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Exploring *Stevia rebaudiana*: Characterization, Biological Activities, and its Impact on Pancreatic Health.

Abbas Shahid [1*], Drakhshaan [2], Aiza Ashfaq [3], Abdul Maajid Khokhar [4], Saliha Khalid [5], Sidra Ahmad [6], Abu Baker Sidiq [7], Sania Arif Dar [8]

[1*] Faculty of Science & Technology, Department of Biochemistry, University of Central Punjab, Lahore, Pakistan.
[2] Institute of Pharmaceutical Sciences, University of Veterinary and Animal Sciences Lahore.
[3] Department of Chemistry, Ostrava University, Czechia.
[4] Department of Biochemistry, Riphah International University, Faisalabad.
[5] Department of Material Science and Nanotechnology, School of Engineering and Natural Sciences, Kadir Has University, Istanbul Turkey.
[6] Institute of Biotechnology and Genetic Engineering, The University of Agriculture Peshawar, Pakistan.
[7] Department of Plant Breeding & Genetics, Faculty of Agriculture, Gomal University, Dera Ismail Khan, Pakistan.
[8] Department of Epidemiology and Public Health, University of Veterinary and Animal Science Lahore, Pakistan.

Corresponding Author: Abbas Shahid
Faculty of Science & Technology,
Department of Biochemistry,
University of Central Punjab, Lahore, Pakistan.
Email: sh.abbas.shahid@gmail.com

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Abstract

Stevia rebaudiana, a natural, non-caloric sweetener, has gained widespread attention for its health benefits, particularly in metabolic disorders. This review explores the chemical properties, biological activities and therapeutic potential of *Stevia* with a special focus on pancreatic health. *Stevia* contains bioactive compounds, mainly steviosides and rebaudiosides, which exhibit antioxidant, anti-inflammatory, antimicrobial and anti-diabetic properties. These compounds help regulate glucose metabolism and improve insulin sensitivity, making *Stevia* an ideal alternative to artificial sweeteners for diabetics. Additionally, emerging studies suggest that *Stevia* promotes

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insulin secretion by increasing pancreatic beta-cell function and offers protective effects against inflammatory pancreatic diseases such as pancreatitis. Despite the numerous benefits, the safety profile and long-term effects of *Stevia* use are still being studied, although current evidence indicates a favorable toxicity profile. This review highlights the potential of *S. rebaudiana* as a natural therapeutic agent in diabetes management and supporting pancreatic health while indicating future research directions to fully realize its therapeutic uses.

Keywords: *Stevia rebaudiana*, Pancreatic disorders, Non-caloric, Sweetener, Sugar

Introduction

Stevia rebaudiana (*S. rebaudiana Bertoni*) is a South American herb that originated in the hills of north-eastern Paraguay in the Rio Monday valley (Katayama *et al.,* 2018). It is also recognized by several other names, including sweet weed, honey leaf, candy leaf, and sweet herbs. *Stevia* is becoming increasingly popular around the world and is anticipated to be a significant source of a powerful sweetener in the future (AR *et al.*, 2012). The leaves of this popular plant are sweet and ideal for people who are conscious of sugar and carbohydrate intake. With zero calories, the plant is being recognized as a great replacement for sugar and other sweeteners (VOA, 2015).

Figure 1: Stevia rebaudiana

Stevia has been grown on 32,000 hectares of land worldwide, with China accounting for the majority (75%). It is a plant that is used as a natural sweetener and is widely produced commercially in China, Thailand, Korea, Brazil, Paraguay, and Central America (Megeji *et al.*, 2015). Currently, Japan uses a significant quantity of *Stevia* (Sumida, 2013). With the help of this organic sweetener, Kenyan farmers may have the chance to join a global supply chain that is quickly expanding and involves a number of other nations (VOA, 2015). Currently, its commercially cultivated in many countries (Madan *et al* .,2010). Plants like *Stevia* have compounds with carbohydrates that are 200–300 times sweeter than regular sugar. Stevioside is said to have insulinotropic effects on pancreatic beta cells since it boosts insulin secretion and lowers blood sugar levels as a result. It may be collected and utilized as a substitute for sugars in sweeteners (Midmore and Rank, 2012).

The biological characteristics of *Stevia* were initially documented in 1887 by a South American scientist named Dr. Moies Santigo Bertoni, who served as the dean of the college of agriculture in Asuncion. In 1900, Ovidio Rebaudi discovered glycosides, which were the first active components in *Stevia* leaf extract that give it its sweetness. In 1931, the characterization of several *Stevia* glycosides was finished. *Stevia* was first grown in 1961. In contrast to Canada, which has approved *stevia* for use in foods and drinks, the United States of America recognized *Stevia* as a legitimate natural sweetener in 2008 (Hossain *et al*., 2017).

In 1964, the first study on commercial agriculture in Paraguay was published (Lewis, 2016). Since 1990, it has been cultivated in a variety of nations such as Brazil, Korea, Mexico, the United States, Indonesia, Tanzania, and Canada (Fors, 2017). Japan is currently the largest market, with China serving as its primary market (Kinghorn & DD, 2012). More counties in Kenya, including Kericho, Nandi, Nakuru, Laikipia, Uasin Gishu, Narok, sweeteners Meru, and Bungoma, are growing calorie-free sweetener, which has multiple health advantages. A natural sweetener called *Stevia* is expanding farming prospects in Kenya and expanding export markets in China, Malaysia, Paraguay, and Brazil (BDA, 2016). World Health Organization research showed that *Stevia* controls blood pressure, prevents cavities, stimulates the pancreas to create more insulin, and serves as an antibacterial agent. In any of these nations where *Stevia* is widely accessible, there have been no harmful clinical findings (Mahmud *et al*., 2014). Worldwide, the use of medicinal plants to treat various ailments is growing in popularity (Mostofa *et al.,* 2011).

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Additionally, it exhibited cardiotonic, hypotensive, diuretic, anti-bacterial, antiseptic, antiinflammatory, anti-fertility, and other properties. Dermatitis, eczema, wrinkles, skin imperfections, acne breakouts, scars, rashes, and itching have all been successfully treated with it. Steviol acts as a digestive stimulant and controls blood sugar levels in insulin-deficient mice by improving both insulin production and consumption. People with diabetes who want sweets should find hope in it (Ranjan *et al*., 2011). Its leaves contain around 10% stevioside, which are very sweet compounds that are especially advantageous to diabetics (Midmore and Rank, 2012).

The raw material of *Stevia* has anti-cancer action against prostate cancers, cholesterol-lowering properties, and rheumatoid arthritis-fighting properties. It can cure skin conditions, reduce hypertension, control blood sugar, and prevent dental decay, among other medical applications.
For diabetics, *Stevia*-derived compounds are regarded as the best source of an alternate sweetener. This new crop can have a significant increase in added value. According to statistics, steviosidelike sweetness products can replace up to 30% of the sugar that some nations require (Hossain *et al*., 2017).

Stevioside and rebaudioside, which are found in *Stevia* leaves and are said to be 300 times sweeter than sugar yet have no impact on blood sugar, are beneficial for type 2 diabetes and hypoglycemia (Soejarto, 2012; Ramesh. 2009). The pancreas is nourished by it, which aids in regaining normal function. *Stevia* also has a significant antioxidant activity since it has a high concentration of phenols and flavonoids (Shukla *et al*., 2019; Tadhani *et al*., 2009). The secondary metabolites known as phenols reduce the risk of cancer and heart disease (Dragovi *et al*., 2010). The herb may have heart-rhythm-regulating and blood pressure-normalizing effects (Ranjan *et al.*, 2011).

Both animals with hypertension and those with normotension exhibit vasodilator effects from the plant. *Stevia* has improved diuretic and natriuretic effects in rats and has also assisted in lowering blood pressure situations (Ranjan *et al*., 2011). Dental cavities have been linked to dietary sugar. It is thought that sugar alternatives can lower the frequency of tooth caries. Dental caries has

been shown to decrease with stevioside. It can work in three distinct ways: by causing a low-acid environment, acting as an anti-bacterial, and acting as an anti-plaque (Basu, 2015). Artificial sweeteners provide a further advantage by lowering the consumption of sucrose, in addition to its application in calorie control and for diabetes (Grenby, 2015).

Along with its many other applications, *Stevia* has anti-fungal and anti-bacterial properties. It is safe to use in everyday items like toothpaste and mouthwash as well as herbal remedies, tonics for diabetes patients, and other products. Additionally, a sweet *Stevia* leaf tea is a fantastic stomach settler (Goyal *et al*., 2010). Although there appears to be no hazard to the public health when *S. rebaudiana* sweeteners are used carefully, caution should be required at larger daily intake levels (Schardt, 2000). No evidence of negative effects from consuming *S. rebaudiana* extracts of stevioside by humans has been revealed in scientific publications, although their extensive usage in many regions of the world (Kinghorn, 2012). The Food & Drug Administration (FDA), the Food and Agriculture Organization of the United Nations, and the World Health Organization (WHO) have concluded that high-quality *Stevia* extract is safe for ingestion by the common person when used in the specified quantities (Hossain *et al*., 2017).

The possible biological uses of *S. rebaudiana*, it is worth mentioning that green synthesis methods have attracted a lot of interest because they are efficient and environmentally friendly ways to make nanoparticles. *S. rebaudiana* has the ability to play a role in the synthesis of nanoparticles, which could improve their therapeutic properties like antioxidant and antimicrobial activities. This could be compared to the way *Agaricus avensis*-mediated silver nanoparticles have improved the catalytic efficiency of enzymes like tyrosine hydroxylase, leading to advances in biomedicine (Ali *et al*., 2024). This opens up new opportunities for future study into Stevia-mediated nanoparticles for specific biomedical purposes.

Research on *S. rebaudiana* and its uses requires precise methodology selection to provide credible and significant results. Investigations into the biological activities and possible biomedical uses of Stevia need methodology that is just as strong as that used to study inorganic chemistry, where rigorous experimental design and analytical approaches have been emphasized (Malik *et al*., 2024). Using proper analytical techniques, including as spectroscopy and

chromatography, can enable accurate characterization of Stevia's bioactive components, opening the path for future advances in this field of study.

The most well-known natural compounds derived from *S. rebaudiana* are steviol and its glycosides, including stevioside, rebaudioside (A-F), steviolbioside, dihydroisosteviol, riboside, and dulcoside A. *Stevia* contains a variety of nutrients, such as water (80-85%), protein, fiber, monosaccharides, lipids, essential oils, vitamin C, β -carotene, vitamin B2, and vitamin B1. Including anti-oxidant substances like apigenin, quercetin, isoquercitrin, luteolin, miocene, kaempferol, chlorogenic acid, and caffeine to your diet. Include minerals like potassium, phosphorus, magnesium, cobalt, and iron as well (Savita *et al*., 2004). The Guarani people utilized *S. rebaudiana* as a sweetener in herbal treatments. *Stevia* has several uses across the world. In the culinary and pharmaceutical industries, steviol glycosides were initially marketed in Japan. Since then, China, Malaysia, Singapore, South Korea, Taiwan, and Thailand have all added cultivation to their regions (Lemus *et al*., 2012).

For the treatment of diabetes mellitus, obesity, hypertension, and cavities, steviol glycosides have been used in place of sucrose. Steviol glycosides may have clinical benefits due to their impact on hyperglycemia, hypertension, inflammation, tumors, anti-diarrhea, and the immune system (Jaroslav *et al*., 2007) . In comparison to many other sweeteners, *Stevia* leaves offer better functional and sensory qualities (Chatsudthipong and Muanprasat, 2009).

The goal of this study is to provide a range of fundamental information gleaned from *Stevia* research with a focus on qualities that are practical and healthy. A perennial shrub belonging to the Compositae family, *S. rebaudiana* is grown in many parts of the world. It is well known for being extremely sweet, with steviol glycosides accounting for 100–300 times the sweetness of sucrose. In the food and pharmaceutical industries, it has been utilized as a sugar substitute and sweetener. *Stevia* has positive benefits against a wide range of medical diseases because of its strong nutritional and phytochemical profile.

Carbohydrates

Carbohydrates are one of the three primary macronutrients in the human diet, along with protein and fat. The building blocks of these molecules are carbon, hydrogen, and oxygen atoms. Carbohydrates are extremely important to the human body. They offer energy, help with

cholesterol and triglyceride metabolism, aid in fermentation, and control insulin and blood sugar metabolism. When carbohydrates are ingested, the digestive system begins to convert them into glucose, which is used for fuel. Muscles and the liver are responsible for storing any extra glucose in the circulation until it is needed for energy (Holesh *et al*., 2017).

Flavonoids

Dietary flavonoids have recently attracted more research interest as a result of the substantial evidence of the many health benefits of flavonoids from epidemiological studies. It is very important to look at where the flavonoids in food come from because the amount of flavonoids is directly linked to the amount of vitamins people eat every day. People acquire most of their flavonoids from fruits and vegetables, along with a little amount from tea and wine. It is also hard to get an accurate daily dose of flavonoids because they are found in a lot of different foods, different dietary groups, and nature itself. The good news is that scientists are moving swiftly to uncover flavonoids' health benefits for humans. A number of flavonoids have demonstrated antioxidative, free radical scavenging, coronary heart disease prevention, anti-tumor, and anti-human immunodeficiency virus (HIV) properties. More research in this area will definitely lead to a new era of flavonoids in foods and pharmaceutical products. Therefore, it is necessary to develop a reliable model for quantifying flavonoid intake (yao *et al*., 2004).

Alkaloids

For thousands of years, people have used plant alkaloids as unprocessed extracts as part of their traditional medicine. Individual alkaloids with known and validated pharmacological characteristics, however, have been purified and synthesized commercially as organic solvents since the 20th century. Because of their complexity, alkaloid compounds are typically impractical to create by chemical synthesis, making extraction from a basic plant combination the most practical business method.

Furthermore, plants typically create extremely complex mixes of alkaloids, frequently with low concentrations of the desirable varieties. As a result, the cost of commercially manufactured particular alkaloids is relatively high. Research has concentrated on altering alkaloid biosynthesis to develop transgenic plants or cell lines that keep producing certain alkaloids as plant genetic engineering gets more proficient. To enhance the simplicity of purification, this can be done by

boosting the synthesis of a specific alkaloid and/or suppressing the synthesis of similar compounds (Ozlem Guclu Ustundag *et al*., 2017).

Saponins

The inclusion of a steroid or triterpenoid aglycone and one or more sugar chains in the structure sets apart the large class of compounds known as saponins. The food, cosmetics, and pharmaceutical industries are progressively using a few of their physicochemical and biological properties, which are shared by just a small number of the diverse group's members. Realizing their full economic potential, which is driven by consumer demand for natural products and rising evidence of their health advantages, requires the development of commercially viable processing methods that can handle the processing hurdles provided by their complex nature, including their stability (Tiwari *et al.*, 2011).

The important components of an effective process design are knowledge of the content (qualitative and quantitative) and qualities of the saponins present in the raw material, as well as the impacts of processing on their composition and properties. Several natural resources can are several natural resources that can be used for commercial production due to the availability of saponins in nature and the existence of these compounds in substantial amounts in processing byproducts, such as those produced during the processing of soybeans (Ozlem *et al*., 2017).

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Table 1: Overview of the Biological Activities of *S. rebaudiana*,

	Biological Activity	Mechanism of Action	Health Benefits	Supporting Studies	References
1.	Anti-diabetic activity	Enhances insulin secretion, improves insulin sensitivity, regulates blood glucose levels.	Helps manage type 2 diabetes by reducing postprandial glucose spikes.	In vitro, animal and clinical studies	Geuns, J. M. (2003), (Ameer *et al.*, 2020)
2.	Anti-oxidant Activity	Contains flavonoids, phenolic compounds and other anti-oxidants that neutralize free radicals.	Reduces oxidative stress, potentially lowering the risk of chronic diseases like cardiovascular diseases and cancer.	Several in vitro and animal studies	Gasmalla *et al*., 2014), (Gupta *et al.* 2013)
3.	Anti-Inflammatory Activity	Suppresses proinflammatory cytokines, reduces inflammation in metabolic Tissues	Helps manage metabolic syndrome, diabetes and inflammation related disorders.	Animal and in vitro studies	(Jeppesen *et al.* 2000), (Chatsudthipong *et al*. 2009)
4.	Anti-microbial Activity	Inhibits the growth of bacteria, fungi and viruses.	Promotes oral health by preventing dental carries, combat microbial infections.	Studies on oral health and microbial	(Ghosh *et al*., 2008), (Tadhani *et al*.,2006)
5.	Anti- Cancer Activity	May inhibit the growth of cancer cells involves antioxidant and antiinflammatory properties.	Potential in preventing cancer, especially in pancreatic, breast and lung cancer.	Emerging research needs further validation	(Wang *et al*.,2020), (Ghanta *et al*.,2007)
6.	Pancreatic Health	Protects pancreatic beta cells enhances insulin secretion.	Improves pancreatic function, potentially preventing or managing diabetes.	Animal studies on beta- cell function	Jeppesen *et al*., 2003), (Liu *et al*., 2003)

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7.	Safety and Tolerability	Generally recognized as safe, few long term toxicity studies available.	Safe for consumption at recommended doses, but long term effecs need further research.	Limited human studies	(Anton *et al.*, 2010), (Joint *et al.*,2005)

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S. rebaudiana demonstrates a variety of biological activity, mainly because of the abundance of bioactive substances in its composition, including steviosides, rebaudiosides, and other phytochemicals (Lemus-Mondaca *et al*., 2012). One of its most significant functions is its antidiabetic action. Compounds in *Stevia*, especially steviosides and rebaudiosides, are very important for keeping blood sugar levels steady (Samuel *et al*., 2018). *Stevia* is a natural way to help people with type 2 diabetes because it increases insulin production from beta cells in the pancreas and makes tissues more sensitive to insulin (Assaei *et al*., 2016). It reduces postprandial blood glucose rises, making it a good sugar alternative for diabetics since it lessens the likelihood of insulin resistance (Papakonstantinou *et al*., 2022).

Stevia is very active as an antioxidant and has anti-diabetic effects as well. A lot of flavonoids, phenolic substances, and other antioxidants are found in it. These help fight free radicals and lower oxidative stress in the body (Gaweł-Bęben *et al*., 2015). This antioxidant activity protects cells from harm and may help prevent chronic oxidative stress-related disorders like cardiovascular disease and cancer (Engwa *et al*., 2022).

The anti-inflammatory characteristics of *Stevia* are particularly useful in the treatment of metabolic syndrome and diabetes, where inflammation plays a significant role (Rojas *et al*., 2018). Its antiinflammatory properties are assumed to be due to its capacity to decrease pro-inflammatory cytokines, hence reducing inflammation-related tissue damage, particularly to the pancreas (Takahashi *et al*., 2013).

Stevia also has antibacterial properties and is effective against a variety of pathogens such as bacteria, fungus, and viruses. Because it prevents the growth of bacteria that cause tooth decay, it is excellent for promoting oral health. It has also demonstrated potential in fighting a variety of other microbial disease (Chinsembu, K. C. (2016)..

Finally, *Stevia* has anticancer properties, with some research suggesting that its components can prevent the proliferation of cancer cells, particularly in the breast, lungs, and pancreas. While study in this area is ongoing, *Stevia*'s antioxidant and anti-inflammatory characteristics may contribute to its capacity to inhibit the onset and progression of some cancers (Hanna *et al*…, 2023). Overall, *S. rebaudiana*'s biological actions make it a diverse natural agent with prospective uses in metabolic disorder management, antioxidant defence, and overall health promotion (Ameer *et al*., 2020).

Impact of *S. rebaudiana* on pancreatic health

S. rebaudiana has been proven to increase insulin secretion, particularly via improving pancreatic beta-cell activity. Among *Stevia*'s primary bioactive components are steviosides, which aid in glucose regulation without triggering hypoglycemia by stimulating insulin secretion from the pancreas (Chowdhury *et al*., 2022). This makes *Stevia* a useful natural sweetener for people who have diabetes or insulin resistance (Ritu *et al*., 2016).

Antioxidant and anti-inflammatory effects

Chronic inflammatory disorders and oxidative stress can damage the pancreas, making it more susceptible to diseases like diabetes and pancreatitis. *Stevia*'s high antioxidant content, including polyphenols and flavonoids, aids in the neutralisation of free radicals, thereby lowering oxidative stress (Jarosz *et al*., 2017). A protective impact against pancreatic inflammation is essential for the prevention or management of pancreatitis and other pancreatic illnesses; *Stevia*'s antiinflammatory characteristics assist reduce inflammatory marker levels (Zhang *et al*., 2016).

Prevention of pancreatic damage

Oxidative stress and chronic inflammation are major causes to pancreatic damage in both diabetic and non-diabetic individuals. According to research, *Stevia* may help keep pancreatic cells healthy and long-lived by lowering oxidative damage to pancreatic tissues (Shivanna *et al*., 2013). In people with diabetes, the pancreas is particularly vulnerable to metabolic stress, therefore its protective function is important (Dastghaib *et al*., 2022).

Potential role in pancreatic regeneration

Stevia may facilitate the regeneration of pancreatic beta cells, according to preliminary research. People suffering from poor pancreatic function, especially those in the early stages of type 2 diabetes when beta-cell failure is a major concern, may find therapeutic benefits from this possible regeneration capacity (Eldken *et al*., 2023).

Protection against pancreatitis

Pancreatitis, which is an inflammation of the pancreas, is frequently associated with oxidative stress. *Stevia*'s anti-inflammatory and antioxidant qualities may help to reduce the severity of pancreatic tissues (Kurek *et al*.,2020). While further clinical study is needed, preliminary

findings suggest that using *Stevia* to treat inflammation-related pancreatic diseases is promising (Ballali *et al*., 2012).

Pancreatic cancer research

Though still in its early stages, there is an increasing interest in researching the potential of *Stevia* for cancer prevention, especially pancreatic cancer. Research on *Stevia*'s potential to prevent or reduce the progression of pancreatic cancer should be pursued further due to its anti-inflammatory, anti-oxidant, and perhaps anti-carcinogenic characteristics. However, more extensive research is required to conclusively prove these impacts (Rahman *et al*., 2016).

By increasing insulin output, decreasing oxidative stress and inflammation, and maybe helping to prevent pancreatic damage and regenerate pancreatic cells, *S. rebaudiana* shows great promise in promoting pancreatic health (Masoodi, H. (2020).. Because of these benefits, *Stevia* is being considered as a natural alternative for diabetes management and pancreatic disease prevention. While preliminary data is promising, more research is needed to properly understand the long-term effects and therapeutic potential of *Stevia* for pancreatic health (Deligiannidou *et al*., 2019).

Variability in phytochemical composition

The concentration of bioactive compounds like steviosides and rebaudiosides in *Stevia* can vary significantly depending on factors such as plant cultivation methods, geographic location, and extraction techniques (Raspe *et al*., 2022). This variability affects the consistency of its health benefits. Developing standardized extraction methods and establishing quality control guidelines for *Stevia*-based products will ensure uniformly in their biological effects.

Regulatory frameworks governing the use of *Stevia* as a food additive and therapeutic agent vary by country (Abdel-Rahman*et al*., 2013). While *Stevia* is generally recognized as safe (GRAS) in many regions, discrepancies in dosage limits and labeling requirements create confusion for consumers and manufacturers, harmonizing these regulations will facilitate the broader the broader acceptance and use of *Stevia* in healthcare and food industries (Tavarini *et al*., 2013).

Safety and long term effects

Although *Stevia* has been found to be saw for short term use more extensive studies on its long term effects especially at higher doses, are needed to fully understand its potential health risks

(Hossain *et al.*, 2017). The possibility of adverse interactions with medications or metabolic pathways in individuals with chronic conditions like diabetes or pancreatitis should be investigated (Pecoits-Filho *et al*., 2016).

While studies have not shown carcinogenic effects in *Stevia* consumption, further research is warranted to rule out any geno-toxic risks over prolonged use (Samreen *et al*., 2023). Additionally, studies on the reproductive health impacts of long term *Stevia* intake, especially in pregnant women and children, are sparse and require attention.

Conclusion

In conclusion, *S. rebaudiana* is a diverse plant with extensive biological activities that provide several health benefits, particularly in the treatment of metabolic problems and the promotion of pancreatic health. The bioactive components found in it, including steviosides and rebaudiosides, give it its anti-diabetic effects. These features help manage blood glucose levels and improve insulin sensitivity, making it a potential natural treatment for people with type 2 diabetes. Furthermore, *Stevia* has significant antioxidant and anti-inflammatory properties that help protect cells from oxidative stress and inflammation, which are important factors in the prevention of chronic disorders such as cardiovascular disease, diabetes, and even cancer. The plant's antibacterial action enhances its therapeutic potential, notably in terms of dental health and infection prevention. Further research is needed to completely understand the mechanisms of *Stevia*'s anticancer capabilities, although emerging evidence points to its possible role in suppressing the proliferation of cancer cells. Although *Stevia* has many positive health effects, such as enhancing pancreatic function and preventing damage, there are still challenges to overcome in terms of clinical validation, long-term safety evaluations, and standardization. In order to fill these gaps, researchers in the future should conduct thorough clinical trials, investigate the underlying mechanisms, and look for new therapeutic uses. Overall, *S. rebaudiana* shows significant promise as a natural health-promoting agent with a wide range of uses in metabolic and pancreatic health management.

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