Journal of Advanced Zoology

ISSN: 0253-7214

*Volume **44** Issue **04 Year 2023** Page **1113:1131***

Evaluation of the Plant Stevia rebaudiana (Bert.)'s Pharmacological and Therapeutic Significance

1. Jay prakash singh* 2. Prof. Dr. Shikha Sharma

Ph.D. Research Scholar Lords University, Alwar Rajasthan-301001 Professor at Lords University , Alwar Rajasthan -301001 Corresponding author-574/12 Sarvoday Nagar , Distt. Raebareli Uttar Pradesh 229001, India , Contact-9452025395,7395068194 Email.ID - jpsingh9452@gmail.com

Article History

Received: 13 June 2023
Revised: 12 September 2023
Accepted: 01 December 2023

Abstract

Research on novel compounds with less hazardous side effects and greater potency is underway, and more focus is being placed on medicinal plants as a means of treating the aforementioned issues. Drug candidates made from medicinal plants have been identified. The globe uses The plant-based carbohydrate a sweetener which has therapeutic qualities as well as nutritional, therapeutic, and industrial relevance. The rebaudiana plant's leaves are often referred as as as from honey leaves, and candies, and sweets. The significant sweetening potential of leaves is due to diterpene glycosides. The stevia leaves' phytochemical characteristics of bioactive compounds have a role in supporting human physiological functioning. body. The report also emphasises the significance of the nutritional value of Dried up leaves of stevia, stevia metabolic processes, the impacts of stevia intake on the health of people, and scientific research related to stevia use. The Hepatoprotective, antiviral, antifungal, antibacterial, anti-hyperglycemia, anti-oxidative, hypotensive and and renal protective properties were studied in this study. activities of stevia leaves are reviewed. The main goal of this review is to comprehend stevia's potential as a medicine and its acceptability as a substantial raw food for the human dietary habits.

Keywords: Diabetes, which is botanical compounds Therapeutic Plant, Stevia, Disorders, and Nutritional

Abbreviations TGF- is for "Transforming Growth Factor," "," "PCT" stands for "Proximal Convoluted Tubule," "DCT" refers to "Distal Convoluted Tubule," "PCC" refers to "Protein Carbonyl Content," "BHA" stands for "Butylated Hydroxyanisole," "BHT" stands for "Butylated Hydroxytoluene," "DPPH" stands for "Diphenyl

INTRODUCTION

The development of chemical compounds was a blessing since it allowed for the simultaneous treatment of many diseases, but it also opened the door for dangerous scenarios like a variety of side effects and the creation of resistance. Research on novel compounds with less hazardous side effects and greater potency is underway, while traditional plants are receiving more focus in the effort to solve the aforementioned issues. Our globe is home to a huge variety of therapeutic plants, thanks to nature. Drug candidates made from medicinal plants have been identified. a plant that produces natural sweetness called stevia with industrial, medical, & nutritional relevance, is utilised throughout. the globe. Stevia, or rebaudiana, is a plant in the genus Asteraceae that is indigenous to Paraguay and Argentina. It is grown in a few places in Canada, Asia, and Europe. Despite the presence of the family Arabidopsis more than 200 species, Stevia rebaudiana alone produces the sweetest aroma [1]. Stevia Diterpene glycosides that are such as a compound called and rebaudioside, are produced by leaves., which are potent, non-nutritive sweeteners that can replace sucrose and other artificial sweeteners.

Fig 01- Stevia Plant

being 300 times sweeter than sucrose, sweeteners [2]. The leaves of Stevia rebaudiana are also known as sweets, candies, and honey go. caused by the creation of sweetening molecules called glycosides of stevoil [3]. It is renowned for the sweetness that its glycosides add without disrupting regulation. The stevia glycosides, which are sweet, have examined using chromatography in liquids in conjunction with identification from UV, MS, and ELS; steviol is these factors compounds' typical aglycone structure [4]. According to the results of the phytochemical investigations, there are a variety of potential uses for tannins, alkaloids, glycosides, saponins, sterols, and triterpenes. [5,6]. This review's objective is to comprehend stevia's medical potential furthermore it's adoption as a substantial raw ingredients for human

consumption.

Stevia: An Chemical Characterization

When completely grown, the woody shrub known as stevia grown, can grow to a height of up to 80 cm. There are at least 110 species of stevia in the genus, and there could might total 300. using the southwest of the the highlands to the US of Brazil, it has a range of habitat [7]. There are thought the number of stevia subspecies that can be found in the wild, which is estimated to be 250. fortunately, stevia rebaudiana and other species have been proven to have sweetening effects. Short-day stevia plants can reach heights of 1 m. It has sessile, elliptic leaves that are 3–4 cm long. The plant has a large root system, and its hardwood root and weakly youthful at the base. It blooms in Along with a mouth, white that is somewhat purple. They are tiny in size and are grouped in tiny cymbidium. [1]. Table 1 contains stevia rebaudiana's scientific details.

Taxonomic Characteristics	
Botanical name	***Stevia rebaudiana***
Division of the Kingdom	Plantae
Family	Angiosperms
Genus	Eudicots
Genus	Asterales
Species	Asteraceae
Class	Stevia
Order	*S. rebaudiana*

Table 01- Taxonomic information of S*tevia rebaudiana*.

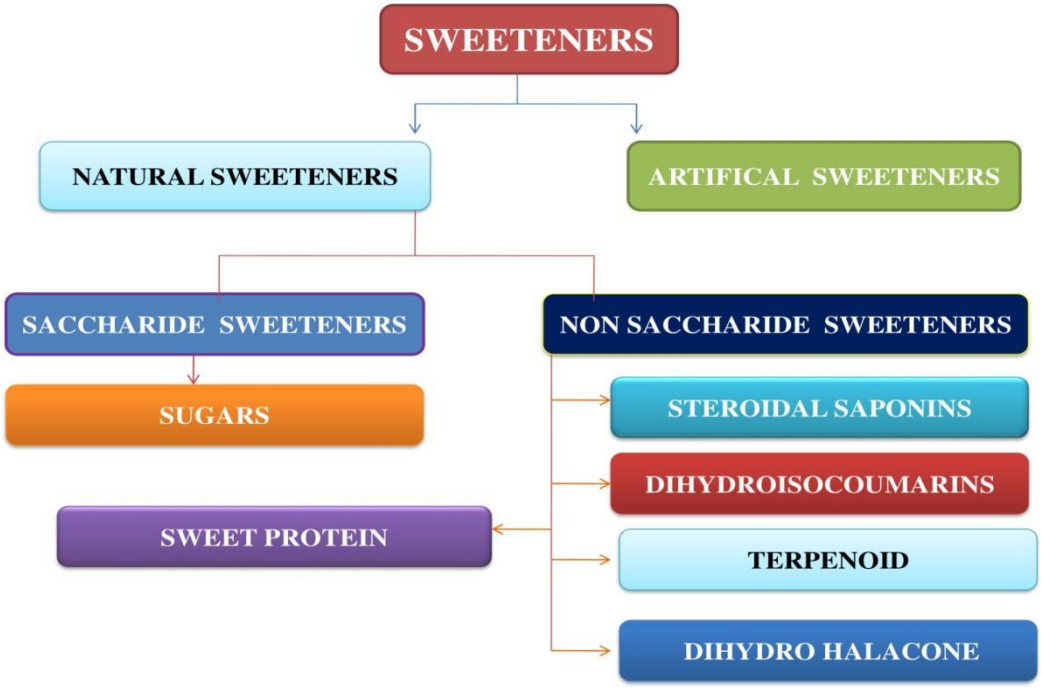

Fig.2 Type of sweeteners

Chemical Formula for Stevia

The significant sweetening potential of leaves is due to diterpene glycosides. Steviol glycosides, also known as stevioside, rebaudioside, steviolbioside, and dulcoside, are extracted and identified. Stevioside, which makes up Stevia leaf' 4–13% dry mass is made up of sugar. the most abundant glycoside, followed by rbaudioside (2–5%) and dulcoside (0–0.7%). Stevioside makes up 4–13 percent of the sweetener derivatives. It tastes harsh or unpleasant when consumed. Compared to sucrose, pure the substance is three hundred times stronger. at a concentration of 0.4%, according to comparative organoleptic investigations [8]. Kroyer [9] steviosides are stable under a variety of processing and storage circumstances, it has been observed. Rebaudioside, which makes up 2-5% of the dry matter in stevia rebaudiana, compared to sucrose, is 250–450 times stronger. In contrast to steviosides, it is the most stable glycoside and has no harsh aftertaste. Rebaudioside is converted by intestinal microbes to stevioside, and then to glucose and a steviol molecule. Sweet leaf also includes diterpenes and triterpenes in addition to diterpene glycosides. [10].

Plant Chemical Components

Plants build up phytochemicals, which are secondary metabolites, to protect themselves from microbial diseases or pest infestations. Active components known as phytochemicals are substances that have medicinal benefits and are therefore regarded as drugs or medicines [11]. With the aid of the appropriate solvent systems, The abundance of many phytonutrients in the stevia leaf extract was shown by the research of Srivastava et al. [12].Table 2 lists the phytochemical characteristics of the bioactive substances found in stevia leaves.

Table -2 lists the therapeutic qualities of the phytonutrients found in stevia.

Plant-based chemicals	Therapeutic Properties	Referenc es for
substances such as phenols is performed,	Plants have anti-aging, both anti-inflammatory in nature and -apoptotic effects.	[21]
saponins,	Detergents with antibacterial, surface-active, and foamy ingredients are employed for the management of diabetes and being obese.	[11]

flavonoids, all	Free radical scavenging action, anti-allergic, anti-cancer, anti-microbial, and ability to prevent intestinal diseases and oxidative damage	[12]
alkaloids,	medicine to relieve pain	[19]
tannins,	used to cure dysentery and diarrhoea, and has wound-healing abilities	[31]
steroids,	Immune system control and hypercholesterolemia reduction	[30]
and coumarins	Avoid hyperproliferative skin conditions	[31]

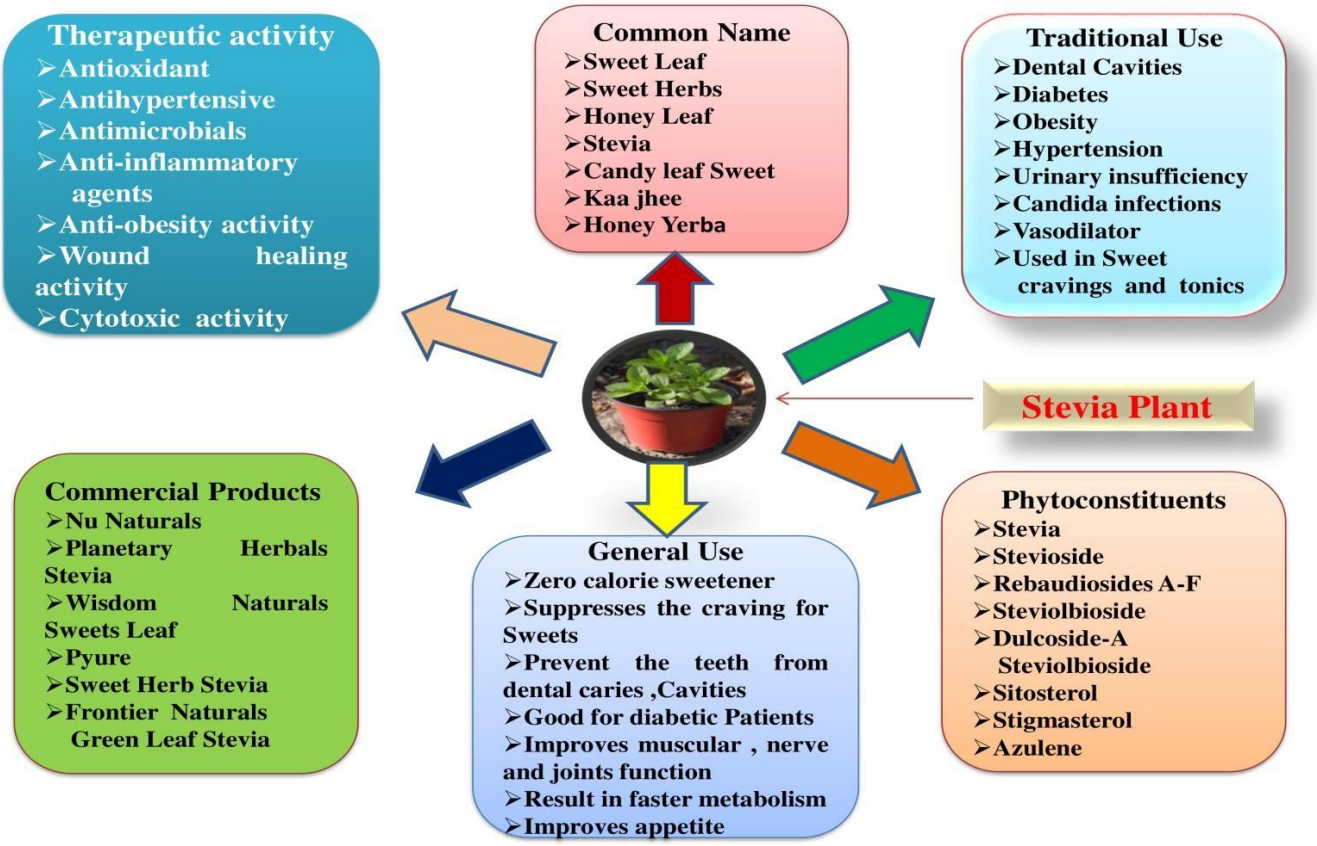

Fig.03 -Medicinal and Pharmaceutical Application

The Nutritional Value of Stevia Leaves

Stevia leaves have 2.7 kcal of energy per gramme of dry weight, making them a low calorie sweetener. The nutritional makeup of stevia leaves, It maintains health and reduces the incidence of many illnesses, and is a significant source of carbs, protein in them, and crude material., is mostly responsible for their health benefits. stevia powdered form, dehydrated contains up to 1.8–4.36 g of fat per 100 g, compared to 52–64.06 g of carbs and 10.0–18.0 g of

protein [12,13]. Table 2 lists the approximate stevia makeup. Carbohydrates are the primary source of energy in stevia leaves because oligo and fructo-oligosaccharides are present, which control Lower blood sugar levels and the breakdown of lipids [3].Additionally, mineral parts found in trace amounts in crushed leaves that are dried but are crucial to several bodily metabolic processes. Minerals are essential for good health, regenerative capacity, growth, and the development of fresh tissues and cells [14]. The amount of micronutrients in drying stems of stevia is shown in Table 3. [15].

Stevia's metabolism in the human body

The leaves of Ste consist of rebaudiosides and stevioside, where have a good taste character, are 300 times sweeter than sucrose, have no calories, and are significantly metabolised by human body without having any negative effects. In both humans and animals, Steviol flavonoids are taken in by the body and eliminated by comparable mechanisms [16]. Rebaudioside is first metabolised into stevioside by colon bacteria, which is then transformed into steviol and glucose in the digestive system. Bacteria in the colon directly consume the glucose produced during this process. instead of being absorbed into the bloodstream. Utilising stevia leaves has the advantage that, following processing, there is no Because all additional components travel through the urine, there cannot be an any buildup of waste materials inside the human organism. The gut microbiota of rats and humans have also been reported to be comparable in terms of both quality and quantity [17]. Another investigation into Human beings have a digestive system system revealed that the metabolised form of stevia does not change at high and low

Surrounding Properties	**G/100g of Ingredients**	**Metals**	**100mg of the substance.**
Ash	5.6	Iron,	33.1
, Fat,	12.4	Potassium,	183.2
Protein,	3.3	Calcium,	2501
Crude	19	Magnesium,	534.2
Fibre,	14.88	Phosphorus,	465.15
and Sugars and carbohydrates	30.2	Phosphorus	302
		and Chloride	49.3

Table-02 Mineral and near-surface composition of dried stevia leaves

doses, contrary to what is observed in faeces. The study also discovered that the kidneys use glucuronide to help release the remaining steviol glycosides through urine after a significant fraction of them are absorbed. bonds. However, only trace amounts of glucuronide were

eliminated through faeces. [18].

Steviosides' The energy Content

It has been established that stevioside cannot be By the human body, absorption through oral means & that no gastrointestinal tract digestive enzymes can break down steviol, the aglycone of stevioside. It is crucial to remember that bacteria present in the human colon may change stevioside into steviol. Since The body is unable to absorb steviosides., they cannot be used as a source of nutritive energy. the bulk of them are flushed through urine after absorption and the remaining trace amounts are removed through faeces [17]. The response of gastric fluids and digestive enzymes on the stevioside compounds demonstrates their inability to breakdown the compounds. Several experiments of digestion and absorption with stevioside compounds have been conducted. Studies have long explored the ability of a number of digestive enzymes to break down steviosides in vitro, and they have discovered that colon bacteria are the only ones who can hydrolyze stevioside both steviol-16, 17 alpha-epoxide and steviol. Steviol 16, 17 alpha-epoxide was subsequently reverted by the body to steviol, which was then removed as steviol glucuronide in urine [19]. This entire procedure illustrates the reason why the body of a person does not require sugar rebaudiana with any additional benefits any calories.

Human Wellness Effects of Stevioside Intake

Beyond its potential as a sweetener, S. rebaudiana has been found to have a number of beneficial properties. These include antibacterial, Benefits include those related to being antifungal, hepatoprotective, hypoglycemic (aqueous extract), and having anticancer, antirotavirus, anti-HIV, and other properties. Stevia and stevioside are also frequently used to promote alertness and combat weariness, notably in Latin America and the East. Additionally, it is thought to enhance gastrointestinal activities including digesting. Stevia and stevioside help the liver, pancreas, and spleen to heal along with controlling your blood sugar levels as well. [18]. The previously presence of phenolic chemicals in the plant is responsible for many of these effects. Said chemicals are frequently present in both edible and non-edible plants, primarily in both the stem and leaves, although to a lesser degree. They are crucial to the plant's healthy growth and defence against bacterial, parasitic, infectious, and damage-causing attacks. Additionally, the oxidative stability and microbiological safety of wounded plants may be significantly impacted by the presence of these chemicals. Despite the fact that phenolic compounds have no recognised nutritional role, their potential as antioxidants makes them potentially significant for human health [20].

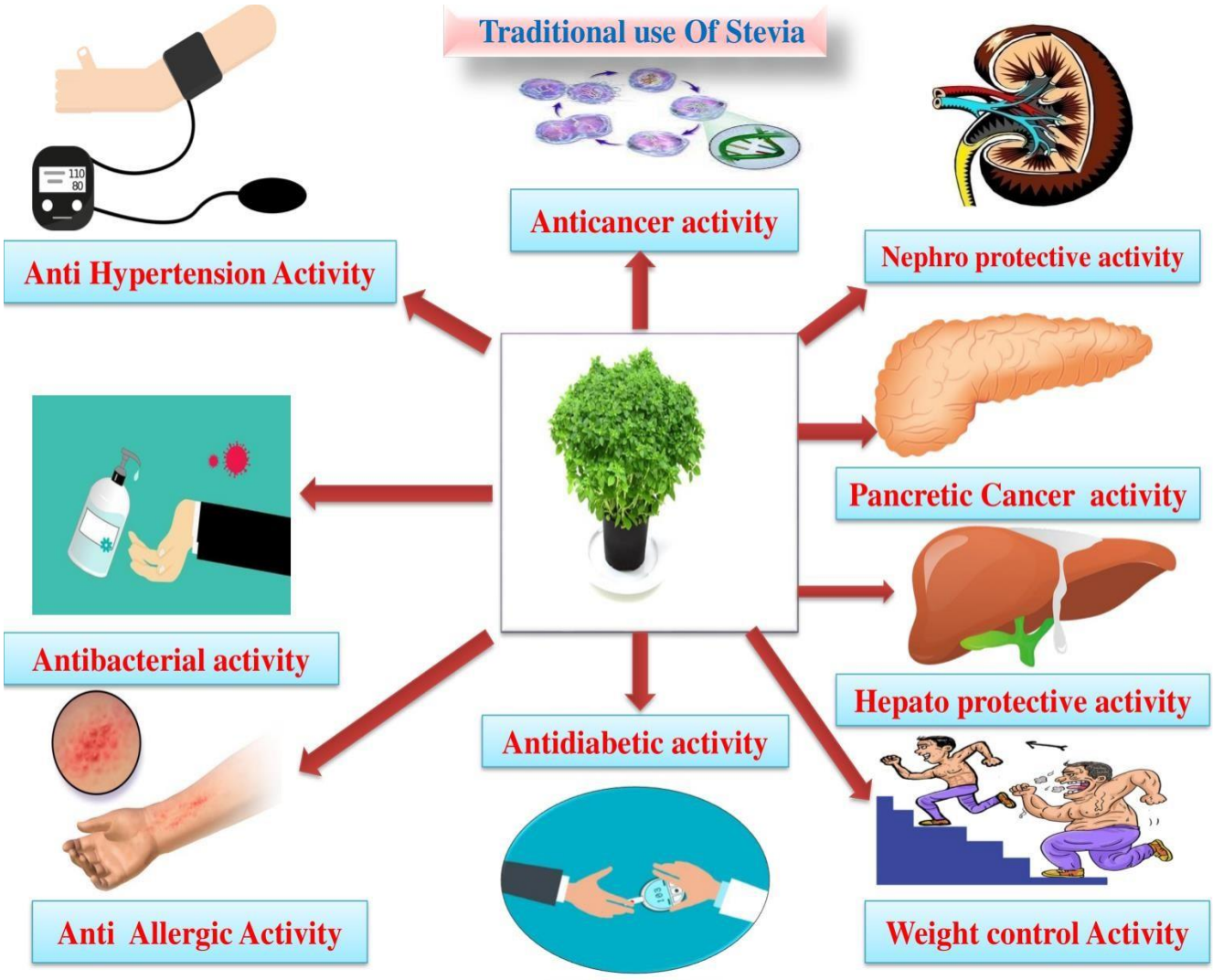

Fig.04 -Medicinal and Pharmaceutical Application Stevia Leaf

Research on Stevia rebaudiana

Despite the fact that there is a wealth of data on the effects of stevia rebaudiana. Numerous investigations with varying dosages, lengths of time, and clinical trial results carried out across various time periods (Table 4). Clinical studies suggest giving stevia to people and STZ rats in powder, aqueous, and stevioside form. Stevia has demonstrably demonstrated hypoglycemic and weight loss benefits.

Stevia's Medical Potential:

Anti-Hyperglycemic agents

. The condition known as diabetes mellitus is a metabolic disorder brought on by either poor insulin production, inadequate sensitivity to insulin, or both. Diabetes mellitus is characterised by persistent hyperglycemia and irregularities in the metabolism of carbohydrates, protein, and lipids. Although the primary ingredient in sweetener employed as a sweetener in meals and drinks, has anti-diabetic benefits via boosting insulin production using the pancreatic the beta mitochondria, encouraging sugar absorption by improving the susceptibility of tissues in the peripheral region to hormone. Stevioside also inhibits the production of glucagon, which lowers the body's capacity to create glucose. [23,24] Steviol glycosides potentiate the calcium-activated transient receptor potential cation channel TRPM5, which is primarily found on intestinal beta cells and peripherals entero-endocrine systems. This process modifies pancreatic beta cell function by accelerating the release of insulin in response to glucose stimulation. Despite the fact that steviol, stevioside, and rebaudioside directly bind to TRPM5, the steviol moiety interacts with the protein. In addition to being novel leads for the development of anti-diabetic medications that target TRPM5, these glycosides can be employed as anti-hyperglycemic medicines. Additionally, unlike synthetic agents, these agents did not cause hypoglycemia, which will be a huge help to diabetic patients [25] [26] The P13k/Akt pathway can be activated by steviol glycosides acting as substrates for the IGF-IR or receptors for insulin (IR).Signal activation causes Glut 4 to move permitting glucose to go from an intracellular pool to the membrane of the plasma cell to enter cells and simulating the effects of insulin. Stevia-infused biscuits were found to suppress -glucosidase activity. In rabbits with hyperglycemia brought on by immobilisation stress, aqueous stevia extract caused improved muscles and liver levels of glycogen and anti-hyperglycemic effects.

Table- 03 Stevia rebaudiana dose that worked in research studies.

Subjects	Dose	Duration	Results	References
diabetic person	10 grammes of stevioside	1 day	Lower postprandial glucose by 20% compared to control	[18]
Rats with diabetes produced by streptozotocin (STZ)	250, 550, and 750 mg/kg/day of stevia water-soluble extract	30 days	Blood sugar is reduced by 500 and 750 mg/kg/day.	[20]
Hypertensive and diabetic people (25–50 years)	0.4-1 grams/kg of candy leaf extract	38 days	The hypotensive and low in glucose effects of stevia powder	[21]
Diabetic rats produced with STZ	Stevia aqueous extract at 300, 400, or 500 ppm/kg	60 days	Reduce body weight by watching your caloric intake.	[22]

Sugar and the a substance called pioglitazone, both of which have antioxidant properties and can serve as receptors on the nuclear hormone receptor PPAR, which can cause the production of insulin and regulate blood glucose levels. Both stevia and pioglitazone can boost the mRNA expression of PPAR-. Its antioxidant properties further support the hypoglycemic impact [27]. reduction in the amount of IL-6, an inflammatory cytokine that increases insulin resistance and is consequently beneficial for type 2 diabetes [28]. By affecting specific targets of NOX-(NADPH oxidase level), stevia may be able to regulate neural synaptic plasticity in settings of metabolic diseases brought on by high dietary fructose consumption, and may therefore have a neuroprotective effect. [29].

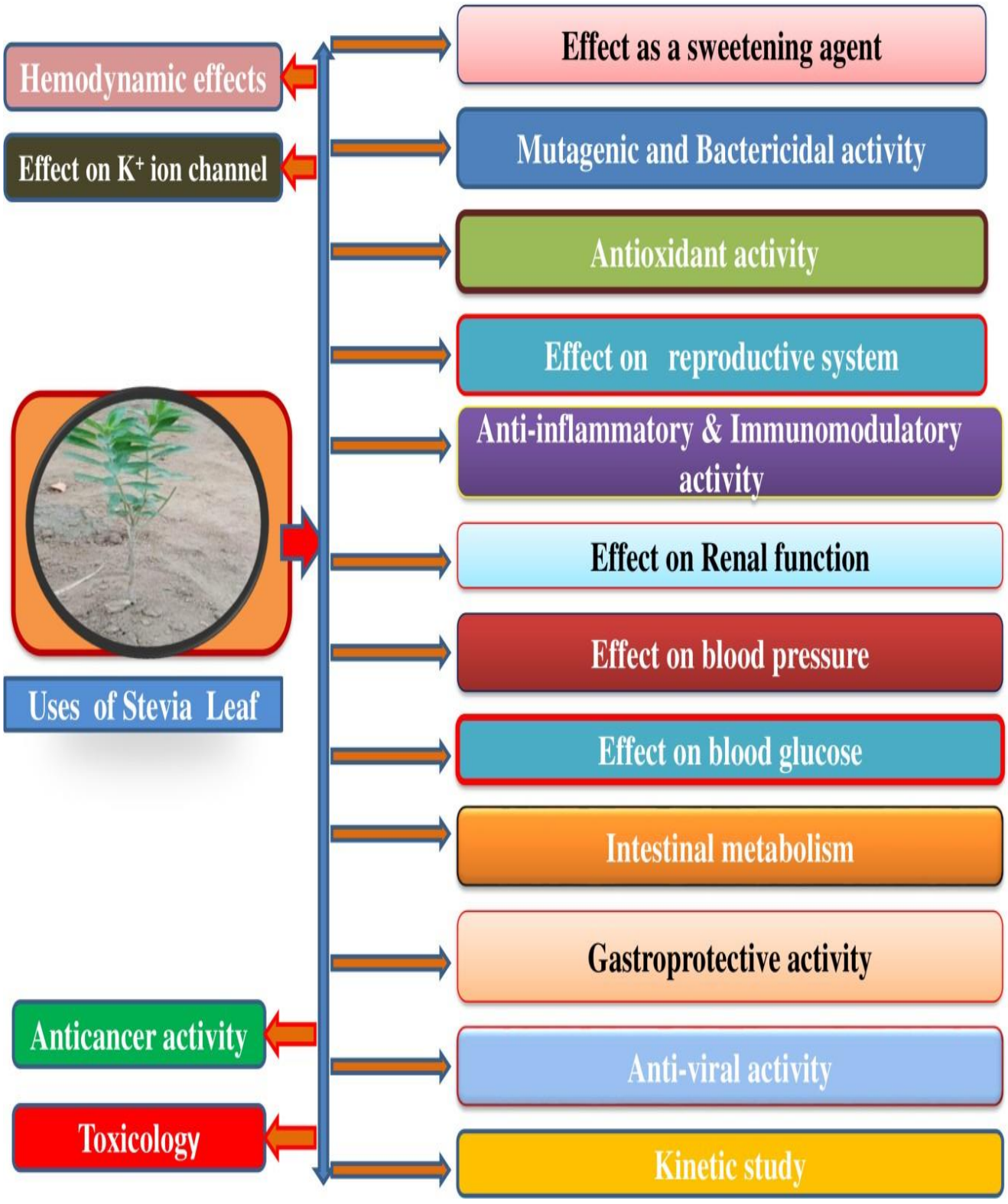

Fig.05 -Medicinal and Pharmaceutical Application Stevia Leaf

Fig.06 - Stevia Dry Leaf

Fig.07 - Stevia Dry Leaf Powder

Fig.08 - Stevia Dry Leaf Crushed Powder

anti-oxidant function

Proteins, lipids, carbohydrates, and nucleic acids (DNA) are some of the biomolecules that sustain oxidative damage to biological components. When there is an imbalance between the release of reactive oxygen species (ROS) and the body's ability to voluntarily detoxify the free radicals to repair the resulting damage, it is said to be under oxidative stress. Diphenyl-1-picrylhydrazylhydrazylhydrate FRAP, or The antimicrobial activity of stevia extracted in vitro was demonstrated using the (ferric ion reducing activity) assay, the phosphomolybdenum experiment, and the (DPPH) radical eradication analysis [30,31]. Eugenol, coumarin, vanillin, hesperidin, ellagic acid, chlorogenic acid, eugenol, and polyphenols are among the polyphenols that are abundant in dried stevia leaves' methanolic and aqueous extracts, making them potential sources of antioxidants. foods and drinks are a promising option for treating ageing, which is brought on by the creation of ROS, as well as diseases including diabetes, cancer, neurological disorders, arthritis, and diabetes. The antioxidant properties of stevia can outperform those of Chemical techniques that involve BHA (butylated hydroxyanisole) and BHT in combination (butylated hydroxytoluene) antioxidant

[32].Increased production of steviol glycosides such rebaudioside and stevioside as well as radicals that aren't enzymes that guard against cellular oxidative damage brought on by hydrogen peroxide, an abiotic stressor, were seen in response to hydrogen peroxide. [31]. The antioxidant action of phenolic chemicals is mediated via the radical scavenging effect of hydrogen donation. Two other techniques for freezing are electron donation and singlet oxygen quenching. radicals. Flavonoids' antioxidant benefits are attributed to their capacity to decrease alpha-tocopherol radicals, chelate metal catalysts, neutralise free radicals, activate antioxidant enzymes, and inhibit the activity of oxidases. Stevia glycosides significantly reduced the levels of Polypeptide carbonyl percentage (PCC), enzymes that protect cells (SOD and CAT), and oxidative stress brought on by CCl4 in a fish model (Cyprinus carpio) are intracellular oxidative indicators.. [33].

Effects on hypertension and anti-hyperlipidemia

Stevia rebaudiana's aqueous extract has a hypolipidemic impact by reducing the production of cholesterol and fatty acids, lowering levels of Increasing levels of HDL cholesterol, overall cholesterol, triglycerides, LDL, and triglycerides [23]. By relaxing airways and reducing calcium accumulation on artery walls, which encourages vasodilator and decreases overall peripheral resistance, stevia leaves help regulate blood pressure. as a result of increased natriuresis and diuresis and increases the volume of extracellular fluid. The effects of hypolipidemia and hypotension work together to protect the heart. [34].

anti-cancer impact

According to numerous cell line studies, stevioside has a notable impact against a number of malignancies, including skin, ovarian, and breast cancer. The mechanisms for anticancer

actions included increasing the production of lethal molecules including Bax, Bc1-2, and caspase 9, which remove free radicals from the body and reduce cell lifespan by inhibiting DNA synthesis and inducing death. Both DNA polymerase and topoisomerase, also known as DNA II are proteins. were inhibited by the breakdown resulting from stevioside, iso-steviol. and inhibits P thirteen and Pkc become phosphorylated. to inactivate the P13K/AKT signalling pathway. Centaureidin, a substance with an antimitotic activity that can be used for tumour therapy, was isolated from the methanolic extract of Stevia. [31,34].

Nephro-protective

Due to connected mechanisms including the prevention of oxidative stress, inflammation, and apoptosis, stevioside and stevia extracts both exhibit nephroprotective effects. Because early stages of diabetes mellitus have been defined by increased cerebral volume (eighty percent and its subcomponents PCT (Proximal Ambiguous Tubule), DCT (Distal ambiguous Tubule), glomeruli that and interstitial tissue rather than medullary volume, renal hypertrophy and glomerular hyper-filtration are two known complications. Hyperglycemia-induced excess generation of free radicals and Transforming Growth Factor (TGF-) synthesis by mesangial constituents are the two molecular causes of the two aforementioned issues.. Inducible nitric oxide expression in response to cytokines, synthase NOS [35]. Stevia and its glycosides mitigate kidney damage brought on by cisplatin as well as diabetes-related kidney damage.Chemotherapeutic drug cisplatin works by triggering DNA repair, apoptosis, and cell cycle arrest. The mechanism of nephron protection involves reducing oxidative and nitrosative stress, reducing p65 and TNF- expression, inhibiting The expulsion of peptides that activate caspase, and encourages cell cycle recovery by upregulating cyclin D1 both approach downregulating p21 communication, which are both related to both apoptosis and arrest of cells. [36].

Hepato-protective

To treat liver damage brought on by oxidative stress, such as cirrhosis and hepatocellular cancer, stevia's antioxidant capability can be used. Stevia has been shown to have hepatoprotective properties preventing lipopolysaccharide- and CCl4-induced cytotoxicity in rat and chicken embryonic models. CCl4's enzyme stimulation by CYP450, which produces the tri-chloro-methyl free radical CCl3, is the cause of the liver damage caused by this chemical. These free radicals promote protein covalent binding and lipid peroxidation. Cell death is caused by the reduction of glutathione, disturbance of the calcium and iron ions, and other factors. An endotoxin, a strong inflammatory agent, and a glycolipid, lipopolysaccharide is a A part of gram-negative microbes membrane, which is a By releasing cytokines that promote inflammation like ROS and tumour necrosis factor it damages the liver. -, IL-1, and IL-6 (interleukins) [37]. The stimulation of the endogenous Nrf2 pathway, which lowers the level of reactive metabolites, is the molecular basis underlying stevia's hepatoprotective activity. By blocking NF-, which in turn causes the pro-inflammatory cascade to be downregulated, immunomodulatory action avoids necrosis, cholestasis, and preserves the

structure and function of the liver parenchyma. [38].

Activity against fungi and bacteria

Many scientists have used plants as a source of inspiration for new medicinal molecules. Researchers looked at the antibacterial properties of stevia leaves using several solvent extractions using petroleum ether, methanol, alcohol, ethylacetate, acetone, and chloroform. It is believed that stevia inhibits the development of certain bacteria and other contagious organisms. Salmonella typhi, Salmonella escherichia coli, the enteric bacteria Enterococcus faecalis Vibrio mirabilis, and P. aeruginosa, among others., among others, the bacterium Aeromonas bacteria hydrophila, a type of Vibrio cholerae, and Staphylococcus aureus are among them. were among the dangerous bacteria whose development was observed. sufficiently inhibited by these extracts in a few tests for antimicrobial properties [19]. fungicide activity was observed against Alternariasolani, Aspergillusniger, and Penicillium chrysogenum. Arya et al.'s experiment [39] used methanolic in extractions of plants. of stevia rebaudiana showed the greatest zone of inhibition against Fusariumoxysporum. In therapeutic procedures, plant extracts and phytochemicals with established antibacterial activities can therefore be quite important. The antibacterial activity may have benefited from the phytochemicals found in leaves. [21].

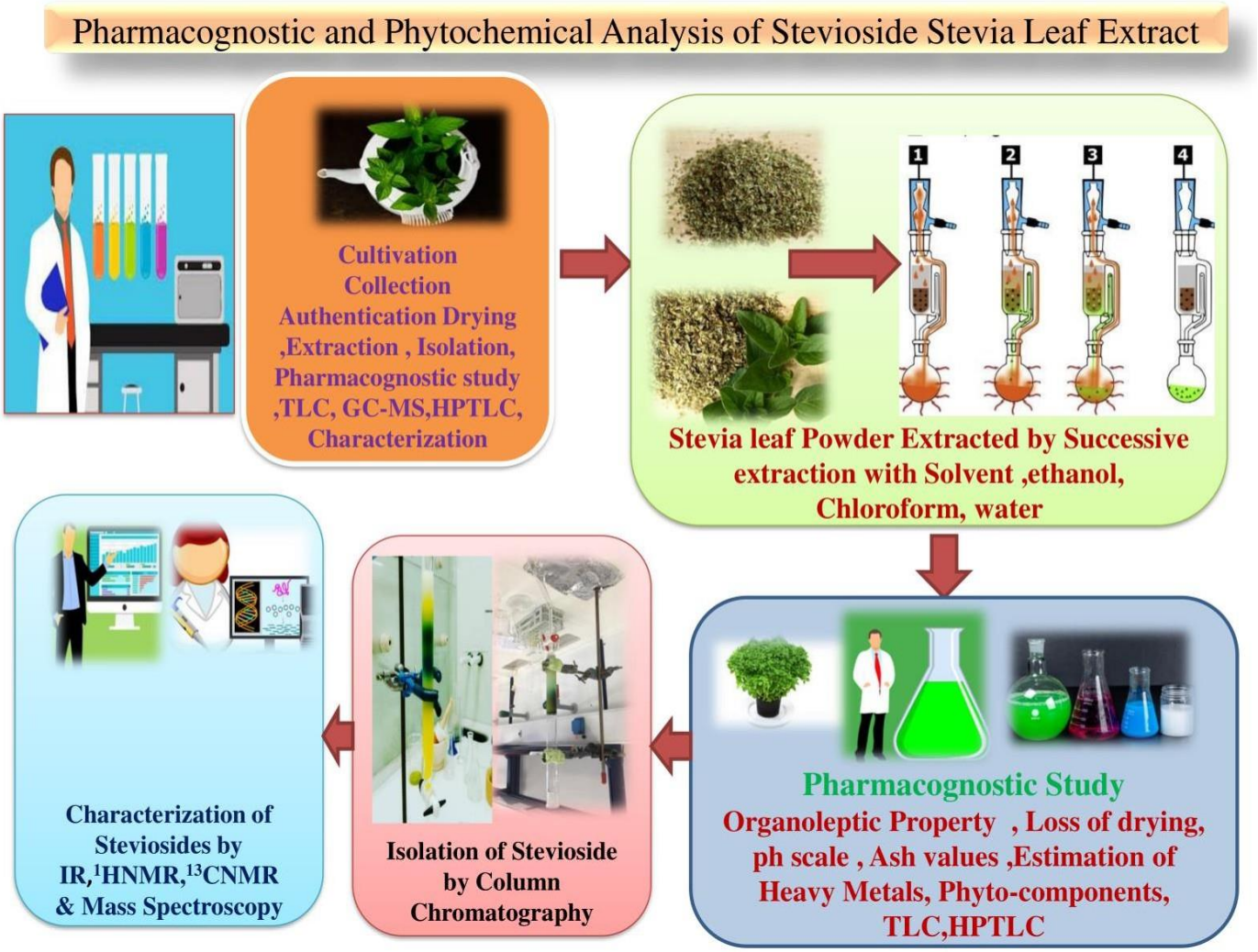

Fig.09 – Pharmacognostic and Phytochemical Analysis Stevia Dry leaf

Conclusion

The medical and therapeutic uses of stevia rebaudiana have made it an important plant that needs to be commercialised right away. The human body can directly utilise honey leaf constituents or consume them in raw form, which has a variety of physiological advantages. Additionally a strong provider of the two important and supplemental micronutrients, dried stevia leaf powder is well known for its effectiveness in treating chronic illnesses. Future studies are also required to ascertain its additional benefits in the fight against illnesses and to assess the precise daily intake that is safe for human consumption.

References

1. Adesh AB, Gopalakrishna B, AkkiKusum S, Tiwari OP (2012) An over- view on stevia: a natural calorie free sweetener. Int J Adv Pharma Biol Che 1: 362-368.
2. Yadav AK, Singh S, Dhyani D, Ahuja PS (2011) A review on the improve- ment of stevia [*Stevia rebaudiana* (Bertoni)]. Can J Plant Sci 91: 127- 130.
3. Braz-De-Oliveira A, Goncalves RAC, Chierrito TPC, Souza L, Gorin PAJ, et al. (2011) Structure and degree of polymerisation of fructooligosac- charides present in roots and leaves of *stevia rebaudiana* bertoni. Food Chem 129(2): 305-311.
4. Cacciola F, Delmontea P, Jaworska K, Dugo P, Mondello L, et al. (2011) Employing ultra-high pressure liquid chromatography as the second dimension in a comprehensive two-dimensional system for analysis ofstevia rebaudiana extracts. J Chromat 1218: 2012-2018.
5. Raut D, Aruna K (2017) Antimicrobial activity of *stevia rebaudiana* against antibiotic resistant ESBL producing uropathogens and evalua- tion of its antioxidant activity. Int J Adv Res Biol Sci 4: 110-118.
6. Miranda-Arambula M, Olvera-Alvarado M, LoboSanchez M, Perez-Xo- chipa I, Rios-Cortes AM (2017) Antibacterial activity of extracts of *ste- via rebaudiana* bertoni against *staphylococcus aureus, staphylococcus epidermidis* and *pseudomonas aeruginosa*. J Med Plant Res 11: 414-418.
7. Goyal S, Samsher R (2010) Stevia a bio-sweetener: a review. Int J Food Sci Nutr 61: 1-10.
8. López-Carbón V, Sayago A, González-Domínguez R, Fernández-Reca- males Á (2019) Simple and efficient green extraction of steviol glyco- sides from stevia rebaudiana leaves. Food 8(9): 402-406.
9. Kroyer G (2010) Stevioside and stevia-sweetener in food, application, stability and interaction with food ingredients. J verb lebensm 5: 225- 229.
10. Marcinek K, Krejpcio Z (2015) *Stevia rebaudiana bertoni*–chemical composition and functional properties. Acta Sci Pol Technol Aliment 14(2): 145-152.
11. Shakya AK (2016) Medicinal plants: future source of new drugs. Int J Herbl Med 4: 59-64.
12. Srivastava S, Chouhan DES, Chawla P (2016) Proximate and phyto- chemical analysis of stevia leaves powder. Int Ayurved med J 4: 2476- 2480.
13. Gasmalla MAA, Yang R, Issoufou A, Hua X (2014) Nutritional composi- tion of *stevia rebaudiana* bertoni leaf: effect of drying method. Trop J Pharm Res 13: 61-65.
14. Kobus-Moryson M, Gramza-Michalowska A, Kobus-Cisowska J, Korczak J (2014) Contents of selected elements in extracts from sweet leaf (*ste- via rebaudiana* Bertoni). Probl Hig Epidemiol 95: 445-448.
15. Ahmed SR, Mukta S (2017) Review on *stevia rebaudiana* as a non-ca- loric natural sweetener producing plant. J Syl Agric Uni 4: 15-25.
16. Shuvo MMA, Al–Mamun M, Chowdhury T, Absar N, Hasanuzzaman M (2015) An assessment of major nutritional components and some sec- ondary metabolites of *in vitro*

propagated *stevia rebaudiana* (cultured in Bangladesh) plant leaves dry powder. Int J Applied Sci Biotechnol 3: 721-26.

17. Gupta E, Purwar S, Sundaram S, Rai GK (2013) Nutritional and thera- peutic values of *stevia rebaudiana*: a review. J Med Plant Res 7: 3343- 53.

18. Escutia-López KN, Sánchez-Pardo ME (2019) A comprehensive review on the nutritionaland therapeutical aspects of *stevia rebaudiana ber- toni*. J Appl Biotechnol Bioeng 6: 297-302.

19. Salehi B, López MD, Martínez-López S, Victoriano M, Sharifi-Rad J, et al. (2019) *Stevia rebaudiana bertoni* bioactive effects: from in vivo to clinical trials towards future therapeutic approaches. Phytotherap Res 33(11): 2904-2917.

20. Shannon M, Rehfeld A, Frizzell C (2016) *In vitro* bioassay investigations of the endocrine-disrupting potential of steviol glycosides and their metabolite steviol, components of the natural sweetener stevia. Mol cell endocrinol 427: 65-72.

21. Singh DP, Kumari M, Prakash HG, Rao GP, Solomon S (2019) Phyto- chemical and pharmacological importance of stevia: a calorie-free nat- ural sweetener. Sugar Tech 21: 227-34.

22. Ahmad U, Ahmad RS (2018) Antidiabetic property of aqueous extract of *stevia rebaudiana bertoni* leaves in streptozotocin-induced diabetes in albino rats. BMC Compl Alter med 18: 179-182.

23. Scaria A, Kamath JV, Chakraborty M (2017) Antihyperglycemic, Anti- oxidant, Anti hyperlipidemic & nephroprotective effect of stevioside in diabetic rats. Int J Ayurved Med 8: 178-813.

24. Ilić V, Vukmirović, Tilinović N, Čapo I, Arsenović M, Mili ašević B (2017) Insight into anti-diabetic effect of low dose of stevioside. Biomed Phar- maco 90: 216-221.

25. Prata C, Zambonin L, Rizzo B, Maraldi T, Angeloni C, et al. (2017) Gly- cosides from *stevia rebaudiana bertoni* possess insulin-mimetic and antioxidant activities in rat cardiac fibroblasts. Oxidat med cell longev 11: 140-148.

26. Aghajanyan A, Movsisyan Z, Trchounian A (2017) Antihyperglycemic and antihyperlipidemic activity of hydroponic *stevia rebaudiana* aque- ous extract in hyperglycemia induced by immobilization stress in rab- bits. BioMed Res int 10: 120-123.

27. Assaei R, Mokarram P, Dastghaib S, Darbandi S, Darbandi M, et al. (2016) Hypoglycemic effect of aquatic extract of stevia in pancreas of diabetic rats: PPARγ-dependent regulation or antioxidant potential. Avi J Med Biotechnol 8: 65-69.

28. Bayat E, Dastgheib S, Egdar S, Mokarram P (2017) Effect of the aquat- ic extract of stevia on the serum level of interleukin-6 in streptozoto- cin-nicotinamide induced diabetic rats. Shiraz E-Med J 18: 160-170.

29. Chavushyan VA, Simonyan KV, Simonyan RM, Isoyan AS, Simonyan GM, et al. (2017) Effects of stevia on synaptic plasticity and NADPH oxidase level of CNS in conditions of metabolic disorders caused by fructose. BMC Compl Alter Med 17(1): 540-543.

30. Najafian S, Moradi M (2017) Polyphenolic compounds (HPLC analysis) and antioxidant activity of stevia rebaudiana (Asteraceae) by FRAP and DPPH assay in greenhouse and free space condition. Int J Farm Allied Sci 6: 49-55.

31. Mohammad AM (2018) *In vitro* determination of total phenolics, fla- vonoids and free radical scavenging activities of stevia rebaudiana dry leaves powder in different solvents extract. EC Nutr 13: 71-78.

32. Yücesan B, Gurel E (2018) Hydrogen peroxide-induced steviol glyco- sides accumulation and enhancement of antioxidant activities in leaf tissues of *stevia rebaudiana bertoni*. Sugar Tech 20: 100-104.

33. Ruiz-Ruiz JC, Moguel-Ordoñez YB, Matus-Basto AJ, SeguraCampos MR (2015) Antidiabetic and antioxidant activity of stevia rebaudiana ex- tracts and their incorporation into a potential functional bread. J Food Sci Technol 52: 7894-7903.

34. Li XY, Lu WM, Shen WF, Wu Y, Liu YP, et al. (2017) Growth inhibito- ry effect of stevioside on ovarian cancer through AKT/ERK pathway. Biomed Res 28: 1820-1827.

35. Potocnjak I, Broznic D, Kindl M, Kropek M, Vladimir Knezevic S, et al. (2017) Stevia and stevioside protect against cisplatin nephrotoxici- ty through inhibition of ERK1/2, STAT3, and NF-kB activation. Food Chem Toxicol 107: 215-225.

36. Hagh-Nazari L, Goodarzi N, Zangeneh MM, Zangeneh A, Tahvilian R, et al. (2017) Stereological study of kidney in streptozotocin-induced di- abetic mice treated with ethanolic extract of *Stevia rebaudiana* (bitter fraction). Comp Clinic Pathol 26: 455-463.

37. Wang Y, Li L, Wang Y, Zhu X, Jiang M, Song E, Song Y (2018) New appli- cation of the commercial sweetener rebaudioside as a hepatoprotec- tive candidate: induction of the Nrf2 signaling pathway. Europ J Phar- macol 8: 128-137.