti-inflammatory and immunomodulatory Property The anti-inflammatory and immunomodulatory activities of stevioside and its metabolite, steviol, on human colon carcinoma cell line (Caco-2) were evaluated.	Stevioside and steviol attenuate LPS-induced pro-inflammatory cytokine productions by affecting cytokine gene expression via IκBα/NF-κB signalling pathway [25].
Hypotensive Property The hypotensive effect of stevioside in dogs has been evaluated	This study confirmed that stevioside is an effective antihypertensive natural product, and its hypotensive mechanism may be probably due to inhibition of the Ca(2+) influx [26].
Anti-hyperuricemia effect of stevia Hyperuricemia effect of stevia residue extract (STVRE)in mice has been reported	The Stevia residue extract remarkably attenuated oxidative stress mediated by uric acid and downregulated inflammatory-related response markers such as COX-2, NF-κB, PGE2, IL-1β, and TNF-α. Furthermore, also Stevia residue extract reversed HUA-induced abnormalities in kidneys compared with the control group [27].
Antitumor property The effects of stevioside on the cytotoxicity, induction of apoptosis, and the putative pathways of its action in human breast cancer cells (MCF-7) has been reported.	stevioside, a natural compound isolated from the leaf of Stevia rebaudiana, induced apoptosis of human breast cancer cells and inhibits cell proliferation. It induces apoptosis through overexpression of Bax in MCF-7. Thus, stevioside has antitumor property, which is mediated through G1 arrest and involves signaling pathways, with ROS being a prime initiating signaling candidate [28].

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