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AN COMPREHENSIVE EXAMINATION OF THE THERAPEUTIC AND DIETARY ATTRIBUTES OF STEVIA

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ABSTRACT

Introduction

Stevia rebaudiana, an indigenous plant of South America, is becoming increasingly popular because of its potent sweetness obtained from steviol glycosides, which are considerably sweeter than sucrose. Due to its low calorie content and this characteristic, Stevia is considered a favoured sugar alternative in a wide range of food products. In addition to being a substitute for sugar, Stevia provides a range of metabolic benefits. Studies have shown that extracts from this plant have antihypertensive and antihyperlipidemic qualities, can control blood glucose and insulin levels, enhance kidney function, and may have potential anticancer effects. The wide range of advantageous characteristics linked to Stevia highlights its promise as a subject for further exploration of its health-promoting effects. This article offers an analysis of scientific research and reliable sources, presenting the metabolic advantages and health impacts of steviol glycosides obtained from Stevia in the human body.

Aim of the study

This review aims to identify the metabolic benefits of Stevia rebaudiana on the human body. The main objective is to present its action as a component in the fight against obesity, diabetes, hypertension, dyslipidaemia and cancer cells.

Material and method

This article presents the current state of knowledge about the range of metabolic benefits of Stevia rebaudiana. Publications describing the effects of Stevia rebaudiana use on the metabolism and health of the human body were reviewed using the PubMed platform. The search included the keywords 'stevia', 'artificial sweetener', 'sugar substitute', 'obesity'.

Keywords
stevia; obesity; sugar substitute; artificial sweetener

Introduction

Stevia rebaudiana Bertoni is a small plant of the *Asteraceae* family, growing naturally in South America, in mountainous areas of Argentina, Brazil and Paraguay. The native groups of peoples have utilised the leaves of this plant for medicinal purposes and as a natural sweetener in beverages like green tea for many generations [1].

Stevia leaves contain a variety of components, including sweet substances, carbohydrates, protein, lipids, oils, vitamins and minerals [2]. The variety of substances contained in this plant allows its potential to be exploited in many ways.

Chemical compounds known as steviol glycosides are responsible for the plant's intense sweet taste [1,3]. More than 30 steviol glycosides are known, but the two most important are the main sources of sweet taste - stevioside (major glycoside in stevia) and rebaudioside A [2].

There are several ways to use stevia preparations including fresh, crushed or dried leaves and liquid extracts. Steviol glycosides in extracts from the plant are approximately 300 times sweeter than sucrose and are widely used in the food industry as a calorie-free sweetener [2,4].

Upon oral intake, steviol glycosides evade metabolic degradation by enzymes such as salivary and pancreatic α-amylase, pepsin, and pancreatin, which are typically present in saliva and upper gastrointestinal secretions. Steviol glycosides digestion only takes place in the large intestine. This process involves the intestinal microflora, which will use them as an energy source. It is worth noting that the molecules do not enter the bloodstream, so they do not deliver any calories to the body [5,6]. This property has earned stevia the title of one of the more commonly used zero-calorie sweeteners in food processing.

Stevia is currently the subject of much research due to its potential broad spectrum of attributes. The substances contained in Stevia not only have flavour benefits, but also health-

promoting properties. It has been discovered that the consumption of Stevia can result in anti-diabetic, anti-hypertensive, anti-obesity, anti-oxidant, anti-hyperlipidemic and even anti-cancer effects [2,4]. Early research indicated that Stevia had antioxidant and anti-inflammatory properties that could prevent cardiovascular and metabolic problems. Given the correlation between cardiovascular disease, diabetes, oxidative stress, and inflammation, it is important to investigate how Stevia rebaudiana might protect against and affect these processes [7]. This entire spectrum of beneficial characteristics makes stevia a promising candidate for further research into its health-promoting attributes.

Helpful in fighting obesity

Obesity has significantly increased to epidemic levels in several nations worldwide during the last 20 years. As to the World Health Organisation (WHO), more than 1 billion individuals worldwide have a body mass index (BMI) equal to or greater than 25, indicating overweight. Children and teenagers are showing similar patterns, which may result in severe health issues in maturity [8]. Excess weight and obesity are linked to several serious health conditions, such as high blood pressure, heart disease, diabetes and some types of cancer like breast, prostate, endometrial and colon cancer [8,9].

An inadequate diet, consisting mainly of simple carbohydrates, with high glycemic index, is most predisposing to abdominal obesity. Calorie-free sweeteners are beneficial for managing calorie intake in a diet, promoting weight loss, and do not have any negative effects when ingested. Additionally, they help minimize the occurrence of abdominal obesity, which is linked to multiple health conditions [4].

A 10-week study was conducted in which one group of people consumed sucrose-sweetened foods and beverages and the other group consumed foods and beverages sweetened with sweeteners. Body weight was then compared between study participants in both groups. A weight gain of 1.6kg was observed in the first group consuming sucrose-sweetened products and a weight reduction of approximately 1.0kg was observed in the second group of people using sweeteners [10].

Based on the sources provided, we can conclude that replacing sugar with sweeteners that are free of calories, like Stevia in commonly available foods, such as drinks, can help to control weight and prevent obesity [11].

Impact of *Stevia rebaudiana* on insulin and glucose metabolism

Diabetes mellitus is a metabolic disorder that interferes with the processes that regulate blood glucose levels due to insufficient insulin production or resistance to insulin [12]. It is one of the most common metabolic diseases of the world today and a significant global health problem.

The effectiveness of stevia as part of the diet of people with pre-diabetic conditions, diabetes, insulin resistance or impaired glucose tolerance is still under investigation. Stevia, a substance with a long history of use in the traditional medicine of Paraguay and Brazil, has been used for many years not only as a sweetener, but also as an herbal remedy to alleviate the symptoms of diabetes and hyperglycemia [2].

Consumption of stevia-containing products was associated with reduced post-meal blood insulin levels, compared to levels recorded after consuming products with sucrose or aspartame. Blood glucose levels were also lower after a stevia-containing meal, compared to sucrose. Thus, stevia may be useful in controlling elevated blood glucose levels after a meal, which is associated with the progression of type 2 diabetes and insulin resistance [13].

Stevioside also has the ability to increase insulin sensitivity. Specifically, very small quantities of stevioside have been shown to enhance the impact of insulin on the transportation of glucose into skeletal muscle. The properties of the compounds contained in Stevia are also known to reduce plasma glycated haemoglobin concentrations [14].

The study discovered that stevia extract enhances the functioning of pancreatic β-cells in rats with diabetes. This is achieved by the steviol glycosides' capacity to stimulate insulin secretion by pancreatic islets [15].

An additional beneficial effect of stevioside as a substance with antihyperglycaemic properties is that its insulinotropic effect ends when blood glucose levels fall to normal levels [16].

All the properties of Stevia described above are just some of its beneficial effects on carbohydrate metabolism in the human body. It is believed that the chemical compounds contained in Stevia are a promising and forward-looking direction in the formulation of new treatments for type 2 diabetes.

Effects on blood pressure

With regard to cardiovascular events, such as cardiac mortality, coronary heart disease, and ischemic or hemorrhagic stroke, hypertension is the most significant risk factor that may be

modified. Accordingly, it is crucial to comprehend the methods of preventing hypertension and the most effective medical interventions for treating hypertension in order to decrease cardiovascular mortality [17].

Firstly, the treatment of hypertension involves lifestyle changes, including limiting salt intake, implementing regular physical activity and controlling body weight. In this management, the use of calorie-free sweeteners such as Stevia is useful, because it helps to reduce the amount of sugar consumed [18].

The action of the substances contained in Stevia in promoting weight loss, preventing diabetes or improving metabolic parameters in patients with impaired glucose tolerance indirectly reduces the risk of hypertension in this patient group by eliminating factors that predispose to high blood pressure.

A study was conducted in which a group of hypertensive patients were given stevioside for 1 year. Already after a period of 3 months, a reduction in both systolic and diastolic blood pressure values was observed. No negative effects of stevioside use on the biochemical parameters of the patients were observed during the study [19].

In another study, stevioside was used on a group of spontaneously hypertensive rats. It was shown that by affecting ions, specifically by inhibiting the inflow of Ca2+ ions in blood vessels, stevioside caused vasodilation of these vessels and thus reduced blood pressure in the group of rats studied [20].

Impact on dyslipidemia

Dyslipidemia is one of the most often diagnosed and managed chronic medical conditions. Traditionally, they are identified by elevated blood levels of triglycerides, cholesterol, or both, together with elevated levels of associated lipoproteins. Dyslipidemia is most typically linked to an elevated risk of atherosclerotic cardiovascular disease (ASCVD). Obesity and type 2 diabetes are also predisposing factors for elevated blood lipid parameters.

Managing dyslipidemia requires prioritizing lifestyle modifications. Adopting a nutritious diet abundant in fresh produce alongside regular physical activity plays a pivotal role in maintaining optimal body weight and thwarting obesity. [21].

A study was conducted in which participants were given extracts containing substances from Stevia rebaudiana. The results showed a reduction in blood cholesterol levels, a reduction in triglycerides, LDL (low-density lipoprotein) and an increase in HDL (high-density lipoprotein) levels [4].

Another experiment investigated the effect of administering Stevia extract to rats with induced hyperlipidaemia. In rats that received Stevia extracts, a significant improvement in lipid profile was observed, manifested by a decrease in blood cholesterol, triglycerides and low density lipoprotein (LDL). Stevioside's properties, which bind biliary cholesterol (or cholesterol from the diet) in the colon and promote the elimination of bile acids with the faeces, are responsible for the cholesterol-lowering action. Triglyceride concentration decreased as a result of lipid catabolism, which was catalysed by a rise in the activity of the liver-produced enzyme lipase. This was also the effect of stevioside. Stevioside decreased LDL levels in hyperlipidemic rats via regulating LDL receptor activity. This confirms the significant effect of the administration of stevia-extracted compounds on metabolism and blood lipid levels [22].

The substances contained in Stevia still require in-depth research to be considered as agents for the treatment of dyslipidemia. However, it is important to note that the use of this calorie-free sweetener helps to reduce excessive body weight and to prevent obesity, which is highly associated with abnormal blood lipid levels.

Improvement of renal function

The kidneys are critical organs responsible, e.g., for eliminating metabolic byproducts, regulating blood pressure and controlling water-salt balance [23]. Diabetic nephropathy affects 25% to 40% of individuals with diabetes mellitus and is the primary reason of kidney failure globally. Identifying high-risk individuals early is crucial due to the significant risk of gradual decline in kidney function leading to end-stage renal failure [24]. Hypertension is also an important risk factor for developing kidney disease [7].

Orally administered Stevia extract in rats caused increased diuresis, natriuresis, and showed signs of kidney blood vessel dilation. It also led to higher flow of plasma through the kidneys and lower mean blood pressure [25]. In addition it was shown that stevioside administration resulted in a decrease in serum uric acid levels and also alleviated microalbuminuria [7].

As a substance, used in the diet as a substitute for sucrose, characterised among other things by its effect on arterial blood pressure, glucose and insulin levels, reducing the risk of developing diabetes, it can be concluded that the use of Stevia indirectly reduces the risk of developing kidney failure.

Impact on body weight	• supporting weight loss • reduces incidence of abdominal obesity
Carbohydrate metabolism	• increased insulin sensitivity • reduction in postprandial blood glucose levels
Effects on blood lipid levels	• reduction in blood cholesterol and triglyceride levels • decrease of LDL-cholesterol level • increase of HDL-cholesterol level
Impact on kidney function	• increased diuresis and natriuresis • vasodilation of renal blood vessels • reduction of serum uric acid levels • reduction of microalbuminuria

Table 1. Summary of stevia's effects on individual metabolic aspects

Anti-cancer features of *Stevia rebaudiana*

Cancer is a very important global health problem. New methods of treatment, but also of prevention, are constantly being investigated for the various types of carcinomas. It is assumed that lifestyle and habit-related risk factors, such as an inadequate diet that is low in nutritious products such as fruit and vegetables, smoking and consuming large amounts of alcohol, are responsible for one-third of malignant neoplasms [26]. High intake of sugars is a well-known long-standing determinant for obesity. Excess body weight is a significant risk factor for a number of cancers, including colorectal, breast, endometrial and haematological cancers. Obesity is also linked to increased death rates for some types of malignancies [27]. Preventing obesity by promoting a healthy lifestyle, changing eating habits and diet is an important factor in cancer prevention.

The use of Stevia as a calorie-free sweetener is a valuable component of a diet which aims to decrease blood glucose levels. It is a great substitute for sugar due to its strong sweet taste.

This reduces the amount of calories supplied to the body, resulting in a lower obesity rate. By consuming less sugar, the delivery of nutrients to cancerous cells can be minimised. Low blood glucose levels also reduce inflammation and oxidative stress in the organism [6].

Implementing these strategies for fighting obesity, such as modifying daily dietary patterns and reducing caloric intake, can serve as a preventive strategy against several types of neoplasms.

Strong cancer cell growth inhibitory effects are demonstrated by stevia compounds like steviol glycosides and aglycone steviol in a wide range of formulations [6].

The antiproliferative effects of steviol, the only colonic metabolite of steviol glycosides, have been observed in various human cancer cell lines, including colorectal and gastric cells [28]. Steviol was also shown to exhibit strong cytotoxic effects in breast cancer cells [29].

The primary mechanism by which stevia metabolites affect cancer cells is through a stop of the cell cycle and the induction of apoptosis in these cells. These chemicals probably also have the ability to inhibit DNA replication enzymes as well [6, 29].

In addition to their direct cytotixic effects on cancer cells, stevia extracts can also fight cancer indirectly by working as antioxidants and controlling the level of lipids. Stevia also includes polyphenols and flavonoids that help defend the cells from oxidative damage, resulting in decreasing the possibility of contributing to tumour formation [6].

Considering the metabolic properties of steviol and its ability to cause cell death in human cancer cells, steviol has the potential to be used as a chemotherapeutic agent for treating cancer in future [28].

Safety of *Stevia rebaudiana*

The use of sweeteners that do not contain calories, including Stevia, continues to raise concerns among consumers about their safety [30]. The approved daily dose of stevia dry extract as defined by food and drug safety organisations is 4 mg/kg body weight [31].

In studies on rats, stevia extracts were shown to have negative effects on fertility and reproductive function in these animals. Rats in the group treated with stevia extracts showed a reduced weight of the testes and seminal vesicles, resulting in a reduced number of sperm stored in them [32]. This point requires more in-depth and up-to-date research.

The safety of stevia consumption has been confirmed by the absence of any adverse effects in the population of Japanese people, in whose culture stevia is frequently used [2]. Furthermore, the majority of research on the effects of stevia on the human body has not revealed any negative side effects [2,33]. Some reports suggest that Stevia extracts may cause allergic

reactions in some people. This is an individual issue and more research on the subject is needed [2,34].

Conclusion

Stevia rebaudiana, a plant native to the mountainous regions of South America, is now cultivated worldwide as a source of sweetener, used widely in the food industry and characterised by its calorie-free character. Stevioside glycosides are the compounds in the plant that are responsible for its sweet taste, which is determined to be up to 300 times stronger than sucrose. Around 30 such compounds are currently known, but the two most important are stevioside and rebaudioside A. Stevia extracts and their specific components have been the subject of a variety of preclinical and clinical research, which have been conducted to investigate their potential medicinal and pharmacological uses. The compounds in stevia have been shown to aid weight loss by providing a sweet taste sensation in foods, while at the same time not consuming additional calories. It was observed that people who used Stevia saw a decrease in their blood pressure measurements. The reason behind this decrease was a direct vasodilatory action on the blood vessels as well as a reduction in the risk factors associated with hypertension. Additionally, the metabolic advantages associated with Stevia extracts also include favourable modifications in blood glucose and insulin levels, positive impacts on the blood lipid profile as well as increased renal function. Studies have investigated the anti-cancer properties of the chemical compounds isolated from stevia. The research produced interesting and promising findings that might indicate potential uses of stevia chemicals in cancer treatment. Further investigation on this issue is required. Stevia's wide range of positive features makes it an appealing candidate for future research into its health-promoting properties.

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Authors do not report any disclosures.

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