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CHIEF -EDITOR:**Prof. Dr. Dr. H. Parlar**

Parlar Research & Technology-PRT

Vimy Str.1e

85354 Freising, Germany

and

Dr.P.Parlar

Parlar Research & Technology

Vimy Str.1e

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Parlar Research & Technology

PRT, Vimy Str.1e

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Callinstr.5, 30167 Hannover

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A COMPREHENSIVE REVIEW OF STEVIA REBAUDIANA BERTONI: THERAPEUTIC PROPERTIES AND HEALTH BENEFITS

Manish^{1,*}, Shiv Kumar¹, Namrata¹, Ravi Kumar²

¹Institute of Food Technology, Bundelkhand University, Jhansi [U.P.] India

²IET [Department of Food Technology], Bundelkhand University, Jhansi [U.P.] India

ABSTRACT

Stevia rebaudiana Bertoni, commonly known as sweet leaf, represents a remarkable botanical species within the Asteraceae family, encompassing approximately 200 species of herbaceous plants and shrubs. This perennial plant, historically recognized by South American indigenous populations as "kaa-hee" meaning sweet herb, has garnered significant scientific attention for its multifaceted therapeutic applications beyond its well-established role as a natural sweetening agent. Traditional medicinal practices of Paraguayan and Brazilian indigenous communities have long utilized this plant for cardiovascular support, blood pressure regulation, hepatic protection, gastrointestinal disorders and as a mild nervous system stimulant. Contemporary scientific investigations have substantiated many of these traditional uses while revealing additional therapeutic properties including antimicrobial, antifungal, anti-inflammatory and potential anticancer activities. The bioactive compounds responsible for these effects, particularly steviol glycosides such as stevioside and rebaudioside A, have demonstrated remarkable safety profiles and efficacy in various clinical applications. This comprehensive review synthesizes current research findings regarding the health-promoting properties of *S. rebaudiana*, examining its mechanisms of action, therapeutic applications and safety considerations for human consumption.

KEYWORDS:

Stevia rebaudiana, steviol glycosides, hypoglycemic activity, antihypertensive effects, natural sweetener, therapeutic application

INTRODUCTION

The quest for natural, health-promoting alternatives to conventional synthetic compounds has intensified in recent decades, particularly in the realm of food additives and therapeutic agents. *Stevia rebaudiana* Bertoni emerges as a compelling candidate in this context, representing a unique convergence of traditional wisdom and modern scientific validation.

Originally classified as *Eupatorium rebaudianum* Bertoni, this remarkable plant has captured the attention of researchers worldwide due to its extraordinary sweetening properties coupled with diverse therapeutic benefits [30]. The historical significance of *S. rebaudiana* extends far beyond its contemporary commercial applications. Indigenous tribes of South America, particularly those in Paraguay and Brazil, have maintained a rich tradition of utilizing this plant for centuries. Their sophisticated understanding of its medicinal properties encompassed cardiovascular health, metabolic regulation, and antimicrobial applications, providing a foundation for modern scientific investigation. The traditional name "kaa-hee" reflects the deep cultural integration of this plant into indigenous healing practices, where it served dual purposes as both a sweetening agent and a therapeutic remedy.

Modern phytochemical analysis has revealed that the therapeutic efficacy of *S. rebaudiana* stems primarily from its content of steviol glycosides, complex diterpene compounds that exhibit remarkable biological activity while maintaining an excellent safety profile. These compounds, including stevioside and rebaudioside A, represent the primary bioactive constituents responsible for the plant's diverse therapeutic effects. The unique chemical structure of these glycosides allows them to interact with various physiological pathways, contributing to their multifaceted therapeutic potential.

NUTRITIONAL PROFILE AND METABOLIC CHARACTERISTICS

The nutritional analysis of *S. rebaudiana* reveals distinctive characteristics that set it apart from conventional sweetening agents. The energy content of stevia preparations approximates 2.7 kcal/g of dry matter, positioning it favorably among low-calorie intensive sweeteners currently available in commercial markets [4]. This reduced caloric density presents significant advantages for individuals seeking to minimize their intake of simple sugars while maintaining dietary palatability. The metabolic fate of steviol glycosides in the human body follows a

unique pathway contributing to their therapeutic efficacy. Unlike conventional sugars that undergo rapid absorption and metabolism, steviol glycosides resist enzymatic degradation in the upper gastrointestinal tract. The initial breakdown occurs through the action of intestinal microflora in the large intestine, where bacterial enzymes cleave the glycosidic bonds to release steviol and glucose molecules. The glucose component remains localized within the intestinal lumen, where it serves as a substrate for bacterial metabolism rather than contributing to systemic glucose levels [3]. The steviol moiety undergoes hepatic conjugation with glucuronic acid, forming steviol glucuronide, which facilitates its elimination through both urinary and fecal excretion pathways. This metabolic pathway ensures efficient clearance while minimizing systemic accumulation, contributing to the excellent safety profile observed in clinical studies.

Regulatory authorities have established acceptable daily intake [ADI] levels for steviol glycosides at 4 mg/kg body weight per day, expressed as steviol equivalents. However, extensive safety evaluations suggest that consumption levels up to 5 mg/kg body weight per day demonstrate no teratogenic or carcinogenic effects [11, 4]. Toxicological studies in animal models indicate that adverse effects occur only at extremely high doses of 1500 mg/kg body weight, doses far exceeding typical human consumption patterns [4].

CARDIOVASCULAR EFFECTS AND BLOOD PRESSURE REGULATION

The cardiovascular benefits of *S. rebaudiana* represent one of the most extensively studied therapeutic applications, with particular emphasis on blood pressure regulation and vascular health. The antihypertensive mechanisms of stevioside involve complex interactions with calcium ion channels in vascular smooth muscle cells, resulting in vasodilation and reduced peripheral vascular resistance [8].

Mechanisms of Blood Pressure Reduction.

The hypotensive action of stevioside operates through multiple complementary mechanisms. The primary pathway involves the inhibition of calcium influx into vascular smooth muscle cells, effectively blocking voltage-dependent calcium channels and promoting arterial relaxation. This vasodilatory effect reduces total peripheral resistance, contributing to sustained blood pressure reduction. Additionally, stevioside enhances diuresis and natriuresis, reducing extracellular fluid volume and further supporting blood pressure normalization.

Clinical Evidence for Antihypertensive Effects. Comprehensive clinical investigations have documented significant antihypertensive effects in

hypertensive populations while demonstrating minimal impact on normotensive individuals. A landmark study by [10] involved 106 women aged 28-75 years with mild to moderate hypertension [diastolic blood pressure 95-100 mmHg]. Participants received 0.25 g stevioside three times daily for one year, resulting in remarkable reductions in both systolic and diastolic blood pressure within seven days of treatment initiation. The observed reductions of 14 mmHg systolic and 14.3 mmHg diastolic pressure were maintained throughout the study period, suggesting sustainable therapeutic benefits. [5] conducted a long-term evaluation demonstrating approximately 7% reduction in arterial tension among patients consuming stevioside compared to placebo controls. This effect persisted for up to two years of continuous treatment, indicating the potential for stevioside as a long-term therapeutic intervention. Furthermore, the study revealed reduced incidence of left ventricular hypertrophy in the treatment group, suggesting cardioprotective benefits beyond blood pressure reduction.

Selectivity for Hypertensive Populations. A particularly noteworthy characteristic of stevioside's antihypertensive action is its apparent selectivity for individuals with elevated blood pressure. [17] observed that the blood pressure-lowering effects manifest specifically in hypertensive individuals while showing minimal impact on normotensive subjects. This selectivity suggests that stevioside may function as a physiological normalizer rather than a general hypotensive agent, reducing the risk of excessive blood pressure reduction in healthy individuals. Meta-analytical reviews of existing clinical data indicate that while effects on systolic blood pressure show variability, consistent and appreciable reductions in diastolic blood pressure have been documented across multiple studies [29]. The therapeutic benefits appear to require sustained administration over extended periods, with studies of 1-2 years duration showing more pronounced effects than short-term interventions.

GLYCEMIC CONTROL AND ANTIDIABETIC PROPERTIES

The antidiabetic properties of *S. rebaudiana* have attracted considerable scientific attention, particularly given the plant's historical use in traditional medicine for blood sugar regulation. Contemporary research has validated these traditional applications while elucidating the complex mechanisms underlying stevioside's glycemic effects.

Historical Context and Traditional Use. Indigenous communities of Paraguay and Brazil have employed *S. rebaudiana* extracts for blood sugar management for centuries, long before the scientific characterization of diabetes mellitus. This traditional

knowledge provided the foundation for systematic scientific investigation into the plant's antidiabetic potential.

Clinical Evidence for Hypoglycemic Effects.

Early clinical investigations by [13] demonstrated enhanced glucose tolerance in healthy individuals consuming aqueous extracts of *S. rebaudiana* leaves. Sixteen participants consumed 5 g of leaf extract or arabinose solution for three days at six-hour intervals, with glucose tolerance tests conducted before and after intervention. The stevia group showed significantly improved glucose tolerance, suggesting beneficial effects on glucose metabolism even in healthy populations. [18] conducted a more targeted investigation involving twelve participants with established type 2 diabetes of at least four years duration. Daily supplementation with 1 g stevioside or 1 g maize starch revealed reduced postprandial glycemia and lower insulin index values in the stevioside group. These findings suggest that stevioside may improve postprandial glucose control while potentially enhancing insulin sensitivity.

Mechanisms of Glycemic Control. The hypoglycemic mechanisms of stevioside involve multiple pathways affecting glucose homeostasis. [12] investigated these mechanisms using diabetic rat models, employing both streptozotocin-induced hyperglycemia and fructose-induced insulin-dependent diabetes. Stevioside administration resulted in reduced insulin resistance and simultaneous suppression of glucagon secretion, suggesting dual benefits for glucose regulation. The molecular mechanisms underlying these effects involve enhanced mRNA expression of key metabolic enzymes, including carnitine palmitoyltransferase, peroxisome proliferator-activated receptor alpha [PPAR- α], and stearoyl-CoA desaturase [12]. These enzymatic changes promote improved fatty acid oxidation and glucose utilization, contributing to overall metabolic improvement.

Insulin Secretion and Beta Cell Function.

Research by [21] using GK rats, a non-obese Wistar substrain developing early-onset type 2 diabetes, demonstrated that stevioside administration at 0.025 g/kg body weight produces hypoglycemic effects through increased insulin secretion and enhanced expression of glycolytic genes. This suggests that stevioside may support pancreatic beta cell function while promoting glucose utilization. The insulin-stimulating effects of steviol glycosides demonstrate dose-dependency and require the presence of extracellular calcium ions [1]. The mechanism involves closure of ATP-dependent potassium channels, leading to beta cell depolarization and activation of voltage-dependent calcium channels, ultimately resulting in enhanced insulin release. Rebaudioside A demonstrates similar hypoglycemic properties to stevioside, with [30] showing significant reductions in

blood glucose concentrations and protective effects on pancreatic tissue in diabetic rats. The structural similarities between these compounds likely account for their comparable therapeutic effects.

ANTI-INFLAMMATORY AND IMMUNOMODULATORY ACTIVITIES

Recent research has revealed significant anti-inflammatory and immunomodulatory properties of *S. rebaudiana* compounds, expanding the therapeutic potential beyond metabolic applications. These effects involve complex interactions with inflammatory mediators and immune system components.

Inflammatory Mediator Modulation. Conducted comprehensive investigations into the anti-inflammatory effects of stevioside using THP-1 cell cultures [6]. Their findings revealed that stevioside significantly inhibits lipopolysaccharide-induced enhancement of pro-inflammatory cytokine production, specifically interleukin-1 β [IL-1 β] and tumor necrosis factor- α [TNF- α] by macrophages and monocytes. The mechanism involves interaction with toll-like receptor 4 [TLR4], the primary receptor for lipopolysaccharides from gram-negative bacteria. In the presence of infection or inflammatory stimuli, stevioside prevents excessive inflammatory responses while maintaining appropriate immune activation in healthy conditions. This selective modulation suggests sophisticated regulatory mechanisms that preserve beneficial immune functions while limiting harmful inflammatory cascades.

Respiratory Anti-inflammatory Effects. Research investigated the pulmonary anti-inflammatory effects of stevioside using male BALB/c mice subjected to lipopolysaccharide-induced acute lung injury. Stevioside administration one hour prior to inflammatory challenge limited lung injury severity and inhibited production of pro-inflammatory cytokines. The treatment also suppressed cyclooxygenase II expression, inducible nitric oxide synthase activity. These findings suggest potential therapeutic applications for stevioside in respiratory inflammatory conditions, though further clinical investigation is required to establish therapeutic protocols and efficacy in human populations.

Anti-apoptotic Properties. Extensive investigations into the anti-inflammatory and anti-apoptotic effects of stevioside in mammary gland epithelium infected with *Staphylococcus aureus* have been conducted. These findings suggest that stevioside exerts its anti-inflammatory effects primarily through post-transcriptional mechanisms, potentially offering therapeutic advantages in conditions characterized by excessive inflammatory responses.

ANTIMICROBIAL AND ANTICANCER PROPERTIES

The antimicrobial properties of *S. rebaudiana* extend beyond its anti-inflammatory effects, encompassing antibacterial, antifungal and antiviral activities that contribute to its therapeutic versatility.

Dental Health Applications. The anticaries properties of steviol glycosides have received particular attention due to their potential applications in oral health maintenance. [7] conducted controlled studies involving 20 volunteers who rinsed with solutions containing 10% stevioside, rebaudioside A, or sucrose. The results demonstrated that stevia-derived solutions maintained significantly higher plaque pH levels compared to sucrose solutions, indicating reduced cariogenic potential. Furthermore, stevioside demonstrated specific inhibitory activity against *Streptococcus mutans*, the primary bacterial species responsible for dental caries development. This dual benefit of sweetening without promoting dental decay represents a significant advantage over conventional sugar-based sweeteners.

Broad-spectrum Antimicrobial Activity. Comprehensive antimicrobial screening revealed that *S. rebaudiana* leaf extracts demonstrate activity against various bacterial and fungal pathogens, with notable exceptions including *Bacillus cereus* and *Bacillus megaterium*. The antimicrobial spectrum includes both gram-positive and gram-negative bacteria, suggesting multiple mechanisms of action. [2] compared the antimicrobial efficacy of aqueous and alcoholic stevia extracts, finding superior antibacterial activity in alcoholic preparations against *Streptococcus mutans* and *Lactobacillus acidophilus*. This suggests that extraction methods may influence the bioavailability and potency of antimicrobial compounds.

Antiviral Properties. Research demonstrated that stevia-derived compounds inhibit replication of four human rotavirus serotypes in vitro, suggesting potential applications as antirotavirus agents. The antiviral mechanisms remain under investigation, but the findings indicate therapeutic potential in viral gastroenteritis management.

Anticancer Potential. Emerging research has identified potential anticancer properties of *S. rebaudiana* compounds, particularly isosteviol derivatives. [27] demonstrated that isosteviol, produced through acid hydrolysis of steviol glycosides, strongly inhibits DNA polymerase and topoisomerase II activity, effectively delaying growth of three different cancer cell lines. Recent investigations by [26] and [22] have explored the cytotoxic activity of isosteviol derivatives against tumor cells derived from primary and metastatic cancers. While these findings are

promising, extensive additional research is required to establish therapeutic protocols and clinical efficacy. [14] reported that methanolic and ethanolic extracts of *S. rebaudiana* exhibit anticancer activity against Caco-2 cell lines, further supporting the potential oncological applications of stevia-derived compounds.

HEPATOPROTECTIVE AND NEPHROPROTECTIVE EFFECTS

Investigations into the organ-protective properties of *S. rebaudiana* have revealed significant hepatoprotective and nephroprotective effects, expanding the therapeutic applications beyond metabolic and cardiovascular benefits. Comprehensive studies using 80 Wistar rats were conducted to evaluate the protective effects of whole stevia leaf powder on liver and kidney function. The research demonstrated beneficial effects in alleviating hepatic and renal diseases while reducing oxidative stress markers. The protective mechanisms likely involve antioxidant activity and modulation of inflammatory pathways, though detailed mechanistic studies are needed. The hepatoprotective effects may be particularly relevant in metabolic syndrome and diabetes management, where hepatic steatosis and oxidative stress contribute to disease progression. The nephroprotective properties suggest potential applications in diabetic nephropathy prevention, though clinical validation remains necessary.

SAFETY ASSESSMENT AND REGULATORY STATUS

The safety evaluation of *S. rebaudiana* and its derived compounds has received extensive attention from regulatory authorities worldwide, resulting in comprehensive safety assessments and approval for human consumption.

Allergenicity Considerations. Concerns regarding potential allergenic reactions to stevia have been raised due to its taxonomic relationship with other Asteraceae family members, including ragweed, goldenrod, chrysanthemum, and other potentially allergenic plants. However, comprehensive literature reviews found minimal substantiated scientific evidence supporting allergy warnings for highly purified steviol glycosides. The available data suggests that hypersensitivity reactions to stevia in any form are exceptionally rare, indicating that the taxonomic relationship does not translate to clinically significant cross-reactivity. This finding supports the safety of stevia-derived products for general population consumption.

Regulatory Approvals. The safety assessment process for steviol glycosides has involved multiple international regulatory agencies. In 2008, the Joint FAO/WHO Expert Committee on Food Additives [JECFA] concluded that steviol glycosides obtained from *S. rebaudiana* are safe for human consumption, leading to their authorization for use in the United States. The European Food Safety Authority [EFSA] conducted independent safety evaluations and established the acceptable daily intake [ADI] for steviol glycosides at 4 mg/kg body weight per day, expressed as steviol equivalents [15]. This assessment was confirmed in November 2011 through European Commission Regulation No. 1131/2011, which established maximum permissible levels of steviol glycosides [E960] in various food categories.

Conversion Factors and Practical Applications. The regulatory framework establishes specific conversion coefficients for calculating steviol equivalents from different glycoside forms. Rebaudioside A and stevioside have conversion factors of 0.33 and 0.4, respectively, reflecting their different molecular structures and metabolic pathways [9]. These conversion factors enable accurate assessment of steviol glycoside intake across different product formulations, ensuring consumer safety while facilitating product development and regulatory compliance.

FUTURE RESEARCH DIRECTIONS AND CLINICAL APPLICATIONS

The expanding body of research on *S. rebaudiana* suggests numerous opportunities for future investigation and clinical application development. Several areas warrant particular attention to fully realize the therapeutic potential of stevia-derived compounds.

Long-term Clinical Studies. While existing clinical data demonstrate promising therapeutic effects, most studies have been relatively short-term or involved small participant populations. Large-scale, long-term clinical trials are needed to establish optimal dosing protocols, identify potential interactions with medications, and confirm sustained therapeutic benefits. Particular attention should be directed toward cardiovascular outcome studies in hypertensive populations, glycemic control investigations in diabetic patients, and comprehensive safety evaluations in vulnerable populations including children, pregnant women, and elderly individuals.

Mechanistic Investigations. Despite significant progress in understanding the therapeutic mechanisms of steviol glycosides, many aspects require further clarification. The molecular pathways underlying cardiovascular protection, the specific receptors involved in glycemic control, and the detailed

mechanisms of anti-inflammatory activity warrant additional investigation. Advanced molecular biology techniques, including proteomics and metabolomics approaches, may provide deeper insights into the complex interactions between steviol glycosides and human physiology.

Formulation Development. The development of optimized delivery systems for steviol glycosides represents an important area for future research. Enhanced bioavailability formulations, targeted delivery systems, and combination preparations with complementary therapeutic agents could significantly improve clinical efficacy. Investigation into the interactions between steviol glycosides and food components, as well as the effects of processing conditions on bioactivity, will inform optimal product development strategies.

CONCLUSION

Stevia rebaudiana Bertonii represents a remarkable example of successful translation from traditional medicine to modern therapeutic application. The extensive body of research accumulated over recent decades has validated many traditional uses while revealing additional therapeutic properties that extend far beyond the plant's role as a natural sweetener. The cardiovascular benefits, particularly blood pressure regulation, demonstrate clinically relevant effects that may contribute to the management of hypertension and reduction of cardiovascular disease risk. The antidiabetic properties offer promising applications in diabetes prevention and management, while the anti-inflammatory and antimicrobial activities suggest broader therapeutic potential. The excellent safety profile established through comprehensive toxicological studies and regulatory evaluations supports the integration of steviol glycosides into dietary and therapeutic applications. The selective effects observed in clinical studies, where therapeutic benefits manifest primarily in individuals with existing health conditions while showing minimal impact on healthy populations, represent a particularly attractive characteristic for therapeutic agents. However, several important areas require continued investigation to fully realize the therapeutic potential of *S. rebaudiana*. Long-term clinical studies, detailed mechanistic investigations, and optimized formulation development will be essential for establishing evidence-based therapeutic protocols and maximizing clinical benefits. The unique combination of therapeutic efficacy, excellent safety profile, and natural origin positions *S. rebaudiana* as a valuable addition to the therapeutic armamentarium for multiple health conditions. Continued research investment and clinical development efforts are warranted to fully exploit the remarkable therapeutic potential of this exceptional plant.

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CORRESPONDING AUTHOR

Manish

Institute of Food Technology,
Bundelkhand University, Jhansi [U.P.]
India

e-mail: manishuboriya@gmail.com