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Review Article

A Nutraceutical and Therapeutic Potentials of *Stevia Rebaudiana* Bertoni

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ABSTRACT

Stevia is a unique ingredient rising in the world, valued for being calorie-free as it helps reduce energy intake and added sugar in food. Like all other natural sugars, Stevia is plant-based, belonging to the Asteraceae Family. The leaves of stevia are mainly used as a sweetener and flavor enhancer in the food and beverage industry. The chemical compound obtained from stevia is considered to be the best alternative source of sugar especially for diabetes and obese patients. Several studies have shown that steviosides and similar substances, such as rebaudioside A and isosteviol, may have therapeutic benefits in addition to its sweetness. These benefits include anti-hyperglycemic, anti-hypertensive, anti-inflammatory, anti-tumor, anti-diarrheal, antibacterial, diuretic, antiseptic, anti-inflammatory, anti-fertility, hypotensive, and immunomodulatory actions. The use of Stevia prevents hypertension, acts as a bactericidal agent, and stimulates insulin production and utilization which in turn helps to control type-II diabetes and obesity. The drying temperature affects the quality of the stevia product; high temperatures reduce the medicinal and economic value. Multiple worldwide regulatory authorities have concluded that consuming high-quality stevia products in specified amounts is safe for everyone. Studies revealed that Stevia has been used throughout the world since ancient times for various purposes; for example, as a sweetener and a medicine. We conducted a systematic literature review to summarize and quantify the past and current evidence for Stevia. We searched relevant papers up to 2007 in various databases. As we know that the leaves of Stevia plants have functional and sensory properties superior to those of many other high-potency sweeteners, Stevia is likely to become a major source of high-potency sweetener for the growing natural food market in the future. Although Stevia can be helpful to anyone, there are certain groups who are more likely to benefit from its remarkable sweetening potential. These include diabetic patients, those interested in decreasing caloric intake, and children. 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. Its white crystalline compound (stevioside) is the natural herbal sweetener with no calories and is over 100–300 times sweeter than table sugar.

INTRODUCTION

People usually explore their options of natural sweeteners when they are looking to replace table sugar, which is far more commonly used, hence its name. This may predominantly be due to being diagnosed as diabetic, obese, or both. Stevia rebaudiana Bertoni, known to the general public as stevia, sweet weed, or honey leaf, manifests itself on the top of the page as the most widely available and beneficial natural sweetener. It has slowly made its way into sugar-substitute products in low and high percentages. Historically, stevia has been grown and used in South America, mainly Paraguay and Brazil, for centuries as a sweetener with medical properties capable of aiding human health and recovery. Although, the first documentation of the commercial uses and properties of stevia was made by a botanist named Santiago Bertoni in 1901. The report on various glycosides of stevia was

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finalized in 1931. Cultivation commenced in 1961. It was standardized as a natural sweetener by the USA in 2008, while it was already used in food products and drinks in Canada [1].

Cultivation

S. rebaudiana Bertoni is a perennial plant belonging to the Asteraceae family that has been successfully cultivated in not only South America, but in Asia, North America, and Europe.Almost 100 species are grown in Mexico alone[2].

Climate

Plants cultivated at upper latitudes have more quantity of glycosides that are sweeter in taste. 6 The nutrients provided and the climate, play a significant part in the development and secondary metabolites of the plant. Vegetative growth of stevia is slow in winters when the average daily temperatures range below 20 degrees Celsius. Although, some species are unaffected by temperature, are photo-insensitive. The most favorable climate for stevia growth is the subtropical region. The duration of daylight affects growth more than any other factor. Summer and spring have longer days hence, produce more yield[1].

Soil

Stevia grows best in fertile clay with little moisture but enriched with organic matter. A constant and steady provision of moisture works better than suddenly logging the field with water. Fertilizer is needed three times during planting; once at the base and the next two times after cutting of leaves. High potassium and phosphorus, and low nitrogen is needed[3].

Irrigation

Arid conditions are not suitable for growing stevia. Sprinkler systems are considered to be most suitable as the crop is easily damaged due to hydro-stress, but simultaneously needs constant water supply. Irrigation with a break of 3 to 5 days is most effective in summers.[2]

Harvest

The harvesting period is influenced by the type of land and stevia and the growing term. The opening harvest is carried out four months after implantation, and successive harvests four times per year. The optimal period of harvest is when it is 50 to 70cm tall[1].

Extraction Techniques

Numerous techniques are used to extract and purify bioactive compounds from plants for commercial and medicinal purposes. Beginning from the most conventional methods; Soxhlet extraction and cold maceration is favorable with regard to time and solvent volume. Microwave-assisted extraction utilizes lesser solvent and time, imparts lower damage to the environment [4]. Water and ethanol leaching consumes more time and labor than necessary. Supercritical and pressurized fluid extractions are not preferable as the need for a co-solvent and stable temperatures arises respectively[5].

Water extraction is currently the most widely accepted method as it is optimal in terms of temperature, pH, pressure, and time taken. Figure 1 demonstrates the extraction, filtration, and purification process of steviol glycosides from raw leaves. It is quite analogous to the purification method used for other plant-based natural ingredients. The first step of the procedure is to take dried stevia leaves and soaking them in hot water. The liquid is then filtered to remove the small particles, where later it is treated with activated carbon dioxide to remove organic residues. After concentrating the glycosides, they are spray-dried to form the final highly pure extract[6].

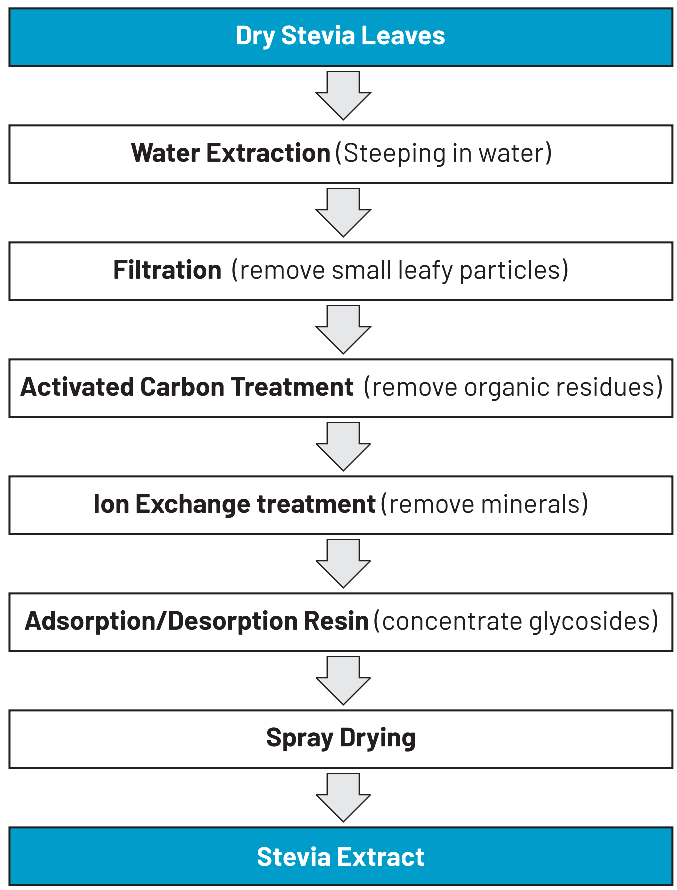

Figure 1: Extraction of steviol glycosides into 95% pure extracts[6].

Effect of Temperature

With the increase in temperature, solvent properties such as viscosity, surface tension, density, and polarity decrease leading to easier mass transfer. Therefore, the extraction of glycosides is more efficient at elevated temperatures[7].

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Effect of Pressure

Pressure changes during solvent extraction mainly affect the solvent than the ingredient to be extracted. High pressure is maintained in the apparatus to reduce vapor loss and to keep the water liquefied. The yield of the extract nearly remains unchanged under changes in pressure.

Effect of Grinding

Grinding the dry leaves before putting them in the extractor produces a higher yield as it gives a broader surface area to the solvent to work upon.

Effect of Stirring

Experimenting with the extraction method with and without stirring shows different results. There is no active raw material for extraction in the top part of the extractor if it is not stirred, which leads to low produced extract. If it is stirred, the raw leaves instead of settling down keep moving up.

Effect of extraction time

At the onset of the experiment, the yield of the extract in rises suddenly due to the high substrate concentration. But after some time, the solvent saturates and the yield remains constant [7].

Effect of supercritical CO_2

There are no substantial changes after treating the raw leaves with supercritical CO_2, but it is believed that this treatment may provide more surface area by opening the internal pores of the leaves [7].

Chemical Composition

All the steviol glycosides, stevioside and rebaudioside A are the most abundant. 110 species of stevia were tested for their sweetness and the result derived from the experiment was that merely 18 species own this property [8]. Other chemical constituents are also present that are not sweet in taste or may even produce a bitter sensation. After the final extraction stevioside presents itself in powder form as white crystals. It is relatively resistant to heat as it can withstand temperatures up to 198 degrees Celsius and is not fermentable.

Table 1.1: Chemical properties of compounds isolated or extracted from the leaves of stevia [3].

Glycoside	Molecular Formula	Sweetness Compared to sucrose	Concentration in leaf (%w/w)
Stevioside	$C_{38}H_{60}O_{18}$	150-300	4-14
Rebaudioside A	$C_{44}H_{70}O_{23}$	250-450	2-4
Rebaudioside B	$C_{38}H_{60}O_{18}$	300-350	<0.4
Rebaudioside C	$C_{44}H_{70}O_{22}$	120-500	1-2
Rebaudioside D	$C_{50}H_{80}O_{28}$	250-450	<0.4
Rebaudioside E	$C_{44}H_{70}O_{23}$	150-300	<0.4
Rebaudioside F	$C_{43}H_{68}O_{22}$	Undefined	<0.4
Steviolbioside	$C_{32}H_{50}O_{13}$	100-120	<0.4
Dulcoside A	$C_{38}H_{60}O_{17}$	50-120	0.4-0.7

Nutritional Composition

The nutritional composition of stevia is altered by the extent and method of drying. Extract from unprocessed leaves has 25% amino acids, 19% proteins, 31% carbohydrate, and 25% reduced sugars. Extract from dried leaves has 10% amino acids, 18% proteins, 33% carbohydrates, and 39% reduced sugars [9].

Proteins

Glutamic acid, aspartic acid, lysine, serine, alanine, proline, tyrosine, isoleucine, and methionine are the nine amino acids that were primarily discovered in stevia leaves [10]. Later on, 17 amino acids were isolated in the extract [11].

Carbohydrates

Carbohydrates present in dried stevia leaves are linked to the promotion of probiotic activity, and the polysaccharides along with fructo-oligosaccharides that breakdown lipids and maintaining blood glucose levels. Carbohydrates are the main energy source and also have a significant role in the basic cellular structures [12].

Lipids

Lipids are a key building block of cellular membranes. They store energy in fat cells and release it by breaking down when needed by the body. In an analysis of stevia leaves, it was concluded that they contain palmitic, oleopalmitic, linoleic, linolenic, stearic, and oleic acids [13]. All these fatty acids play a part in boosting immunity and lowering triglyceride levels in the blood.

Vitamins and Minerals

Minerals and vitamins are crucial for the effective functioning of the body. They are micronutrients that are needed in low amounts but their absence can wreak havoc in our bodies. Stevia extracts contain vitamin B9, vitamin B6, and vitamin C. It also comprises of various minerals in small quantities such as potassium, calcium, magnesium, sulphur, sodium, phosphorus, cobalt, iron, manganese, selenium, and molybdenum [13]. Minerals present in appreciable quantities are zinc and copper. Although, calcium and iron absorption are hindered by the presence of oxalates [14].

Antioxidants

Antioxidants are elements or compounds that fight against cellular oxidation by free radicals, the activating agents for

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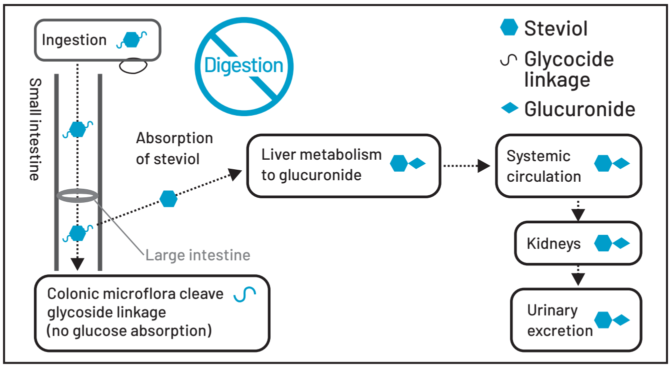
multiple diseases mainly cancer, neurodegenerative disorders, accelerated aging, inflammation, cardiovascular disorders, etc. Stevia contains polyphenols that display anti-oxidative characteristics[15].

1.1. Metabolism

Stevia leaves contain multiple glycosides such as stevioside, rebaudioside, etc. Steviol glycosides are broken down to their basic unit, diterpene steviol, by the colonic bacteria.

Figure 2: Pathway followed by steviol glycosides in the human body[16].



1.2. Absorption

Stevioside, one of the two most abundant steviol glycosides, has a notable molecular weight of 804.9 g/mol, leading to its failure of being absorbed in the small intestine. Intestinal enzymes and gastric juice are unsuccessful in completely breakdown stevioside but can convert it into steviol, its aglycone, by cleaving the glycosidic linkage. A study showed that the transportation rate of stevioside is lower than that of steviol. Steviol travels from the intestine into the blood through passive diffusion and carrier-mediated passive transport[16].

1.3. Distribution

The distribution and accumulation of steviol in fundamental organs of the body such as the brain may be detrimental to health as it may cause undesirable effects there. But for medicinal purposes, its accretion in the targeted organ may do better than harm [17]. Steviol is metabolized to steviol glucuronide in the liver, after which it becomes a part of the systemic circulation.

1.4. Excretion

Urinary excretion is the major pathway employed by the body to eliminate steviol glucuronide, the final end-product in the metabolism of stevioside. A study conducted in 2008 established that 3 days after oral ingestion of stevia, 62% steviol glucuronide in urine and 5.2% free steviol in feces makes up the administered dose of stevia[18].

Functional Properties:

The following table shows various functional properties of Stevia rebaudiana Bertoni, more specifically its leaf powder.

Table 1.2: Functional properties of stevia leaf powder[19].

Properties	Values
Water Holding Capacity	4.7ml/g
Bulk Density	0.443g/ml
Fat Absorption Capacity	4.5ml/g
Emulsification Value	5.0ml/g
Swelling Index	5.01g/g
Solubility	0.365g/g
pH	5.95

Taste

Stevia leaves have a slight licorice flavor and sweet aftertaste that remains for hours. The stem consists of the sweet part and is blanketed by the bitter compounds in the veins of the leaves [1]. The leaves may be used to prepare various pastes but are commonly used in herbal and green teas. They can also be used as a flavor enhancer in salads, coffees, custards, etc. This is the most unprocessed, unrefined and natural state of stevia leaves, which is 100-300 times sweeter than simple sugar[20].

Stability

The high protein amount of stevia powder increases its water holding capacity. This increases the swelling capacity, which is significant in the production of viscous foods for instance broths, dough, gravies, and bakery items. It can assist in the formation and stabilization of emulsions, which makes it vital in the production of various food items, such as milk powders, coffee powders, frozen foods, etc. It is also capable to trap oil particles, known as fat absorption capacity. This makes it important in the processing of food by causing flavor retention. Steviol glycosides are thermally stable and have a resistance to heat. They can endure 100 degrees Celsius for 1 hour[21].

Food Uses

Based on the remarkable functional properties of stevia, it can very well be used as a stabilizer or binder in the food industry. It can also improve the nutritional content of low nutrient-dense foods [22]. Stevia leaves after quality dissemination can mainly be distributed into three markets or industries; food and beverage, health and pharmaceuticals, and by-product market. In the food and beverage industry, it is already being used as a natural sweetener in sugar replacement tablets, low-sugar, and sugar-free foods for diabetics, low-calorie snacks for fitness conscious people, green tea packets, energy drinks and so much more. In the health industry, it can be used as a

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binder or stabilizer in various drugs instead of chemicals that are being used. It is used in herbal teas as a sweetener, replacing sugar consumption which leads to various health disorders. Finally, in the by-product market, the lowest quality leaves are placed. They can be dried, crushed, and used as fertilizer for plants, or even animal feed. It has various phytochemicals that can help in better growth of plants[1].

Therapeutic Effects of Stevia

Anti-Diabetic Effect

Diabetes Mellitus is a metabolic disorder that constitutes by chronic hyperglycemia. It disrupts the metabolism of protein, carbohydrates, and fats. It occurs due to a lack of proper insulin secretion or insulin sensitivity or in some cases both. Various studies have been conducted to examine the anti-diabetic and glucose-lowering effect of stevia and its glycosides. These studies were conducted on both animals and humans [24].

In 2013 Saravanan et al., conducted a 45-day experiment on diabetic Wistar rats with healthy rats. They observed the effect of rebaudioside on insulin levels, blood glucose levels, and also studied complete lipid profiles. It was found that after the rats were treated with rebaudioside A, not only did the levels of enzymatic and non-enzymatic antioxidants were regulated but it also improved insulin levels and blood glucose absorption in the blood[25].

In 2016 Rith et al., conducted a study of 60 days on 20 patients diagnosed with diabetes type-II. They aimed to test if stevia should a lipid and glucose-lowering effect after oral administration of 1g/day. At the end of the experiment it was observed that postprandial and fasting blood glucose levels significantly decreased along with cholesterol, triglycerides, and very-low-density lipoprotein VLDL[26].

In another in-vivo trial conducted by Philippaert et al., 2017, the preventive effect of stevioside was examined in reducing hyperglycemia and also had a precautionary effect in the development of glucose intolerance. After the experiment the researchers concluded that a glycone-Ca component of steviol glycoside could be the responsible agent in exhibiting anti-diabetic properties. Hence it can be deduced that stevia may be of sheer importance in the prevention and treatment of diabetes type-II[27].

Nephroprotective Effect

Stevia and its extracts exert a nephroprotective action because of its certain therapeutic properties such as it suppresses apoptosis, inflammation, and oxidative stress. Stevia and its glycosides suppress diabetic complications along with nephrotoxicity that is caused by cisplatin (a chemotherapeutic agent that repairs DNA and activates cell cycle arrest). Stevioside suppresses the release of caspase-activating proteins which in turn lowers apoptosis. It also decreases TNFα and p65 expression which reduces inflammation[27]. It also reduces oxidative and nitrosative stress. Stevioside inserts a restoration action of the cell cycle. It increases cyclin D1 expression and reduces p21 expression. All of these help in eliminating various complications such as glomerular hyperfiltration and renal hypertrophy[28].

Hepatoprotective Effect

Cirrhosis, liver cancers, and other liver injuries that are caused by oxidative stress can be reduced by various therapeutic activities of steviol such as its antioxidative nature [29]. When tested on rats and chicken embryo stevia reduced lipopolysaccharide (an endotoxin, a potential inflammatory agent and a glycolipid component of a cell membrane. It releases inflammatory cytokines which cause liver injuries) and CCL_4 (it causes liver injury by the formation of free radical CCL_3 a trichloromethyl free radical) induced injury [30]. They disturb calcium and iron ions, stimulate lipid peroxidation and protein covalent binding which leads to death [31]. Stevia has an immunomodulatory action because it inhibits NF-$\kappa\beta$ which prevents cholestasis, necrosis and it preserves liver function[32].

Antioxidative Effect

Oxidative stress is the cause of imbalance that occurs between reactive oxygen and biological system. Oxidation is essential for human beings for the production of energy by biological processes. When the production of free radicals of oxygen is uncontrolled, it leads to the onset of many disorders that include immunodeficiencies, aging, neurologic disorders, arthritis, and inflammation, arteriosclerosis, coronary heart disease, ischemia, stroke, Parkinson's disease, Alzheimer's disease, diabetes mellitus, and some cancers. Enzymes protect organisms against free radical damage e.g. superoxide dismutase and catalase. Some compounds also do this function of protection that includes ascorbic acid, tocopherols, etc [33]. When the cycle of antioxidant protection is disturbed, the physiological functions of an organism's body are deteriorated and further leads to the onset of certain disorders as named above. Naturally, the balance between Reactive Oxygen Species generation and their removal by antioxidants is maintained by the organism. Due to all this, natural foods and medicinal plants are mainly focused to perform this function. Many experiments have been performed that determined its efficiency to protect against free radicals' damage. Results from various experiments proved that the antioxidant capacity of crude leave extracts is higher than purified steviol glycosides suggesting that the polyphenols present in crude leaves extract are responsible for the antioxidant property of Stevia. Due to this ability of Stevia it is majorly used as an

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ingredient in many food products.[34] In another research done on rats, it was analyzed that steviol glycoside not only stimulated glucose uptake but also up-regulated endogenous antioxidant defense system.[35]

Anti-Cancerous Effect

Stevia demonstrates anticancerous properties that benefit human life. Breast cancer is a rising health problem that is responsible in the increment of female mortality rate. Research is being done to discover natural products to treat and prevent breast cancer instead of medicines as they affect both cancerous and normal cells. Stevia is therefore of immense importance in this aspect. Studies have been done to see the effect of steviol on breast cancer cell line (MCF-7). Results from these studies and research have shown that a certain dose of steviol inhibits MCF-7 cell growth and arrest cell cycle at the G2/M phase. The results of this study also demonstrated the dose-dependent reduction in viability of MCF-7 cells by Stevia. Stevia decreases cell proliferation and induces the death of MCF07 cells. The effects of Stevia on cell cycle distribution were also analyzed by the method of flow cytometry. Stevia also induces apoptosis. On an interesting note, 26% of cells had undergone apoptosis when given 250μM Steviol dose for 48 hours. [36] Functions of Stevia that it offers in treating breast cancer include suppression of cell viability, cell cycle arrest, induction of apoptosis in cancerous cells, inhibition of proliferation of cancer cells, and reduction in cell survival ability. Stevia has antitumor property, cytotoxic and anticancerous effects. Stevia has also shown anticancer effects on human gastrointestinal cancer cells. [37] The inhibition cycle includes the mitochondrial apoptic pathway. It is highly recommended by the experts to add steviol in the chemotherapy of cancer patients as it can act as a potential chemotherapeutic agent. Digestion of steviol glycosides occurs in the colon where it is hydrolysed to steviol. From there it enters enterohepatic circulation and is glucuronated in liver and rest steviol is excreted through feces. [38] Results of the same study revealed that steviol has an intensive inhibitory effect on human gastrointestinal cancer cells.[39]

Investigations of Mizushina et al., 2005 demonstrated that isosteviol (product of acid hydrolysis of steviol glycoside) inhibits DNA polymerase and topoisomerase II that further delays the onset of some cancers. [40] Hence Stevia is non-toxic to normal human cells and portrays anti-proliferative properties against cancerous cells.[41]

Anti-microbial Effect

Stevia has always shown deleterious effects against microbial damage. Traditionally, due to its anti-microbial activity it was used for healing of wounds, sores, gum disease, etc.When experimented in rats, it showed potent antimicrobial and hepatoprotective effects against CCl4 that induced a liver injury. [42] Anti-microbial examinations were carried out by the Standard Kirby-Bauer method against different micro-organisms that cause spoilage in food or substances and diseases in organism and the results were positive.[43]

Anti-Bacterial Effect

When referring to the past, studies of Tomita were aimed at the bactericidal activity of stevia against various food-borne pathogenic bacteria.[44] Certain amounts of Stevia when added to obtain results for in respect of antibacterial effects showed inhibitory effects on bacterial growth.[42] It showed effects against some bacterial species namely Staphylococcus aureus, Salmonella typhii, Escherichia coli, Bacillus subtilis, Aeromonas hydrophilia, and Vibrio cholera.[43]

Stevia has shown anti-bacterial effects on micro-organisms that cause tooth decay. Streptococcus mutants and Lactobacillus acidophilus are present in tooth decay lesions and are highly responsible for tooth decay. [45] Streptococcus sobrinus is also involved in tooth decay. Stevia has been of immense importance for tooth caries as well.[46]

Anti-Fungal Effect

When studied, evidences were seen that the growth of the fungus was inhibited by Stevia. Graphs of growth showed that there was a decline in fungal growth.[42] Crude stevia plant extract is said to show more anti-microbial activity than the isolated extract from the original one. Due to this property of stevia, it is and can be commercially used as an anti-microbial agent in soaps, sanitizers, moisturizing creams, toothpaste, mouth wash, and many more products.[47]

Antihyperlipidemic Effect

Among the vast benefits of stevia, one is that it is directly linked with pathology and complications of hyperlipidemia. [48] In 2018, when studied in albino rats, stevia showed lowering effects of hyperlipidemia. Different concentrations of stevia were induced that not only effected weight gain and feed intake but also acted as antihyperlipidemic by lowering the lipid profile of the albino rats. Feed intake was mainly suppressed due to the stevioside present in stevia that may not stimulate the appetite. Water intake was affected by glycoside that decreases water consumption. Provision of doses of stevia at 200, 300, 400, and 500 ppm/kg b. Wt. showed that weight gain was reduced and this decrease was mainly due to stevioside. Stevioside reduces weight gain by decreasing glucose levels and promoting insulin sensitivity. [49] Stevioside has the potential ability to decrease fat absorption and lipogenic enzymes and increase fat excretion. Stevioside lowers total cholesterol levels by its ability to increase bile acid excretion and prevention

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reabsorption from the small intestine. The rise in bile acid and cholesterol excretion activates cholesterol 7α-hydroxylase. This enhances the conversion of liver cholesterol to bile acid and so leads to a reduction in cholesterol. This mechanism is stimulated by stevia.[50]
Recent researches reveal that stevioside can bind dietary cholesterol in the colon and reduce total cholesterol by its fecal excretion.[51, 52]
Stevia is used in traditional Armenian medicine that is used to reduce levels of blood pressure, glucose, cholesterol, and also modulates immune function.[53]

Anti-Inflammatory Effect

Inflammation is multifactorial and involves many systems of the body. It is a dynamic process that is very complex. [54] Inflammation occurs in response to injury by mammalian tissue and can be in the form of painful swelling, edema, change in color of skin, etc. [55, 56] Inflammation can be acute or chronic, by the research of Arya et al., 2012 it was revealed that stevia inhibits edema from the start and disrupts the whole cycle of inflammation. [57] Investigations by Boonkaewwan et al. (2006) revealed that stevioside inhibits lipopolysaccharides which enhance the production and generation of proinflammatory cytokines: IL-beta and TNF-alpha. Stevioside being an active agent inhibits the inflammatory response and lowers down the severity of the response by reducing undesirable effects. Stevia when consumed by normal healthy person improves the activity of monocytes.[15] Pathogenic bacteria and other infecting agents directly activate monocytes or macrophages that lead to an inflammatory response by the organism. Stevia in this major aspect disrupts this normal and usual response by an individual's body. [54] Stevia along with its polyphenolic compounds exerts anti-inflammatory effects on the epithelial cells of the colon. Stevia can help treat Inflammatory Bowel Disease. IBD is a family of inflammatory conditions and stevia can be productive in ways of treating it. [58] Studies have suggested that stevia can be a potent source for the production of phytomedicine in the future [59] as the consumption of stevioside protects against inflammatory diseases.[60]

Hemolytic Potential Effect

Pathogenicity of Listeria Monocytogenes is displayed by a pore-forming toxin Listerolysin O, but its hemolytic abilities are reduced by Stevia. The process of lysis is done by LLO which then is accountable for relinquishing of primary vacuoles into the cytosol part of host cells. There it increases in every way leading to a ceaseless infection of the host.[15]

Blood Pressure Regulation

Blood Pressure of a human person under normal circumstances is systolic 120 mmHg and diastolic 80 mmHg but in extreme hypertensive cases the blood pressure is systolic 140 mmHg and diastolic 90 mmHg. In the hypertensive case the pressure in medium-sized veins rises which leads to many other heart problems. So, Stevia holds the ability to reduce the high blood pressure to normal. It also is capable enough to regulate the heartbeat of cardiopulmonary signals. Stevia extracts are capable of lowering the pressure of the blood by dilating the arterial walls due to its hypotensive capacity at the membrane level. [61] Stevia contains phytosterols that protect against cardiovascular defects like calcium channel blocking agent medicine. Stevia possesses the ability of vasorelaxation.
Stevia when consumed regularly it decreases the cholesterol component in blood. It also helps in the blood coagulation and cell regeneration, reduces neoplastic growth, and fortifies the blood vessels. It avoids the accumulation of calcium on the arterial walls of the blood vessels. Stevia decreases LDL (low-density lipoproteins) and cholesterols and increases HDL (high-density lipoproteins). The conclusion of this is that Stevia contains a hypolipidemic effect.[62]

Obesity Preventive Effect

Obesity is the symptom of excessive food consumption, non-nutritious food choices, lack of physical activity. Obesity is associated with many problems which include hyperlipidemia, hypertension, renal and pulmonary problems, diabetes, cancer, etc. One of the major reasons why obesity occurs is the consumption of calorie-rich sweeteners and sweetened snacks also beverages. Stevia is a low-calorie sweetener or in other words an empty calorie sugar, so stevia does not metabolize to create energy or a sweet taste that is 300 times stronger than in sucrose when consumed by a human. [63] Substituting regular sugar with Stevia will decrease the hankering of sweet and fatty foods and is quite functional in weight loss programs. A total of 95g of Stevia powder if taken in controlled amounts in the diet replacing normal sugar results in a weight loss of 1 pound in 9-10 days or it is a net deficit of 380 kcal/day.[61]

Dental Protection

An oral infection disease also known as tooth decay or dental caries is quite prevailing among the public worldwide and it can be liable in individuals throughout their life. Tooth decay is mostly caused by bacteria e.g., Streptococcus mutants or Lactobacillus casein etc. which can ferment carbohydrates residue left in the mouth. Several processes like metabolism of oral microbes can cause loss of minerals from the tooth enamel and tooth structure is destroyed by the rapid proteolytic process.[61]
All of this is the result of overconsumption of regular sweeteners that releases energy from the carbohydrates

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which allows the formation of plaque and gingivitis in the mouth, encouraged by the growth of harmful bacteria. Stevia holds bactericidal properties that prohibit the dental decay and gingivitis. Stevia is the natural sucrose substitute with very high nutritive value. It has several extracts or derivatives e.g., Steviol, Stevioside, Rebaudiana A, etc. which are non-cariogenic that suppresses bacterial growth and releases less acid on the stevioside media. Consumption of nutritive sweeteners regularly can increase the formation of cavities, plaque, and gingivitis in the mouth. So, replacement with stevia can reduce the chances of it happening because stevia reduces glucan which prompts cariogenic organisms.[64]

Role in Inflammatory Bowel Disorder

IBD or inflammatory bowel disorder is the inflammation of the intestines and colon-occurring in patients of both genders at ages between 15-30 years. However, Stevia consists of a high number of polyphenols that hold the ability to fight the harmful diseases which also includes intestinal ones in which smooth muscles of the intestines lead to hypermotility of microvilli resulting in diarrhea.[65] Stevia consists of anti-inflammatory properties which affect the colonic epithelial cells. [66] IBD is also associated with Crohn's Disease and ulcerative colitis. Stevia holds gastro-protective properties that reduce gastric abnormalities; also, it reduces excess acidity in the GI system which inhibits the formation of gastric lesions. [59]

Wound Healing Effect

Wound healing properties of Stevia were only found when experimented on Dawley rats, further studies are being conducted for human use. Stevia holds the ability to treat skin ulceration in folklore medicine. The study as the hand has shown that if stevia was induced at the toxic level through oral means did not affect 2000mg/kg, there was no difference in the physical characteristics of the body seen, but at the wound area of the rat, there was a significant reduction in the size of the incision or wound. [67] Other effects of Stevia which help in wound healing include formation of tissue granules speed up, fibroblast increases in quantity, patterns of collagen fiber are more organized, alignment of tissue is greater, and activities of inflammatory cells and the production of chemical mediators are inhibited.[68]

Product Development

Industries like baking, confectioneries, beverages and many others use regular sweeteners but if they are replaced by stevia sweeteners, they help in ways like cost reduction, greater consumer acceptability, awareness about Stevia's abilities to convince the public to consume stevia regularly through foods like cereals, yogurt, snacks, beverages, etc. [66] Certain factors are carefully monitored during the extraction and development of products in which stevia is used, such as temperature, pH environment, product stability, and physiological characteristics.

Stability of Temperature

Stevia can sustain its original form and remain stable during high-temperature processing. When stevia is cooked it does not caramelize or changes its color to brown. They remain stable at the temperature at 95°C and do not decompose during baking. But if the temperature is raised to 200°C the disintegration starts. Since stevia displays no such change in color and taste after heating. It is highly recommended that stevia be used in baking and beverages with the combination of sucrose for good quality. Stevia is 100% stable when added with other ingredients.[69]

Stability of pH

Stevia does not degenerate against a wide range of pH even in acidic conditions and against fermentation. If stevia is dissolved for more than 2 hours at 60°C in any range of pH of 1-10, it does not degrade. But if it is dissolved in pH of 2-10 and heated up to 80°C than a minimal loss of 5% is seen in the nutritive value of Stevia. Stevia does degenerate when it is dissolved in pH 9 or more up to 14 and heated at 100°C for 1 hour. It is seen that a stevia derivative known a Rebaudioside A which gives a sweet taste for at least 26 weeks when consumed as cola, lemon-lime, or chewing gum. Rebaudioside A can tolerate a temperature of pasteurization of 88°C for 5 min and can resist the process of fermentation for the production of plain yogurt and give it an appropriate sweetness for 6 weeks.[70]

Product Stability of Stevioside

Stevia is combined with sucrose to reduce the intake of calorie-rich sugars in industries like confectionery and bakery. Stevia has a symbiotic effect when added to peach juice in the proportions 160mg/L and 34 mg/L of Stevioside and sucrose respectively, with no metallic or bitter aftertaste of the final product. When Stevia is compared with other sugars like saccharin, it is seen that stevia does not metabolize in the human body to give low calories and does not contribute to certain diseases in any way; with saccharine it is all vice versa. In products like muffins when Rebaudioside A is combined with inulin and polydextrose it gives the muffins bulkiness and gives energy 5kJ/100kg less. With sugar replaced with stevia foods like cookies are more suitable than bread because of its status, texture, quality, and shelf life. Overall, when stevia is added it contributes to many sensory attributes like color, texture, odor flavor, energy, appearance, etc. Stevia gives cakes firmness, thickness, and moisture but low shelf life which is considered healthy because longer shelf life indicates

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more use of sugar as a preservative and extra added calorie.[71]

Market Use and Future Prospectives

Sugar has been excessively used and this is alarming that our generations are at increased risk of precarious health conditions that will lead to chronic diseases. Major calories for a person are incorporated from sugar and people being unaware that this is not correct. Sugar is being the culprit of the coming generations. Now recent studies have evolved better ideas and substitutes. All over the world stevia is being highly researched and people are eager to research more about it. It's some benefits are discovered and seem like countless are being undiscovered. Those who discovered its functionality are slowly and gradually incorporating stevia into their diets. [72] Many countries are now aware of the fact that sugar is implementing hazardous effects on our health and are now keener towards the use of stevia. Stevia is undoubtedly a natural, safe, and sugar substitute. It serves as an alternative sweetener used as a food ingredient to sweeten a diverse variety of consumer products that include soft drinks, toothpaste, ice creams, confectionery, and ointments.[73] Stevia has vast benefits and so it can be used in several ways. One cannot only use stevia for manufacturing edibles, snacks, and products but also used for making medicines. Stevia is better from sugar in all aspects. It is cheaper than local sugar and it is more efficient and beneficial than local sugar. It tastes sweeter than sugar. Stevia can be efficiently incorporated into daily routines. It can be used in a number of products e.g. skin products, dental products that include toothpaste and mouthwashes, edible products, sanitary products, flavouring products, sweetening products. Present use of stevia is although less but the ongoing researches plus the coming researches will greatly influence people to switch from sugar to stevia. It's something sweeter than sugar and zero in calories. It is said to be herbal sugar and magical sweetener. [38] Stevia rebaudiana has undoubtedly a valuable future as its magical health benefits are countless. According to WHO, stevia will increase its share in the future sweetener market. What we see is stevia is the future of today's sugar.

CONCLUSIONS:

Stevia Rebaudiana is a promising non-caloric, non-nutritive sugar substitute that aims at promoting health. It has high phenols, minerals, and flavonoids contents. Stevia has proved itself beneficial in being an antioxidant, a good regulator of blood pressure, and blood glucose level. After several experiments and trials conducted on both animals and human stevia has proven to be an efficient medication in the prevention and treatment of several chronic diseases such as controlling obesity, diabetes, managing of IBD, preventing dental caries, and other diseases related to kidney and liver. Stevia is a nutraceutical spectacle that has a promising future in the medicinal and herbal treatment of various diseases.

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