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STEVIA: A BIOGENIC SWEETENER ENRICHED WITH THERAPEUTIC BENEFITS

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ABSTRACT:

In recent times, there has been a global upsurge in the exploration of plant research, resulting in a substantial body of evidence underscoring the considerable potential of medicinal plants across various traditional systems. Scientific investigations have compellingly shown that different plant parts, such as leaves, roots, rhizomes, fruits, stems, bark, and seeds, contain compounds that contribute to human diet health and nutrition. Stevia has gained significant attention due to its inherent sweetness and potential health benefits. This comprehensive review thoroughly investigates Stevia, examining its botanical characteristics, collection and cultivation methods, geographical distribution, phytoconstituents, therapeutic uses and toxicity study. The focus is on Stevia's phytochemical profile, particularly its sweetening components known as steviol glycosides, elucidating their unique chemical structures and diverse pharmacological properties.

Additionally, the review synthesizes existing scientific literature on the potential therapeutic advantages of Stevia, including its possible role in addressing conditions like diabetes, obesity, and hypertension. A meticulous assessment of Stevia's safety profile, encompassing potential side effects, is also presented. In conclusion, this review aims to consolidate the current understanding of Stevia, providing a valuable resource for researchers and healthcare professionals. The multifaceted nature of Stevia, ranging from its botanical origins to its applications in health and nutrition, underscores its significance as a natural sweetener with promising implications for the future of food and medicine.

KEYWORDS: Natural Sweetener, Candy Leaf, Sweet Leaf.

INTRODUCTION:

Stevia rebaudiana Bertoni, commonly known as Stevia is a perennial herb originating from the lush landscapes of South America, specifically Brazil and Paraguay. This botanical marvel belongs to the Asteraceae family and has captivated attention globally for its exceptional sweetness attributed to unique compounds called steviol glycosides. Out of the 230 species within the Stevia genus, only the rebaudiana and phlebophylla species are capable of producing steviol glycosides.[1] The primary allure of Stevia lies in its sweetening capabilities, driven by steviol glycosides such as stevioside and rebaudioside ephebophilia glycosides present in stevia are not metabolized by the human body, rendering it a non-nutritive sweetener. Despite its intense sweetness, Stevia stands apart as a non- caloric sweetener, making it an appealing choice for health-conscious individuals seeking alternatives to traditional sugar. Unlike sugar, stevia exhibits a taste profile characterized by a slower onset and prolonged duration. However, it's noteworthy that at elevated concentrations, certain extracts of stevia may introduce an aftertaste, often likened to licorice or bitterness. Extensive research has shed light on Stevia's potential therapeutic and medicinal benefits. This has positioned Stevia as a promising candidate for dietary considerations and management of various health conditions. [1,2]

History:

Stevia, scientifically labeled as Stevia rebaudiana, has an intriguing history as a natural sweetener deeply embedded in South American traditions. Its historical use dates back centuries to the Guarani Indians of South America, who cultivated and employed Stevia to enhance the sweetness of their beverages, particularly tea. In 1887, Dr. Moies Santigo Bertoni, a South American scientist and Director of the College of Agriculture in Asuncion, provided the initial description of Stevia's biological properties. Ovidio Rebaudi then accomplished the isolation of glycosides, the active components responsible for Stevia's sweetness, in 1900. [3,4] Originally known as Eupatorium rebaudianum, its name was changed to Stevia rebaudiana Bertoni in the year 1905.The comprehensive characterization of various glycosides within Stevia occurred in 1931 when researchers identified the steviol glycosides responsible for its unique taste. In contemporary times, Stevia has gained widespread acceptance and usage, especially in Japan and Brazil, where its extracts are utilized as a non-caloric sweetener and food additive.[4]

Biological source:

Stevia is a natural sweetener obtained through the extraction of leaves of plant *Stevia rebaudiana* belonging to the family Asteraceae. It is commonly referred to as meethi patti, candy leaf, sweet leaf, and sugar leaf. [5]

Table 1: Taxonomical Classification of Stevia.[6]

Taxonomical Classification	
Kingdom	Plantae
Division	Angiosperms
Class	Eudicots
Order	Asterales
Family	Asteraceae
Genus	Stevia
Species	S. rebaudiana

Morphological characteristics:

Stevia is a small, perennial shrub that typically reaches a height of around 50-80cm in its natural habitat, and can attain up to 1m in height under cultivation. The leaves, positioned in an opposing arrangement, are brief, lack stipules, and exhibit a lanceolate or ovoid shape with a serrated margin, gently curling downward. The underside of the leaf is characterized by a greater presence of pubescence, particularly over the veins and along the edge of the leaf blade. The upper side of the leaf blade exhibits a green color, while the lower side is slightly lighter. The leaves possess a sweet flavor accompanied by a subtle bitter aftertaste and the odor of the leaves is pleasant and aromatic.[7]

Fig.1: Stevia Leaves.

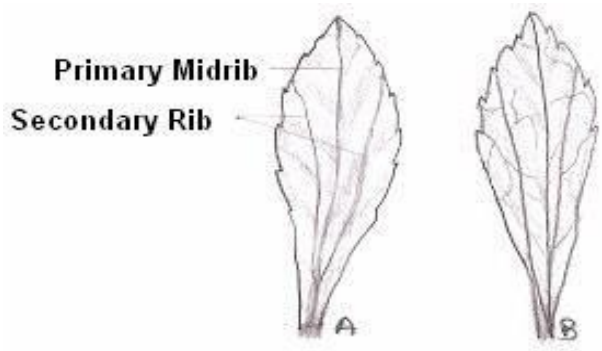

Fig.2: Stevia Leaf, A: Dorsal Surface, B: Ventral Surface.[7]

Microscopy:

A cross-section of the leaf reveals the presence of non-lignified, multi-cellular, uniseriate covering trichomes on both surfaces. The leaf exhibits a single layer of rectangular epidermal cells with a thin cuticle. The mesophyll is isobilateral and lacks differentiation into palisade and spongy parenchyma, primarily consisting of loosely arranged, thin-walled spongy parenchyma. In the midrib region, there are conjoint, collateral, lignified vascular bundles, accompanied by a few lignified sclerenchymatous cells above them. Starch grains are notably absent, while cystoliths of various sizes are dispersed throughout. The occurrence of anomocytic type stomata was noted on both ventral and dorsal surfaces. [8,9]

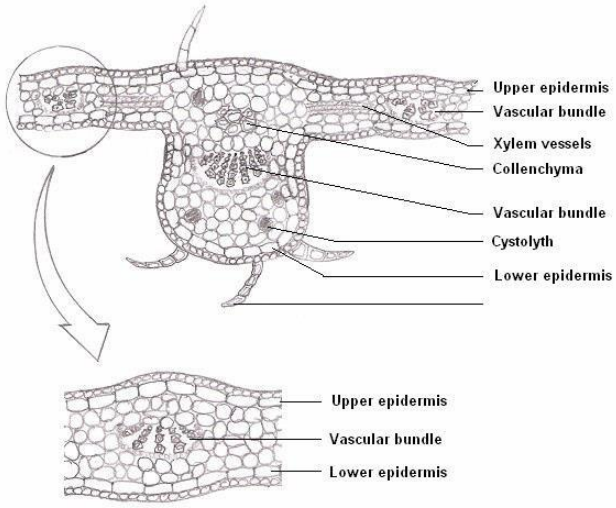

Fig.3: Cellular Diagram, T. S. of leaf [8]

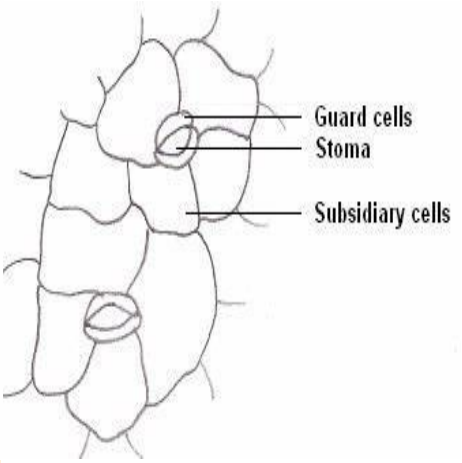

Fig.4: Anomocytic Type Stomata [8]

Medicinal parts of plant:

The leaves of stevia plant are the essential component with numerous therapeutic and medicinal benefits. Diterpene glycosides are. It contains a class of diterpene glycosides known as Steviol glycosides which are responsible for high sweetening potential of leaves. Stevia leaves also encompass numerous vital phytochemical components, including alkaloids, flavonoids, chlorophyll, xanthophyll, oligosaccharides, amino acids, essential oils, lipids, proteins, free sugars, trace elements, and hydroxycinnamic acids like chlorogenic acid and caffeic acid.[1, 3] In addition to its sweetening attributes, various research studies have indicated that Stevia possesses properties such as anti-diabetic, antihyperlipidemic, antihypertensive, antiobesity, anticancer, antioxidant, antibacterial and anticariogenic activity, contributing to the enhancement of liver and kidney function.[4]

Adulterants:

Adulteration in plants refers to the deliberate or unintentional contamination or addition of impurities to plant-based products. This can involve the mixing of lower quality or cheaper substances with genuine plant materials, compromising the quality, authenticity, and nutritional value of the final product. Adulteration is a common concern in various industries, such as the food, herbal medicine, and essential oil sectors. It can have adverse effects on consumer health, economic integrity, and the overall reliability of plant-derived products. Regulatory measures and quality control processes are implemented to detect and prevent adulteration, ensuring the safety and authenticity of plant-based products. [10]

Table 2: Adulteration in Stevia [10]

Sr.No.	Adulterant	Purpose of Adulteration
1	Artificial sweeteners (e.g. Cyclamate, Saccharin)	To increase sweetness levels without using genuine Stevia
2	Sugar	Dilution and cheaper alternative to Stevia
3	Dextrose	Bulking agent, often added to Stevia powder
4	Maltodextrin	Bulking agent and filler in Stevia products

Allied species:

The Asteraceae family houses the Stevia genus, consisting of approximately 230 species spread from the southern United States to the South American Andean region. Besides the well-known S. rebaudiana, numerous other species within the Stevia genus possess medicinal properties and have been traditionally utilized to treat diverse ailments some of which are mentioned in the Table. Within this genus, sesquiterpene lactones, diterpenes, longipinanes, and flavonoids are the primary categories of phytochemicals produced by its members. Stevia extracts and isolated compounds have demonstrated various pharmacological activities, with antioxidant, antiparasitic, antiviral, anti- inflammatory, and antiproliferative effects being among the most frequently cited.[11]

Table 3: Allied Species of Stevia rebaudiana [11]

Species	Ethnobotanical Uses
S. cardiatica	Cardiac ailments.
S. collina	Sweetener.
S. eupatoria Wild	Anti-hyperglycemic, Analgesic, Anti-inflammatory, Anti-hypertensive, Diuretic, Antimalarial, Stomachache treatment.
S. salicifolia	Anti-rheumatic and Anti-parasitic.
S. lucida	Anti-rheumatic, Anti-inflammatory and to cure wounds.
S. glandulosa	Anti-pyretic.

GEOGRAPHICAL DISTRIBUTION:

Stevia, scientifically identified as S. rebaudiana, originated in the rainforests of Brazil and Paraguay. Presently, it is cultivated in various countries including Japan, Korea, Thailand, China, and India. South America is home to approximately 200 native species of Stevia, and it is also found in Israel and Central America. Indigenous Brazilians and Paraguayans have been using Stevia leaves as a sweetening agent for centuries. In India, Stevia cultivation is widespread in regions such as Gujarat, Maharashtra, Rajasthan, Punjab, and others. [2,3,8]

CULTIVATION AND COLLECTION:

Stevia, a perennial herbaceous plant thriving in higher latitudes with elevated sweet glycoside levels, is best propagated vegetatively due to its low seed germination capacity. The herb is not well-suited for growth in dry conditions, making sprinkler irrigation particularly advantageous. Given its sensitivity to water stress, Stevia necessitates frequent, light irrigation to flourish. Optimal watering intervals of 3-5 days during the summer yield the best results.

The initial harvest of the crop is possible four months after planting, followed by subsequent harvests every three months. The most favorable harvesting period is from mid-September to late September when the plants reach a height of 50-70 cm, just before flowering. Harvesting at this stage ensures the maximum content of steviol glycosides in the leaves. An efficient harvesting method involves cutting branches with pruning shears before stripping the leaves. Additionally, the tips of the stems, containing as much stevioside as the leaves, can be clipped off and included in the harvest. On average, three commercial harvests can be obtained in a year. [4,5]

PHYTOCONSTITUENTS:

Stevia leaves contain a complex mixture of naturally sweet diterpene glycosides- stevioside (4-13% dry leaf), rebaudioside A (2-24%), rebaudioside C (1-2%), dulcoside A (0.4-0.7%), steviolbioside and rebaudioside B, D, E,

F, and M. Stevioside was reported to be the most abundant Stevia glycoside and is known for its sweetness (about 200-300 times sweeter than sucrose), while rebaudioside A (Reb-A) is more soluble and gives a flavor that is more similar to sucrose. Apart from their sweetness, numerous studies have shown that these two steviol glycosides (SGs) from *S. rebaudiana* leaves have beneficial health effects. A high concentration of phenolic compounds in Stevia leaves contributes to total antioxidant activity. The leaves of the plant also comprise of alkaloids, steroids, saponins, flavonoids, glycosides, sterols, triterpenes, anthraquinones, chlorophyll,

xanthophyll, oligosaccharides, amino acids, essential oils, lipids, proteins, free sugars, trace elements, and hydroxycinnamic acids like chlorogenic acid and caffeic acid... In conjunction with its nutritional components, Stevia serves as a reservoir for various non-nutritive substances, notably oxalic acid and tannins. [12, 13]

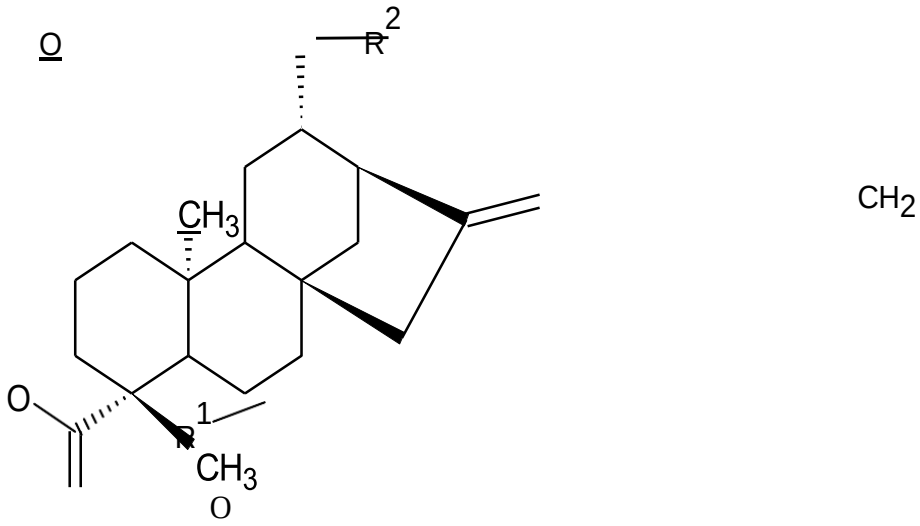

Fig. 5: General Molecular Structure of Steviol glycoside Table 4: Molecular Structure of Steviol Glycosides [12]

Compound Name	R1	R2	Relative Sweetness to Sucrose
Steviol	H	H	200-400
Stevioside	β-Glc	β-Glc-(2→1)-β-Glc	150-300
Steviolbioside	H	β-Glc-(2→1)-β-Glc	100-125
Rebaudioside A	β-Glc	β-Glc-(2→1)-β-Glc	250-450
		\ (3→1)-β-Glc	
Rebaudioside B	H	β-Glc-(2→1)-β-Glc	300-350
		\ (3→1)-β-Glc	
Rebaudioside C	β-Glc	β-Glc-(2→1)-α-Rha	50-120
		\ (3→1)-β-Glc	
Rebaudioside D	β-Glc-(2→1)-β-Glc	β-Glc-(2→1)-β-Glc	200-300
		\ (3→1)-β-Glc	
Dulcoside A	β-Glc	β-Glc-(2→1)-α-Rha	50-120
Note: Glc = Glucose, Rha = Rhamnose			

THERAPEUTIC USES:

Antioxidant activity:

Stevia leaves harbor various phenolic compounds with the ability to counteract free radicals and bind transition metal ions, thereby preventing their participation in free radical generation through the Fenton reaction. The components found in Stevia extracts, such as steviol glycosides, flavonoids, quinic acid, caffeic acid, and their derivatives, are active biological molecules capable of suppressing the expression of inflammatory proteins and cytokines. This suppression is achieved by eliminating Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) due to their antioxidant capacity. Furthermore, the flavonoids and proanthocyanidins present in Stevia can impede the production of Nitric Oxide in macrophages. [15,19,29]

Anti-diabetic activity:

The extract from Stevia leaves has the capability to lower plasma glucose levels and notably improve glucose tolerance by enhancing the effectiveness of insulin on the cell membrane.[14]. This, in turn, boosts insulin production and maintains blood sugar levels at a stable level. Stevia leaves, whether in powdered or dried form, are utilized as supplementary food products for individuals with diabetes. This not only amplifies natural sweetness but also aids in revitalizing the pancreatic glands. Stevioside specifically improves insulin secretion triggered by glucose, without influencing fasting insulin levels. [19, 20, 21]

Renal protective activity:

Research has examined the impact of stevioside derived from the leaves of S. rebaudiana on renal function, demonstrating its role as a typical systemic vasodilator that induces hypotension, diuresis, and natriuresis. Steviol and its analog are utilized in the context of polycystic kidney disease. Additionally, in diabetic rats, Stevia extract exhibited a substantial decrease in Glomerular Filtration Rate (GFR). Rats administered Stevia demonstrated a significant protective effect against kidney failure. [15, 19]

Antihyperlipidemic activity:

Extract of S. rebaudiana exerts a hypolipidemic effect by decreasing cholesterol and fatty acid synthesis, attenuating total cholesterol, triglycerides, and LDL levels and elevating HDL cholesterol [23]. The decrease in overall cholesterol levels is elucidated through the process of enhancing bile acid excretion by hindering reabsorption in the small intestine, disrupting micelle formation. The heightened excretion of bile acid stimulates 7α-hydroxylase cholesterol, promoting the conversion of liver cholesterol into bile acid, consequently leading to a reduction in cholesterol levels. [26,28]

Antihypertensive activity:

Stevia leaves help in regulating the blood pressure by relaxing arteries and prevent the buildup of calcium on artery walls, that promotes vasodilation and reduces total peripheral resistance and volume of extracellular fluid as result of elevated natriuresis and diuresis. Both hypolipidemic and hypotensive effect exerts a cardio-protective action [27,28]

Antiproliferative and anticancer activity:

Stevioside exhibits anti-cancer properties and acts as a sensitizer for breast cancer cells. It enhances the presence of the pro-apoptotic protein Bax while diminishing the levels of the anti-apoptotic protein Bcl-2. Apart from these effects, stevioside hinders DNA synthesis, reduces cell viability, and induces apoptosis through the mitochondrial apoptotic pathway. Additional research has demonstrated that steviol effectively inhibits six types of human digestive cancer cells at a level comparable to 5-FU. The ethanol extract from Stevia has also shown anti- proliferative properties by inhibiting CDK4. [19, 21]

Effect on Obesity:

Obesity is recognized as a severe global issue, and the global prevalence of overweight and obese individuals continues to rise. Nevertheless, obesity is not merely excess weight; it is a complex medical condition associated with numerous metabolic complications, including diabetes, cancer, cardiovascular diseases, stroke, and sleep apnea. The heightened risk of these diseases due to obesity ultimately results in a diminished quality of life. Studies indicate that the consumption of non-nutritive sweeteners can prevent weight gain by curbing energy intake. Stevioside, in particular, has been found to mitigate weight gain through the reduction of glucose levels, diminished fat absorption, inhibition of lipogenic enzymes, increased insulin sensitivity, and enhanced fat excretion. [26,28]

Antibacterial and Anticariogenic activity:

The capacity of Stevia extract to impede the activity of various pathogenic bacteria is evident, showcasing antibacterial effectiveness against strains such as Ralstonia solanacearum, Pseudomonas syringaepv. actinidiae, and Erwinia amylovora. Stevia also exerts antibacterial effects within the oral cavity. In vitro investigations have revealed that S. rebaudiana inhibits the growth of bacteria including Streptococcus mutans, S. sobrinus, and Lactobacillus acidophilus, all of which are implicated in the development of dental caries. [15, 20, 29]

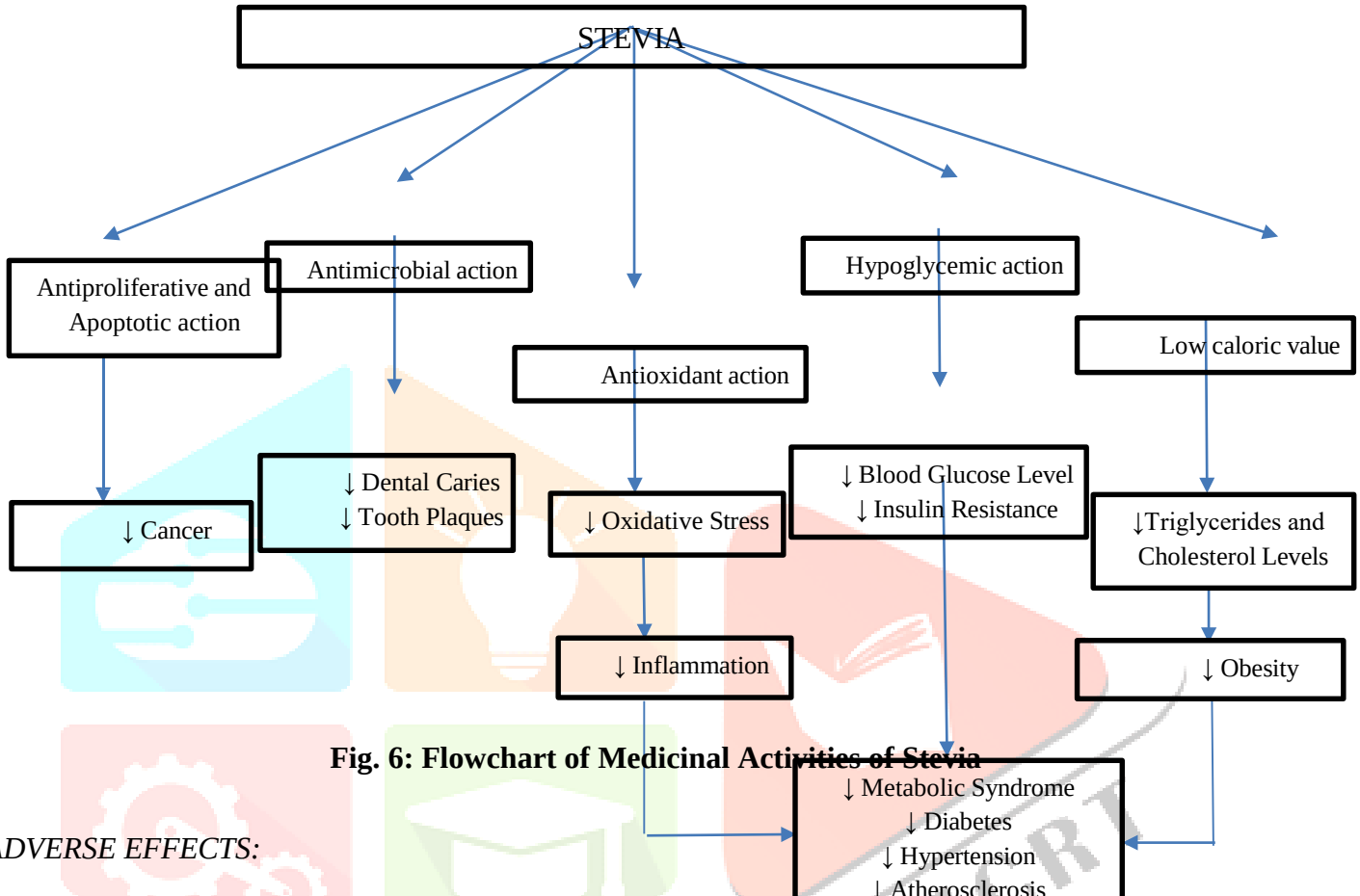

Fig. 6: Flowchart of Medicinal Activities of Stevia

ADVERSE EFFECTS:

For the past 1500 years in Paraguay and the past 30 years in Japan, Stevia has been utilized without any reported complaints, signifying its longstanding use without issues. It offers various benefits and is considered safe for human consumption. The primary recognized adverse effect of Stevia is an itching rash experienced by allergic individuals handling the plants, while not all potential side effects have been fully identified. Certain studies have reported its potential mutagenic properties but it was not supported by any further researches. The ethanolic extract of Stevia rebaudiana Bertoni leaves demonstrates no adverse effects in both genotoxicity and sub chronic oral toxicity studies. Due to the limited understanding of Stevia's impact on developing fetuses and infants, it is advisable for pregnant or breastfeeding women to refrain from its use. Additionally, individuals with kidney problems should avoid consuming Stevia as excessive doses have been associated with renal damage in certain laboratory animals. [31, 32]

MARKETED FORMULATIONS:

At present, a variety of commercial Stevia products are available globally. Stevioside crystal processing constitutes 70% of the world's production, with the remaining 30% designated for herbal applications. The leaf form includes all natural stages of the plant, whether fresh or dried, and extracts from the leaves can be processed into either powders or liquids. [15] The selection of the most appropriate Stevia form depends on the desired level of sweetness in a product and the extent to which it is employed in addressing a specific disease. Some marketed formulations of Stevia are shown in the Table. 5

Table 5: Marketed Formulations of Stevia

Sr. No.	Product Name	Company Name	Type of Medicine	Price
1	Sugar Free Green Stevia	Zydus Wellness Ltd.	Powder	Rs.225
2	Zindagi Stevia Leaves	Jhanil Healthcare Pvt. Ltd.	Dried Leaves	RS.180
3	Cerovia Stevia Sachets	Stevia World AgrotechPvt. Ltd.	Granules	Rs.190
4	Keeros Stevia Drops	Alantra Healthcare Pvt. Ltd.	Liquid Drops	RS.274
5	Sweetmate Stevia Tablets	Tevos Pharmaceuticals	Tablets	Rs.180
6	Better Stevia Liquid Extract	Now Foods, USA	Liquid Extract	Rs.2484

HOMEMADE REMEDIES:

Stevia Syrup:

1. **Ingredients**: Stevia leaves, water.
2. **Method:** Gather a handful of dried Stevia leaves. Grind them into a finely powdered form. Combine 1 tablespoon of Stevia powder with 2 cups of water and bring it to a boil. Once boiled, reduce the heat and simmer the mixture for the next 10-15 minutes. Filter the resulting syrup and store it in a tightly sealed container. Employ this homemade syrup as a wholesome and natural sweetener.

Stevia Antiseptic Mouthwash:

1. **Ingredients:** Stevia tincture, water, peppermint essential oil.

Method: Combine stevia tincture with water and a few drops of peppermint oil for an antiseptic mouthwash.

Stevia Infusion for Tea: (Herbal Tea)

1. **Ingredients:** Fresh or dried stevia leaves, hot water.
2. **Method:** Steep a handful of fresh or dried stevia leaves in hot water for a sweet herbal tea. [33, 34]

CONCLUSION:

In conclusion, this comprehensive review underscores the multifaceted nature of Stevia (Stevia rebaudiana) as a remarkable botanical entity with significant implications for both the culinary and health sectors. Through an exploration of its botanical characteristics, cultural history, sweetening properties, health benefits, commercial forms, and contemporary relevance, Stevia emerges as a versatile and promising natural sweetener. The cultural roots of Stevia, intertwined with the practices of indigenous communities like the Guarani Indians, highlight its historical significance. Stevia's journey from traditional use to global recognition emphasizes its enduring appeal and adaptability in various cultural contexts.

The sweetening properties of Stevia, attributed to steviol glycosides like stevioside and rebaudioside A, make it a compelling choice for those seeking alternatives to traditional sugar. Its unique characteristic of being a non-caloric sweetener positions Stevia as an attractive option for individuals mindful of their calorie intake and blood sugar levels. The potential health benefits associated with Stevia, including anti-diabetic, antihypertensive, antioxidant, and antihyperlipidemic properties, contribute to its growing popularity in dietary and health-conscious circles. As research continues to unveil its therapeutic potential, Stevia's role in health management becomes increasingly significant. Commercially, Stevia has found its place in various forms, from dried leaves to liquid extracts and powdered derivatives. Its integration into the food and beverage industry, as well as pharmaceutical applications, underscores its adaptability and market demand.

In the contemporary landscape, Stevia's global cultivation and increased awareness of health-conscious choices propel its significance. As a natural sweetening alternative, Stevia's trajectory reflects its pivotal role in shaping dietary preferences and influencing healthier lifestyles. Further investigations and research are also needed to identify additional positive potentials of Stevia against diseases and to assess its suitability for human consumption without any adverse consequences.

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