International Journal of Current Trends in Pharmaceutical Research

Journal Home Page: www.pharmaresearchlibrary.com/ijctpr

REVIEW ARTICLE

A Brief Study on *Steviarebaudiana*–A Review

T. Usha Kiran Reddy*, R. Gouri, G. Sindhu, R. Harsha, K. Thyagaraju

S V U College of Pharmaceutical Sciences, S.V University, Tirupati–517502.

ABSTRACT

Stevia rebaudiana belongs to Asteraceae family and is popularly known as candy leaf. *Stevia rebaudiana Bertoni* is a sweet tasting medicinal herb; and has been known to contain calorie-free natural sugars, which are up to three hundred times sweeter than sucrose. Due to its sweet taste, it has high commercial value throughout the world as a sugar substitute in medicine, foods products, and beverages. The increased market share of Stevia sweeteners has established a lasting increase in the demand for constant high quality and high purity of Stevia products. Clinical examinations performed on Steviol glycosides have shown that it is nontoxic and exert hypotensive, cardiotonic, anti-obesity, anti-diabetic, anticarcinogenic, anti-inflammatory, anti-viral and anti-bacterial actions. Stevia leaves, stevioside and highly refined extracts of the leaves are now officially used as a low-calorie natural sweetener and dietary supplement in many countries. In the future, there is a possibility that Stevia could become a major source of high potency low-calorie sweetener for growing demand in the natural food market.

Keywords: *Stevia rebaudiana, anti-obesity, anti-carcinogenic, anti-diabetic.*

ARTICLE INFO
Corresponding Author
T. Usha Kiran Reddy
S V U College of Pharmaceutical Sciences,
S.V University, Tirupati–517502.A.P, India.
MS-ID: IJCTPR3785

PAPER QR-CODE

Article History: Received 18 January 2019, **Accepted** 17 February 2019, **Available Online**15 March 2019

Citation: *T. Usha Kiran Reddy, et al.* A Brief Study on Steviarebaudiana– A Review. *Int. J. Curnt. Tren. Pharm, Res., Res.*, 2019, 7(2): 63-70.

CONTENTS

1. Introduction

The term “medicinal plant” includes various types of plant parts like fruit, seed, stem, bark, flower leaf, stigma and root which are used for medicinal purposes asfood, flavonoid, medicine, perfume and also in spiritual activities such as herbalism ("herbology" or "herbal medicine"). Plants have been used for various medicinal purposes long before the prehistoric period. Evidence exists that Unani Hakims, Indian Vaids, European and Mediterranean

cultures were using herbs for over 4000 years as medicine. Recently, WHO (World Health Organization) estimated that 80 percent of people worldwide rely on herbal medicines for some aspect of their primary health care needs. According to WHO, around 21,000 plant species showed potential benefits to be used as medicinal plants. [1] Traditional systems of medicine continue to be widely practiced on many accounts. Population rise, inadequate supply of drugs, the prohibitive cost of treatments, side effects of several synthetic drugs and development of resistance compared to currently used drugs for infectious diseases have led to increased emphasis on the use of plant materials as a source of medicines for a wide variety of human ailments. [2]

Although herbs had been priced for their medicinal, flavoring and aromatic qualities for centuries, the synthetic products of the modern age surpassed their importance for a while. However, the blind dependence on synthetics is over and people are returning to the naturals with the hope of safe and security. Treatment with medicinal plants is considered very safe as there are no or minimal side effects. These remedies are in sync with nature, which is the biggest advantage. The golden fact is that use of herbal treatments is independent of any age groups and the sexes. This is the reason why herbal treatment is growing popularity across the globe [3].

Herbal medicines are complex drugs with multiple potential targets and actions. To treat a complex chronic disease would require covering multiple targets, and in conventional drug therapy, this leads to polypharmacy. In this light, it has to be stressed that herbal medicines, just for the sake of them being based on plant-derived products, are chemically complex mixtures containing multiple major and minor constituents with multiple potential targets and mechanisms. [4]

Description and Cultivation

Stevia, (*Stevia rebaudiana*), also called candy leaf, a flowering plant in the aster family (Asteraceae), grown for its sweet-tasting leaves which are traditionally used as sweetening agents in teas. The plant is native to Paraguay, where it has a long history of use, (more than 1500 years) by the Guaraní people. Stevia is a shrubby perennial herb that reaches 30.5–080 cm (1–2.5 feet) in height. [5] The oblong aromatic leaves are 2.5 cm (1 inch) long with a prominent midrib and are arranged oppositely along the stems. The small tubular flowers have white petals and are borne in terminal clusters; which are usually removed to improve the flavor of the leaves. *Stevia rebaudiana* has a very low seed set. The conventional methods of propagation are either by seeds or by cuttings at the 12 to 15cm. The best season for stevia propagation is from Feb to Mar. The cuttings will be ready for transplanting after 4 weeks of rooting. Since germination rates are poor and seedlings are very slow to establish, it is best grown as an annual or perennial transplanted crop with a preferred temperature of 30^{o}C to 32^{o}C and about 150cm annual rainfall. High temperatures above 45^{o}C and nightly temperatures below 5^{o}C will damage the crop. Germination has been the main hindrance as *Steviarebaudiana* has sporophytic self-incompatibility. Greater viability can be achieved by using selected genotypes which have a greater number of blooms, which in turn increases the number of available reproductive structures, which allows for more cross-pollination and draws the attention of local pollinators. Families of insects previously confirmed to carry stevia pollen are Apidae(Hymenoptera), Calliphoridae (Diptera), Halictidae (Hymenoptera), Syrphidae (Diptera). Stevia prefers a well-drained, rich, red and sandy loam soils. Soil pH range should be acidic to neutral i.e., 6.0 to 7.5. Good organic matter and micronutrients would fetch a good yield of stevia in case of poor soils. Long spring and summer days favor leaf yields and leaf stevioside contents while short days promote blossoming.[6]

Stevia is one of 950 genera of the family Asteraceae. The genus contains 240 species of plants native to South America, Central America, and Mexico, with several species found as far north as Arizona, New Mexico, and Texas. In India, there are 2 most popular verities of Stevia plant developed for low care and high yielding. These varieties are best suitable for Indian climatic conditions and soils. MDS -14 and MDS13 are the improved cultivars of Stevia plant developed for high temperature and drought/low rainy regions.

A fine tilth soil and the land that is not susceptible to flooding and pudding is needed to raise the crop. The raised beds should have 12 to 15 cm in height & 50 to 60 cm in width. Row-to-Row distance should be 40 to 45 cm and Plant-to-Plant distance should be about 30 cm. This calculation gives Stevia plant density as 20,000 to 25,000 plants per 1 acre.[7] Stevia crop responds well to fertilizers and manures like organic manures due to slow release of nitrogen. Adding Farm Yard Manure (FMY), Vermi compost, cow dung/urine will be beneficial for better crop yield. The fertilizer dose of NPK of 28:113:113 kg/hectare is recommended for high yield of Stevia crop.

Drip irrigation system or micro sprinkler system is best for irrigating Stevia crop. Frequent light irrigation should be carried out in hot summer months. In the winter or rainy season, this crop may not need frequent watering as excessive moisture level in the soil is not favorable for its growth. Usually, Stevia plants become ready for first harvesting when they attain 40 to 60 cm in height (or) 4 to 5 months after planting. Thereafter, harvesting can be carried out every 3 months for 3 years. The Stevia plants should be cut just before flowering starts as the sweetener in its leaf would be maximum at this time and also can get good quantity at this point in time. Harvesting can be done by plucking in small quantities or the whole plant leaving 15 cm from the base. An average yield of 2500 to 2700 kgs of dried Stevia leaves per acre can be obtained with crop management practices and good variety.[8]

Taxonomical classification:

Kingdom:Plantae
Subkingdom:viridiplantae
Infrakingdom:Streptopelia

Superdivision:Bryophyta
Division:Tracheophyta
Subdivision:Spermatophyta
Class:Magnoliopsida
Subclass:Asteridae
Order:Asterales
Family: Asteraceae
Tribe:Eupatorium
Genus:*Stevia*
Species*: Rebaudiana*.

Some of the related species of stevia include. *Stevia eupatoria, Stevia lemmoni, Stevia micrantha, Stevia ovata, Stevia plummerae, Stevia rhombifolia, Stevia serrata, Stevia viscida, Stevia commixta,Stevia satureiafilia, Stevia leptophylla, Stevia myriadenai, Stevia ophryphylla, Stevia selloi, Stevia nepetifolia, Stevia oligophylla, Stevia origanoides, Stevia triflora*.[9][10].

2. Morphology

Stevia consists of a group of annual and perennial herbs, shrubs that occur in mountain regions, open forests, borders of rivers and dry valleys [11]. The inflorescence is loosely paniculate with the heads appearing opposite the bracts in irregular sympodial cymes. They are arranged in indeterminate heads. The flowers are small (15-17 mm) and white with pale purple throat corollas. The tiny white florets are perfect (hermaphrodite) borne in small corymbs of two to six florets. The plant can initiate flowering after a minimum of four true leaves has formed. The plant takes more than a month to pass through the various developmental flower stages and produce all its flowers.[12] Anthers are small, five in number. The pollen can be highly allergic. Seeds have a very small endosperm and are dispersed in the wind via hairy pappus. Fertile seeds are usually dark-colored, whereas infertile seeds are usually pale or clear Seeds are very small. Seedlings are slow to develop, reaching a size suitable for transplanting to the field at 45-60 days Two types of seeds are found in Stevia, black and tan colored, with black seeds being heavier than tan seeds and the viability of black seeds was much higher than that of tan-coloredseeds.[13]

Stevia has an alternate leaf arrangement and herbaceous growth habit. Leaves are small, sessile, lanceolate to oblanceolate, oblong, serrate above the middle and somewhat folded upwards. Trichomes on the leaf surface are of two distinct sizes, large (4-5 mm) and small (2.5 mm) Leaves vary widely in quality due to many environmental factors, including soil conditions, irrigation methods, sunlight, air purity, farming practices, sanitation, processing, and storage. The leaf has a pleasantly sweet, refreshing taste that can linger in the mouth for hours. The material contains the sweet components, surrounded by the bitter components.[14] The growth and flowering of Stevia are affected by radiation, day length, temperature, soil moisture, and wind.The plant is grown as a perennial crop in subtropical regions, including parts of the United States, and as an annual crop in mid to high latitude regions, The results indicate that yield depends mainly on the genetic characters of the plant, the phenotypic expression of which is influenced by climatic and environmental factors. the lower, mature leaves of Stevia have fewer glands per leaf surface area than the upper, younger leaves, i.e., there is a positive correlation between gland distribution density and steviol glycoside content. The vegetative organs (including roots) and reproductive organs of *S. rebaudiana*plant the stevioside was obtained from a leaf (the most productive organ), stem and inflorescence. [15]

Chemical Constituents

The most important components of *Stevia rebaudiana* include steviol glycosides, which are estimated to be 300 – 400 times sweeter than other sugars and facilitate the production of foodstuffs with a reduced energy value. The other components of the sweet leaf are of very limited importance.

Leaf:

Aminoacid and Proteins Composition: Stevia leaves contains essential aminoacids like (arginine, lysine, histidine, phenyl alanine, leucine, methionine, valine, threonine and isoleucine)

Nonessential Aminoacidcomposition:

Stevia leaves also contains nonessentialaminoacids like (aspartate, serine, glutamic, proline, glycine, alanine, cystine, tyrosine.

Minerals: Macro minerals like potassium (k), calcium(ca), sodium(Na), magnesium(Mg). Microminerals like copper (cu), manganese(Mn), iron(Fe), zinc(Zn). Zinc and manganese are considered as antioxidants and their presence boost up the immune system and prevents the free radical-mediated diseases. Iron is essential for maintaining normal hemoglobin level in the body. Hence stevia can be used in various sweet preparations for major nutritional disorders like iron deficiency.

Secondary Metabolites:

Tannins, alkaloids, cardiac glycosides, saponins, sterols, triterpenes, reducing compounds and anthraquinones.[16]

Carbohydrates:

Carbohydrates are the main sources of energy and they are found as structural components of cellular elements. Their positive action is connected with prebiotic properties promoting proliferation of beneficial intestinal microflora. Sweet leaf roots and leaves contain fructo- oligosaccharides at 4.6% and polysaccharides, which regulate lipid metabolism and control blood sugar level.[17]

Fatty Acids: Sweet leaf contains fatty acids: palmitic, linolenic, linoleic, oleopalmitic, stearic and oleic acids. An adequate intake of unsaturated fatty acids reduces the risk of ischaemic heart disease and enhances immunity.[18]

Rebaudioside:

Rebaudioside A is one of the most important rebaudioside and is 250–450 times sweeter than sucrose and it is found in Stevia rebaudiana at 2–4% leaf dry matter. It is most stable of glycosides and has no bitterness aftertaste, in contrast to steviosides. Rebaudioside A is metabolized by intestinal microorganisms to stevioside and next, it is transformed into glucose and a molecule of steviol. Apart from diterpene glycosides, sweetleaf contains also labdane diterpenes and triterpenes. Analyses of this plant detected such sterols as stigmasterol, beta-sitosterol, campesterol, anddaucosterol as well as flavonoid glycosides, including apigenin, quercetin, luteolin, kaempferol glycoside (19).

Stevioside

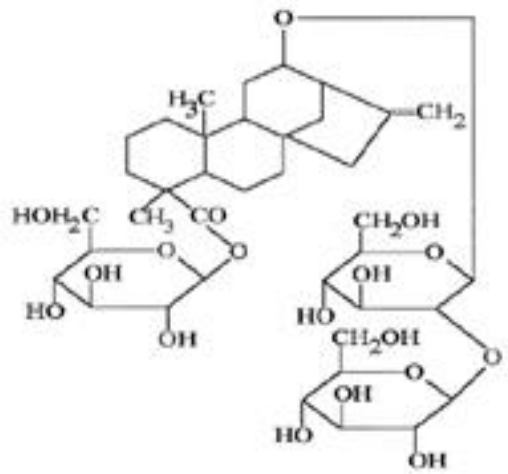
Stevioside accounts for 4 up to 13% all glycosides in stevia. It has a permanent battery or astringentafter taste. Comparative organoleptic analysis showed that pure stevioside is 300 times sweeter than sucrose at a concentration of 0.4%, 150 times sweeter than sucrose when matching a 4% sucrose solution and 100 times when matching a 10% sucrose solution (20)

Diterpene Glycosides

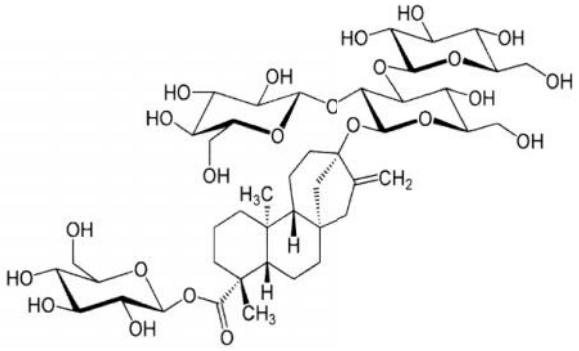
Glycosides are a group of organic compounds, which molecules are composed of the sugar group bonded with an aglycone group. Diterpene glycosides, ent-kaurene derivatives found in sweetleaf, are responsible for its high sweetening potential. Nine such substances have been isolated. Depending on growth conditions, cultivation and tillage techniques their contents range from 4 to 20% fresh leaf weight (21). The levels of glycosides vary in individual plant organs. Leaves are their richest sources, followed by flowers, stems and temperatures up to 198°C. steviosides are stable at various processing and storage conditions and in interactions with water-soluble vitamins, organic acids, sweeteners, and coffee. During thermal processing, they do not participate in the Maillard reactions. Moreover, steviosides do not ferment.[22]

Inflorescence:

Cadinene-gamma, cadinene-delta, cardinal, campesterol, caryophyllene oxide, cineol 1-8, cubebene-alpha, element-gamma, essential oils, limonene, nerolidol, humulene, pinene, selinene, sitosterol, stevioside, stigma sterol.[23]



Stevioside



Rebaudioside A.

Flowers:

Austroinulin-6-acetate, austroinulin-7-acetate, campesterol, channel, rebaudioside A, sitosterol, stevioside, stigmasterol, diterpenes.[24]

Stem: Gibberellins, kaurene, sitosterol, stigmasterol, diterpene, stevioside, steviolbioside, steviol.[25]

Seed:

Indole-3-aceto nitrile, an indole alkaloid, sitosterol, stevioside, stigmasterol.

Roots:

Roots are the only plants that are devoid of steviol glycosides.[26]

Uses of Stevia in Food and Beverages

PureCircle (LSE: PURE), the world's leading producer and innovator of great-tasting stevia sweeteners for the global beverage and food industries, reports that the use of stevia leaf sweetener in beverages and food products continues to expand. Beverage and food products containing stevia have grown steadily since 2012, and in 2017 alone, increased by more than +10% vs. 2016. Looking at results separately for beverages and foods, launches of beverage products containing stevia grew 11% from 2016 to 2017. Launches of food products containing stevia grew 10% from 2016 to 2017. As this data shows, stevia is quickly becoming an important ingredient for beverage and food companies like snacks, juice, soy sauce, dried sea foods, drinks, dairy, carbonated soft drinks, and confectionary. Producers of food and beverage products designed for kids (age 5-12) are also making more use of stevia, as it enables them to formulate products with no- or reduced-calories using a plant-based sweetener. In 2017, launches of products containing stevia with a claim for kids (aged 5-12) increased 16% from 2016.[27] Stevia is a zero-calorie sweetener made from a plant. Other major zero-calorie – or high-intensity sweeteners (aspartame, sucralose, and acesulfame potassium) are not. The usage of stevia leaf sweeteners has grown dramatically. In 2012, stevia was used in 16% of food and beverage products launched with high intensity or diet sweeteners. By 2017, that number has risen to 28%. Aspartame, however, is becoming less widely used. In 2012, aspartame was used in 36% of new foods and beverages utilizing high-intensity sweeteners. By 2017, that number was down to 25%. That means, looking at foods and beverages launched with high-intensity sweeteners in 2017, plant-based stevia was used more than aspartame.[28]

3. Medicinal and Pharmacological Properties

Many biologically active substances have been isolated from stevia and studied for their pharmacological activities.

Cholesterol:

Researchers studying long-term feeding effects of stevioside sweetener on some toxicological parameters of growing male rats found that stevia taken alone in low doses lowered cholesterol and was deemed safe to use and without any toxicological effects on body weight, organ relative weight, hematological and biochemical parameters or enzyme activities, though high-doses (1500mg/kg, an amount unrealistic outside the lab) did increase some toxic parameters.

The interesting part: taken together with an inulin soluble fiber – stevioside also increased HDL and lowered overall lipid contents.[29], [30]

Glucoregulation:

Diabetes mellitus is a group of diseases characterized by hyperglycemia and various degrees of insulin resistance. Stevia leaf extract has been used traditionally in the treatment of diabetes, whose injectioncauses slight suppression of glucose levels, and increased glucose tolerance in normal human adults. Steviol glycosides enhance the insulin secretion by acting directly on the β cells without altering the K^+-ATP channel activity and cAMP level in the islets, thus documenting stevioside and steviol as potent antihyperglycemic agents. Steviosides regulates blood glucose levels not only by insulin secretion but also by insulin utilization in insulin-deficient rats; which was mainly due to decreased phosphoenol pyruvatecarboxykinase(PEPCK) gene expression in rat liver.[31], [32],[33]

Blood Pressure Regulation:

Hypertension is defined is an increase in arterial blood pressure i.e., a systolic pressure of 140mmHg and diastolic pressure of 90mmHg. The hot water extraction of stevia can be used a heart tonic to normalize blood pressure levels, to regulate heartbeat and for other cardiopulmonary indications. Stevia acts at the cell membrane level; the same way ass calcium channel blocking agents. These calcium channel blocking agents are routinely prescribed to help control high blood pressure by relaxing the walls of the arteries. Stevia relaxes arteries and lowers blood pressure. Regular consumption of these compounds decreases the cholesterol content in the blood, improves cell regeneration and blood coagulation, suppress neoplastic growth and strengthens blood vessels. The use of stevioside resulted in spontaneous hypotensive in the hypertensive rats without affecting their heart rates, serum, and catecholamine levels. Phytosterols present in the wax of stevia leaves were found to respond against cardiovascular defects. The previous studies prove the clinical efficacy of stevia leaves in reducing chronic hypertension by relaxing arteries and help prevent the build-up of calcium on artery walls.[34], [35], [36].

Cancer:

Cancer is regarded as a disease of the body's cells. Its development involves damage to the DNA of the cells and this damage accumulates over time. LABDANE SCLAREOL, a compound present in the leaves of stevia has anti-tumorous and cytotoxic properties. Stevia leaf extracts and their polyphenolic contents have demonstrated the inhibitory effects on tumor promotion and initiation. The steviol, isosteviol, stevioside, and the stevia leaf aglycones have been reported to inhibit tumor promotion by blocking Epstein- Barr virus early antigen (EBV- EA) induction as well as by reducing tumour formation in the two-stage mouse skin carcinogenesis model following sequential exposure to 7,12-dimethyl benz anthracene(DMBA) and 12-o-tetradecanoyl phorbol-13-acetate(TPA). The hydrolysis product of stevioside,isosteviol, potently inhibits DNA replication and cancer cell growth. Stevioside, a bioactive compound In stevia was found to be non-mutagenic in mutagenicity tests using bacteria (Reverse mutation assay, Forward mutation assay, Umu test, and Rec assay) cultured mammalian cells (chromosomal aberration test and gene mutation assay)and mice (micronucleus test). It was found that stevioside enhances apoptosis induced by serum deprivation and this enhancement was caused by increased expression of BAX and of cytochrome C released into the cytosol which suggests that stevioside affects the regulation of normal apoptotic condition.[34],[37],[38],[39]

Renal Function:

Chronic kidney disease resulted in 4,00,000 deaths in 1990 and 7,35,000 death in 2010. The kidneys maintain many aspects of the internal environment of the body. The main function of the kidney is to maintain homeostatic balance with respect to fluids, electrolytes, and organic solutes. Various disease conditions disturb the normal functioning of the kidney and nephrons. Constant administration of stevioside from the leaves of Steviarebaudiana in both normal and hypertensive rats increases the glomerular filtration rate and renal plasma flow which was due to vasodilation of both the afferent and efferent arterioles. Studies suggest that stevioside at a pharmacological concentration of 0.70Mm inhibit trans epithelial transport of PAH(Para amino Hippurate) by interfering with the basolateral entry step i.e., the rate-limiting step for transepithelial transport. The lack of effect of stevioside on transepithelial transport of PAH on the luminal side and its reversible inhibitory effect on the basolateral side indicate that stevioside does not permanently change PAH transport and should not harm renal tubular function at normal human intake levels. Melis et.al,(2009) investigated steviol excretion from the renal tubule and observed that steviol causes an increase in the fractional sodium excretion, fractional potassium excretion, urinary flow as a percent of glomerular filtration rate.(34)Results revealed that steviol and steviosideretard cyst progression and kidney weight either by directly inhibiting the cystic fibrosis transmembrane conductance regulator(CFTR) chloride channel activity (or) by reducing CFTR expression and improves renal function.(40) Steviol and its analogs are also used for the treatment of polycystic kidney disease.

Inflammatory Bowel Diseases:

Inflammatory bowels disease is a group of inflammatory conditions of the colon and small intestine whose major forms are Crohn's disease and ulcerative colitis. The ages between 15 and 30 of both sexes are equally affected of

unknown cause but may be of genetic predisposition and immune and auto-immune phenomena. Steviol and steviosideexertanti-inflammatory effects on colonic epithelial cells. Stimulation of intestinal smooth muscle contraction is linked to hypermotility associated diarrhea. Stevioside inhibits the intestinal smooth muscle contraction. Stevioside and its similar compounds steviol, dihydroisosteviol, isosteviol, and isosteviol16-oxime show their antidiarrheal efficacy by cAMP-regulated chloride secretion in human T84 colonic epithelial cells. Similar compounds dihydroisosteviol may be useful for further development as antidiarrheal agents.[41], [42].

Obesity:

Obesity is the most common nutritional disorder. Obesity is a condition of excess body weight more than 20% above the ideal body weight. The factors that support obesity include physical inactivity, excessive food consumption, and unhealthy food choices. Obesity is associated with a wide number of health problems including hypertension, hyperlipidemia, diabetes, surgical risks, pulmonary and renal problems, pregnancy and certain types of cancer. Stevia leaves contain zero calorie ent-kaurene diterpene glycosides (stevioside and rebaudioside) which are not metabolized to produce energy but tastes 300 times sweeter than sucrose. Stevia sweeteners offer an alternative substitute of sugar, assist with weight control and weight loss by restricting (or) controlling calorie intake in the diet. At high doses,steviol glycoside showed a reduction in body weight. Stevia can be used as a substitute to sugar which is not completely absorbed by the digestive system. Consumption of stevia leaves and extract reduces the craving for sweet and fatty foods and are much useful weight loss programs.[43],[44],[45].

Dental Caries:

Dental caries, also known as tooth decay, is a chronic disease of people, throughout their lifetime, in the world. The organic metabolites produced by the oral microorganisms leads to gradual demineralization of tooth enamel, followed by the proteolytic destruction of the tooth surface. Microorganisms like *Streptococcus mutants* is the most prevalent followed by *lactobacilluscasein* and *Streptococcus sanguis* are capable of fermenting dietary carbohydrate. Regular consumptions of nutritive sweeteners (or) caloric sweeteners (or)sugars provide energy in the form of carbohydrates, causes cavities which aids the growth of harmful bacteria in the mouth and contributes to the formation of plaque and gingivitis. [46] Stevia is a non-nutritive sweetener, which is a zero caloric (or) low caloric alternative which have bacteriostatic and bactericidal properties and promotes oral health. Stevioside and rebaudioside A are non-metabolizable, non-caloric, non-fermentable and do not cause dental caries. [47]

Wound Healing:

Wound healing is a complex process of restoring cellular structures and tissue layers in damaged tissues to its normal state, where the area of the wound undergone shrinkage. Wound healing comprises of different phrases such as contraction, granulation, epithelization, andcollagenation. Wound healing can be discussed in three phrases 1) Inflammatory phase 2) Proliferative phase 3) Maturational or remodelingphase [48] Flavanoids are known to reduce lipid peroxidation not only by preventing (or) slowing the onset of cell necrosis but also by improving vascularity. Flavanoidspromote wound healing properties due to their astringent and antimicrobial properties. Stevioside was associated with increase muscle regeneration rates via increasing satellite cell recruitment and increased functional capacity of injured muscle with in 7days of post-injury. [49] Liquid extract of stevia has the ability to treat acne, dermatitis, eczema etc. Stevia is also used commercially for skin shining, skin smoothening, skin tightening and as an anti-wrinkleagent. [50]

Reproductive System:

The effect of active principles of *Stevia rebaudiana* on endocrine parameters of male rats was studied upon chronic administration of concentrated,crude extract of its leaves, starting at prepubertal age (25-30 days old) were revealed by Madan*et. al*, (2010). [51] The SR treated group did not significantly differ from the control group, with the exception of seminal vesicle weight, which fell about by 60%. [52] Thus SR extract does not have the potential to decrease male rat fertility. In addition, the fructose content of the accessory sex glands the epididymal sperm concentration also decreased. Stevia treatment tended to decrease the plasma testosterone level, probably by a putative affinity of glycosides of extract for a certain androgen receptor, but no alteration occurred in luteinizing hormone level. Saenphet *et al.* evaluated that no notable abnormalities were examined in any of the pregnant rats when treated with *Aegle marmelos* and *Stevia rebaudiana*. The number of corpus lutea, implanted and dead fetuses, as well as the sizes of the fetuses in the treated rats, were not significantly different from those of controls[53].Thus, the aqueous extracts of *Aegle marmelos* and *stevia rebaudiana* do not alter the reproduction of female rats. [54]

4. Conclusion

Stevia leaves are mainly used as the low-calorie sweeteners throughout the world in order to replace the high-calorie sugars. From the above literature, it shows that parts of stevia plant such as leaves, flowers, inflorescences, stem, seed,and roots also contain different chemical constituents such as amino acids, minerals, steviosides, rebaudioside, proteins, carbohydrates, fatty acids, tannins, alkaloids, saponins, sterols, triterpenes, reducing compounds and anthraquinones etc. Many of the pharmacological activities have been reported on the stevia leaves. But, extensive investigations on its pharmacodynamics, pharmacokinetics properties, proper standardization and clinical trials are furthur needed to exploit their therapeutics utility to cure many diseases.

5. References

[1] Zahid. Introduction and importance of medicinal plants and herbs. National health portal of India, 2016.

[2] Kalyani Pathak, Ratna Jyoti das. Herbal medicine – A Rational approach in the health care system. International Journal of Herbal medicine, 2013.

[3] Raskin L *et, al*. Plants and human health in the twenty-first century. Trends in biotechnology, 2002.
[4] Nebret Tadesse Btru, Aynalem Gebere, Hordofa Melkamu, Lule Belistie. Influence of plant population density on growth and yield of stevia. International Journal of Advanced Biological and Biomedical research, 2017.
[5] https://www.agrifarming.in/stevia-plant-farming/
[6] Martini A., Tavarini s., Macchia M., Benelli G., Canale A., Romano D. Influence of insect pollinators and harvesting time on the quality of *Steviarebaudiana*(Bert.) Bertoni seeds. Plant Biosystems- An international Journal Dealing with all aspects of Plant biology, (2016).
[7] K. Ramesh, Virendra Singh and Nima W. Megeji. Cultivation of *Stevia rebaudiana*Bertoni, a comprehensive review. Advances in agronomy vol.89, Elsevier publications, 2006.
[8] Ashok Kumar Yadav, S. Singh, D. Dhyani, P.S.Ahuja. A review on the improvement of stevia (*Stevia rebaudianaBertoni*). Canadian Journal of Plant science, 2011.
[9] K. S. Ashwini. Production of multiple shoots and somatic embryogenesis in *Steviarebaudiana* Bertoni through in vitro propagation, M.Sc. (Agri.) thesis UAS Bangalore. India Google Scholar, 1996.
[10] Rafael V. Reis. Morphological and anatomical study of *Stevia rebaudiana* roots grown invitro and invivo. Revista Brasileira de Farmacognosia, 2017.
[11] Sandeep pandey. Morphology, chemical composition and therapeutic potential of *Stevia rebaudiana*. Indo Journal of Pharmaceutical Sciences, 2018.
[12] N.A Hudz, S.M. Marchyshyn, L.M. Sira, O.L. Demydiak. Morphological and anatomical study of stevia leaves (*SteviarebaudianaBertoni*). Ukrainian biopharmaceutical Journal, 2017.
[13] S. Tavarini, I. Pagano, L. Guidi, and L. G. Angelini. Impact of nitrogen supply on growth, steviol glycosides and photosynthesis in *Stevia rebaudiana* Bertoni. Plant Biosystems - An International Journal Dealing with all Aspects of Plant Biology, 2016.
[14] Halimaton saadiah Othman, Mohamad Osman, Zarina Zainuddin. Genetic variabilities of *Stevia rebaudiana* Bertoni cultivated in Malaysia as revealed by morphological, chemical and molecular characterization. Agrivita-Journal of Agricultural Science, 2018.
[15] Abou-Arab AE, Abou-Arab AA, Abu-Salem MF. Physico-chemical assessment of natural sweeteners steviosides produced from *Steviarebaudiana* Bertoni plant. African Journal of Food science, 2010.
[16] Katarzyna Marcinek, Zbigniew krejpcio. *Stevia rebaudiana*bertoni-chemical composition and functionalproperties.Actascientiarumpolonorumtechnolgia, 2015.
[17] SaikatGantait, Arpit das, Joydeep Banerjee. Geographical distribution, Botanical description and self incompatibility of genus stevia.Springer link publications, 2017.
[18] BNMKL; Kochikyan, et.al. Combined enzymatic modification of Stevioside and Rebaudioside A. Appl. Biochem. Microbiol, 2006.
[19] Hojden, B. Source of natural *Stevia rebaudiana* sweeteners,2000.
[20] Gasmallaet.al. Nutritional composition of *Stevia rebaudiana* leaf: Effect of drying method,2014.
[21] Gardena, C., Scaglianti, M., Simonetti, P. Evaluation of steviol and its glycosides in *Stevia rebaudiana* leaves and commercial sweetener by ultra-high performance liquid chromatography-mass spectrometry. Journal of Chromatography, 2010.
[22] Carakostas, M. C., Curry, L. L., Boileau, A. C., Brunswick, D. J. Overview: the history, technical function and Nutritional composition of *Stevia rebaudiana* leaf: Effect of drying method.Tropical Journal of Pharmaceutical research, 2008.
[23] Ahmad N, Fazal H, Zamir R, Khalil SA, and Abbasi BH.Callogenesis and shoot organogenesis from flowers of *Stevia rebaudiana*bertoni. sugar technology- An International Journal of sugar crops and related industries, 2011.
[24] Lata H, Chandra S, Waggy H, Rama V, and Khan A. TDZ-induced high-frequency plant regeneration through direct shoot organogenesis in *Stevia rebaudiana*Bertoni-an important medicinal plant and a natural sweetener, 2013.
[25] Pandey H, Pandey P, Pandey SS, Singh S and Banerjee S. Meeting the challenge of stevioside production in the hairy roots of *Stevia rebaudiana* by probing the underlying process, Plant cell, Tissue, and organ culture, 2016.
[26] https://www.purecirclesteviainstitute.com/
[27] Yadav SK and Guleria P. Steviol glycosides from stevia: biosynthesis pathway review and their application in foods and medicines. critical reviews in Food science and Nutrition, 2012.
[28] Neither A, GoronzyJ.J, Weyand C.M. Immune-mediated mechanisms in atherosclerosis; prevention and treatment of clinical manifestations.Current Pharmaceutical Design, 2017.
[29] Savita, S.M. Sheela, K. Sunandha, S.Shankar, A.G.Ramakrishna, P.Sakeys. Health implications of *stevia rebaudiana*. Journal of Human Ecology.2012.
[30] Geuns J.M, et.al. Metabolism of stevioside healthy subjects.Exp. Biol. Med. 232, (2006).
[31] Melis MS, Rocha ST, and Augusto A. Steviol effect, a glycoside of *stevia rebaudiana*, on glucose clearances in rats. Brazilian Journal of Biology, 2009.
[32] AnushAghajanyan, ZaruhiMovsisyan, and Armen Trchounian. Anti hyperglycemic and Anti hyperlipidemic activity of hydroponic*stevia*

rebaudiana aqueous extract in hyperglycemia induced by immobilization stress in rabbits. Biomed Research International, 2017.

[33] Amir Abbas, Elham Abollahi, Seyed-Alireza esmaeili. A review on the pharmacology and toxicology of steviol glycosides extracted from *steviarebaudiana*. Article in current pharmaceutical designs,2016.

[34] Wrong K-L, Chan P, Yang H-Y etal, Isosteviol acts on potassium channels to relax isolated aortic strips of Wister rats. Life sciences, 2004.

[35] Lee C-N, Wong K-L, Liu J-C et.al. Inhibitory effect of stevioside on calcium influx to produce anti hypertension. Planta Medica, 2001.

[36] Jayaraman S, Manoharan MS, Ilanchezian S. In-vitro anti microbial and anti tumor activities of stevia rebaudiana leaf extracts. A Tropical Journal of Pharmaceutical research, 2008.

[37] Takasaki M, Konoshima J, Kozukam et.al. Cancer preventive agents. Part 8: Chemopreventive effects of stevioside and related compounds.Bio organic and medicinal chemistry, 2009.

[38] L. Chengjiany B, Eryi X, Reining.S, Yuengling W, Haodong S, Zihiyan H. Chronic oral toxicity and carcinogenicity study of stevioside in rats. Food and chemical toxicology, 1992.

[39] Yuajitc, Muanprasat C, Gallagher AR, Fedeles SV, Kittayaruksakuls, Homvisasevonga S and Chatsudthipong V. Steviol retards renal cyst growth through reduction of CFTR expression and inhibition of epithelial cell proliferation in a mouse model of polycystic kidney disease. Biochemical pharmacology, 2014.

[40] Barbara c Olenski, Taryn D. Silverstein, Gioia M Persuitte, YunshengMa, Katherine R.Baldwin, and David Cave- An anti-inflammatory diet as a treatment for inflammatory bowel disease: a case series report.Nutrition journal, 2014.

[41] Ena Gupta, Shalinipurwar, Shanthy Sundaram and G.K Rai. Nutritional and therapeutic values of *Stevia rebaudiana*. A review, Journal of medicinal plants research, 2013.

[42] Megeji N, Kumar J, Singh V, Kaul V, Ahuja PS. Introducing *Stevia rebaudiana*, a natural zero calorie sweetener. Current science, 2005.

[43] Curry LL, Robert A. Subchronic toxicity of rebaudiosideA.Food and chemical toxicology, 2008.

[44] Anton SD, Martin CK, Han H *et al*. Effects of stevia, aspartame and sucrose on food intake, satiety and post prandial glucose and insulin levels.Appetite, 2010.

[45] Sato M, Miyazaki T, Fujiwara S, TanigakiS *et. al.*Comparative study on the anti bacterial activity of phytochemical flavanones against methicillin-resistant*Staphylococcus aureus*.Journal of ethanol pharmacology, 1996.

[46] Sunil lingarajAjagannavar, Supreetha Camaro, Hemant batter, Shreyas tikare, Abdulaziz Abdullah alkheraif, Mohammed Sayed Al EsawyAlsayed. Effect of aqueous and alcoholic stevia extracts against Streptococcusmutans and lactobacillus acidophilus.Journal of the International society of preventive and community dentistry, 2014.

[47] Dewangan H, Bais M, Jaiswal V, Verma VK. Potential wound healing activity of ethanolic extract of SolanumxanthocarpumSchrader and well leaves. A Journal of pharmaceutical sciences, 2012.

[48] Babakhanyan MA, Nahapetyankh H, Hovhannisyan LE, Simonyan KV, Avetisyan LG, Chavushyan VA. The wound healing potential of hydroponic *Stevia rebaudiana*. open access text, 2018.

[49] Pemba HissayBhutia, Amit Baran Sharing, Stevia: Medicinal miracles and therapeutic magic. International journal of crop science and technology, 2016.

[50] Maryamvahedi, RoghayeKarimi, Helen pourmazahuri, Khosrobalilashaki.Bio-technological approaches in *Stevia rebaudiana* and its therapeutic applications. An international journal of biomedicine, natural products and pharmacy, 2017.

[51] Swati madan, Sayeed Ahmad, GN Singh, Kanchan Kohli, Yatendra Kumar, Raman Singh and Madhukar Garg. *Stevia rebaudiana* (Bert.) Bertoni – a review. Indian Journal of natural products and resources, 2009.

[52] Saenphet k, Aritajat S, Saenphet s, Manosroi J and Manosroi A.Safety evaluation of an aqueous extract from *Aeglemarmelos* and *Stevia rebaudiana* on the reproduction of female rats. Southeast Asian journal top med public health, 2006.

[53] Melis MS. Effects of chronic administration of *Steviarebaudiana* on fertility in rats,Journal of ethano pharmacology, 1999.