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A review on the pharmacological properties and medicinal use of *Stevia rebaudiana*

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Abstract
Stevia is a perennial herb that belongs to the Asteraceae family. It is a natural sweetener plant and estimated to be 300 times sweeter than cane sugar. Studies revealed that Stevia has been used throughout the world since ancient times for various purposes; for example, as a sweetener and a medicine. Stevia is a small perennial shrub that has been used for centuries as a bio-sweetener and for other medicinal uses such as to lower blood sugar. Stevia and its glycosdies possess therapeutic effects against several diseases such as cancer, diabetes mellitus and hypertension. Studies have shown that steviol glycosides found in Stevia are not teratogenic, mutagenic. The present review provides a summary on the pharmacological properties of *Stevia rebaudiana* that might be relevant for the treatment of human and animal diseases.

Keywords: *Stevia rebaudiana*, anti-hyperglycemic, anti-hypertensive antifungal, antibacterial

Introduction
Stevia rebaudiana is herbaceous perennial medicinal plant belong to the family Asteraceae. Stevia, commonly known in Sanskrit as "Madhu Patra," meaning sweet leaf is a natural and healthy alternative to sugar. It is also known as honey yerba and honey leaf. It is use medicinally as an anti-diabetic [1, 2], anti-microbial [3], anti-viral [4], anti-fungal [5], anti-tumor [3], anti-hypertensive [6], anti-inflammatory [7], hepatoprotective [8], and immuno-stimulating [9]. It is also a popular ingredient for high-potency sweetener, and substitute to sucrose, being 300 times sweeter than sucrose [10]. The crop is native to Paraguay & Brazil and by mid- 1970s, standardized extract and pure Stevioside was utilized commercially in Japan for sweetening and flavouring foods and beverage as a substitute for several synthetic sweeteners [11]. Plant leaves produce zero-calorie Ent-Kaurene diterpene glycosides (Stevioside and Rebaudiosides), a non-nutritive sweetener. It has been found to be nontoxic, non-addictive, non-carcinogenic, non-mutagenic, plants in several countries like Brazil, Japan, and Paraguay [12]. It has non teratogenic and is devoid of genotoxic effect. It does not affect blood sugar level hence safe for diabetics.

Plant Profile

Kingdom	Plantae
Order	Asterales
Family	Asterceae
Tribe	Eupatoricae
Species	Bertholdii

The genus *Stevia* comprises about 250 species out of which the important ones are namely *S. anisostemma*, *S. micrantha*, *S. bertholdii*, *S. ovate*, *S.crenata*, *S. plummerae*, *S. dianthoidea*, *S.salicifolia*, *S. enigmatica*, *S. serrata*, *S.eupatoria*, *S. vircida*, *S. lemmonii* etc. However, sweetening properties have been found in *Stevia rebaudiana* and in some species. It is a perennial short day shrub that grows up to one metre and has sessile, elliptic, 3-4 cm long leaves. The colours of leaves are green, having no odour and sweet taste. Flowers are small in size throats funnel form which has five lobes. They are white in color and arranged in the form of small corymbs. The stem is woody and weak-pubescent at the bottom and root system of the plant is extensive [13, 14]

Fig 1: Stevia Herb

Active Ingredients of Stevia Leaf

Previous studies have conforms that Stevia leaf having rich nutritive ingredients such as nine essential amino acids (aspartic acid, glutamic acid, lysine, isoleucine, serine, alanine, proline, methionine and tyrosine) [15], water-soluble vitamins (folic acid, vitamin C and vitamin B2) [16], six fatty acids (stearic, oleic, linoleic palmitic, palmitoleic and linolenic acids) [17], active phytochemicals (steviol, austroinullin, β-carotene, rebaudi oxides, dulcoside, nilacin, stevioside, riboflavin and thiamine) [18], minerals (calcium, phosphorous, sodium, potassium, iron, magnesium and zinc) [16, 17, 19-22]. Secondary metabolites (alkaloids, cardiac glycosides, tannins, saponins, sterols and triterpenes, reducing compounds and anthraquinones) [17], Stevia produces steviol glycoside which is main component of the plant commonly known as sweet glycosides [24]. Steviol glycosides are structurally four-ring diterpene. The presence of a hydroxyl group in the C-13 position and a carboxyl group in the C-19 position (Fig.2) is necessary for the sweet taste of these compounds [25]. Main steviol glycosides that are present in Stevia leaf are rebaudioside (A to F), steviolbioside, stevioside and isosteviol (Fig. 3) [26].

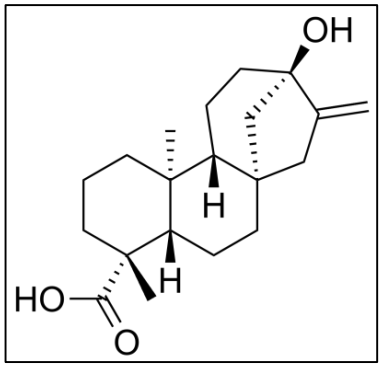

Fig 2: structure of stevioside

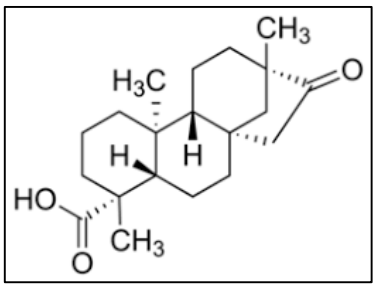

Fig 3: Structure of Isosteviol

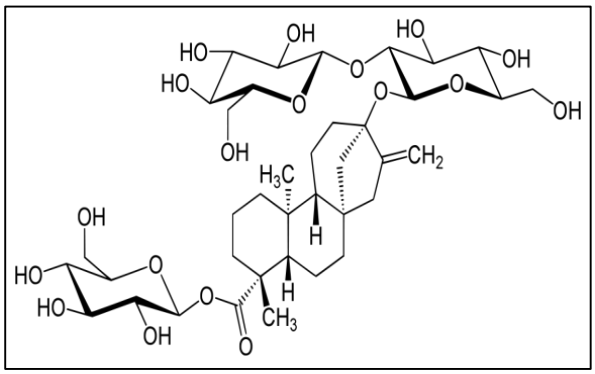

Fig 4: Structure of stevioside

Pharmacological aspect of *Stevia*

Anti-hyperglycemic effect

Stevia has effect on the beta cells of pancreas and improves insulin sensitivity and promotes insulin production. Chen *et al*., 2005 revealed that stevioside was able to regulate blood glucose levels by enhancing not only insulin secretion but also insulin utilization in insulin deficit rats [27]. The later was due to decreased phosphophenol pyruvate carboxykinase gene expression in rat liver by stevioside's causes slowing down glucogenesis. Stevioside reduces the postprandial blood glucose levels. Several human trials conducted in normal healthy volunteers have shown that extracts of *Stevia* leaves could increase glucose tolerance in humans. Therefore stevia may be helpful in the treatment of type 2 diabetes [27-31].

Anti - oxidant effect

Free radicals are considered to be the causative agents in the development of neurological diseases, reduced immunity, inflammations, ageing, ischaemic heart disease, stroke, Alzheimer's and Parkinson's disease as well as cancer[34]. Stevia is potential source of antioxidants. Several antioxidants were obtained from the extracts of *Stevia rebaudiana*, they include, kaempferol. Quereitrin and Opigenin that protect DNA strand damage. Isosteviol inhibits angiotensin II induced cell proliferation and endothelin I secretion while attenuation of reactive oxygen species generation [32-33]. Hence it could be beneficial in many diseases like cancer, reproductive problems and developmental defects.

Antihypertensive activity

Hsieh *et al.* (2003) studied the long-term efficacy of stevioside in patients with mild hypertension. It may be regarded as an alternative or supplementary therapy for patients with hypertension [35]. A study of Lee *et al.* (2001); Liu *et al.* (2003) revealed stevioside possesses antihypertensive activity and its hypotensive mechanism was due to inhibition of the Ca2+ influx. No significant changes were observed in blood biochemistry parameter including lipid and glucose. Additionally no adverse effects were observed. [36, 37]

Anti -cancer effect

Four isolates of steviol glycoside - stevioside, rebaudiosides A & C and ducloside A from *Stevia rebaudiana* have a strong inhibitory effect on 12-0-tetradecanoylphorbol-13-acetate (TPA) induced inflammation in mice which is suggestive of its anticancer effect [38, 39].

Antibacterial activity

Plants have rich source of medicinal property provided a

source of novel drug compounds. Scientists used different solvent extracts (methanol, ethanol, chrolo form, and ethylacetate, and acetone, petroleum ether) to investigate the antimicrobial activity of *Stevia* leaves. In some antimicrobial activity screening studies, these extracts exhibited susceptibility enough to inhibit the growth of certain pathogenic bacteria such as *Escherichia coli*, *Bacillus subtilis*, *Salmonella typhi*, *Enterococcus faecalis*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Vibrio cholerae*, *Aeromonas hydrophila* [40-43].

Antifungal activity

Antifungal effect was observed against *Aspergillus niger*, *Penicillium chrysogenum*, *Alternaria solani* [40]. *Fusarium oxysporum* showed maximum zone of inhibition by methanolic plant extracts of *Stevia rebaudiana* in the study of Arya *et al.* (2012) [43]. Therefore, plant extracts and phytochemicals with known antimicrobial properties can be of great significance in therapeutic treatments [41]. The presence of phytochemicals in leaves might have contributed to the antifungal activity [44].

Conclusion

Stevia is used extensively as a non-caloric sugar substitute. The busy and stressful life styles of present days increase the incidence of diabetes and hypertension. These are to be addressed properly or a serious consequence is inevitable. It has good natural sweetening activity and pharmaceutical properties. It is a good source of carbohydrates, protein, fibre and minerals, as well as important amino acids. Stevia has been consumed by human beings for centuries without any negative effects. This showed the advantages of stevia over other artificial sweeteners as an ingredient for the food industry, thereby making Stevia a more suitable substitute for saccharose in different drinks, beverages and bakery products. Stevia has a natural sweetening activity and pharmaceutical properties, therefore, it can be concluded that some extensive high throughput biotechnological techniques should be implemented for the better known of stevia properties in human and animal health.

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