Cancer Association of South Africa (CANSA)

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Fact Sheet
on the Sugar Substitute Stevia

Introduction

Stevia is a sweetener and sugar substitute that is becoming very popular following the planned introduction of a tax on sugary drinks in many countries of the world because of the contribution of sugar to obesity.

[Picture Credit: Stevia]

The plant *Stevia rebaudiana* has been used for more than 1 500 years by the Guaraní peoples of South America, who called it ka'a he'ê (‘sweet herb’). The leaves have been used traditionally for hundreds of years in both Brazil and Paraguay to sweeten local teas and medicines, and as a ‘sweet treat’.

The legal status of stevia extracts as food additives and supplements varies from country to country. In the United States of America, stevia was banned in 1991 after early studies found that it might be carcinogenic (cancer causing). Following on additional studies, the United States Food and Drug Administration (FDA) approved some specific glycoside extracts of Stevia for use as food additives in 2008

The European Union approved Stevia additives in 2011, and in Japan, Stevia has been widely used as a sweetener for many years.

[Picture Credit: Stevia Blossoms]

Stevia is a tender perennial plant grown as a vegetatively propagated annual. Parent plants brought indoors through winter provide rootable stems in spring. The seeds of Stevia are said to be very reluctant to sprout. Plants are usually grown from rooted cuttings taken from greenhouse-grown plants.

South Africa is said to be planning extensive cultivation of Stevia as from 2017 in frost-free areas especially in KwaZulu-Natal to supply the food and beverages industry with sufficient quantities of this sugar substitute.

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Stamataki, N., Crooks, B., Ahmed, A. & McLaughlin, J.T. 2020.
"Stevia is a non-nutritive sweetener, providing sweet taste with no calories. This randomised, controlled, open-label 2-parallel arm trial examined the effects of daily stevia consumption on glycaemia in healthy adults. Secondary endpoints included body weight (BW) and energy intake (EI). Healthy participants (*n* = 28; aged 25 ± 5y, body mass index 21.2 ± 1.7 kg/m^2) were randomised into either the stevia group (*n* = 14)-required to consume a stevia extract daily-or to the control group (*n* = 14). At weeks 0 and 12, the glucose and insulin responses to an oral glucose tolerance test were measured; BW and EI were assessed at weeks 0, 6, and 12. There was no significant difference in the glucose or insulin responses. There was a significant main effect of group on BW change (F(1,26) = 5.56, *p* = 0.026), as the stevia group maintained their weight as opposed to the control group (mean weight change at week 12: -0.22 kg, 95%CI [-0.96, 0.51] stevia group, +0.89 kg, 95%CI [0.16, 1.63] control group). The energy intake was significantly decreased between week 0 and 12 in the stevia group (*p* = 0.003), however no change was found in the control group (*p* = 0.973). Although not placebo-controlled, these results suggest that daily stevia consumption does not affect glycaemia in healthy individuals, but could aid in weight maintenance and the moderation of EI."

Stevia
Stevia rebaudiana Bertoni is a sweet and nutrient-rich plant belonging to the *Asteraceae* family. Asteraceae or Compositae (Sunflower family) is an exceedingly large and widespread family of flowering plants. The family currently has 32 913 accepted species names, in 1 911 genera and 13 subfamilies.

Stevia leaves contain steviol glycosides including stevioside, rebaudioside (A to F), steviolbioside, and isosteviol, which are responsible for the plant's sweet taste, and have commercial value all over the world as a sugar substitute in foods, beverages and medicines.

Among the various steviol glycosides, stevioside, rebaudioside A and rebaudioside C are the major metabolites and these compounds are on average 250 to 300 times sweeter than sucrose. Steviol is the final product of Stevia metabolism. The metabolised components essentially leave the body and there is no accumulation. Beyond their value as sweeteners, Stevia and its glycosides possess therapeutic effects against several diseases such as cancer, diabetes mellitus, hypertension, inflammation, cystic fibrosis, obesity and tooth decay. Studies have shown that steviol glycosides found in Stevia are not teratogenic (an agent that can disturb the development of the embryo or foetus), mutagenic (a physical or chemical agent that changes the genetic material, usually DNA, of an organism and thus increases the frequency of mutations above the natural background level) or carcinogenic (cancer causing) and cause no acute and subacute toxicity.
(**Momtazi-Borojeni, *et al*.,** 2016).

Ruiz-Ruiz, J.C., Moguel-Ordoñz, Y.B. & Segura-Campos, M.R. 2017.
The leaves of Stevia rebaudiana Bertoni has nutrients and phytochemicals, which make it an adequate source for the extraction and production of functional food ingredients. Preclinical and clinical studies suggest therapeutic and pharmacological applications for stevia and their extracts because they are not toxic and exhibit several biological activities.

Momtazi-Borojeni, A.A., Esmaeli, S-A., Abdollahi, E. & Sahebkar, A. 2017.

Stevia rebaudiana Bertoni is a sweet and nutrient-rich plant belonging to the Asteraceae family. Stevia leaves contain steviol glycosides including stevioside, rebaudioside (A to F), steviolbioside, and isosteviol, which are responsible for the plant's sweet taste, and have commercial value all over the world as a sugar substitute in foods, beverages and medicines. Among the various steviol glycosides, stevioside, rebaudioside A and rebaudioside C are the major metabolites and these compounds are on average 250-300 times sweeter than sucrose. Steviol is the final product of Stevia metabolism. The metabolized components essentially leave the body and there is no accumulation. Beyond their value as sweeteners, Stevia and its glycosdies possess therapeutic effects against several diseases such as cancer, diabetes mellitus, hypertension, inflammation, cystic fibrosis, obesity and tooth decay. Studies have shown that steviol glycosides found in Stevia are not teratogenic, mutagenic or carcinogenic and cause no acute and subacute toxicity. The present review provides a summary on the biological and pharmacological properties of steviol glycosides that might be relevant for the treatment of human diseases.

Stevia Approved for Use in South Africa

Stevia, the natural alternative to sugar, has been approved for use in South Africa with the promulgation (10 September 2012) of new sweetener regulations (Regulations Relating to the Use of Sweeteners in Foodstuffs).

Regulation R733, Regulations Relating to the Use of Sweeteners in Foodstuffs, allows the use of extracts of S*tevia rebaudiana*, in composition and quantities in line with Codex standards, in food and beverages. Steviol glycosides can be used to a maximum level of 330mg/kg.

Stevia was declared GRAS (generally recognised as safe) in the United States in December 2008 by the United States Food and Drug Administration (FDA), it is believed to have close to 10% of the United States of America sugars and sweeteners market.

Kilojoule-free Stevia and Obesity

It looks like sugar, acts like sugar and tastes a lot like sugar. But stevia is a sweetener with no kilojoules, which is having a major impact on the food industry and some say could help to fight obesity and diabetes.

[Picture Credit: Processed Stevia]

Unlike other sugar substitutes, Stevia is an entirely natural product. Native to South America, it can be traced back thousands of years, to when the people of Paraguay and Brazil used it to sweeten foods.

Sold commercially in Japan for more than 40 years, it is only in recent years that it has been more widely available. But, it is rapidly catching on, with an increase of 400 percent sales in the United States of America between 2008 and 2015. Consumers are said to be drawn to its sugar-like qualities, with zero guilt.

Food scientists continue to explore ways to use stevia-based sweeteners. Proposed uses for high-purity stevia leaf extracts include soft drinks, canned fruit and jams, ice cream and other dairy products, cakes and desserts, and alcoholic beverages. Stevia is a natural-origin sweetener that is increasing the options for reduced sugar and reduced energy foods and beverages. Stevia shows promise as a tool to help lower energy intakes, which may lead to the reduction and prevention of obesity.

The backbone of all steviol glycosides is steviol, to which various glycoside (glucose) groups attach to form the variety of sweet compounds in stevia. Steviol glycosides pass through the upper gastrointestinal tract fully intact. Gut bacteria in the colon hydrolyse steviol glycosides into steviol by snipping off their glucose units. Steviol is then absorbed via the portal vein and primarily metabolised by the liver, forming steviol glucuronide, which is primarily excreted in the urine.

Research shows that there is no accumulation of stevia (or any component or by-product of stevia) in the body and that it passes through the body during metabolism. Energy from fermentation of glucose units (usually assessed as 2 kcal/g) is so low that it is minimal, and so, effectively, stevia can be said to provide zero kilojoules.

High-purity stevia leaf extract is not metabolised, so it provides zero kilojoules.
(**Ashwell**, 2015; IOL).

Stevia and Breast Cancer

Stevioside is a diterpene glycoside found in the leaf of Stevia rebaudiana, a traditional oriental medicinal herb, which has been shown to have various biological and ethno-medicinal activities including antitumour activity. In a study, the researchers investigated the effects of stevioside on the cytotoxicity (cell toxicity), induction of apoptosis (cell death), and the putative (denoting a supposition or inference based on what was commonly believed, reputed, or deemed rather than on a direct evidence) pathways of its action in human breast cancer cells (MCF-7).

For the analysis of apoptotic pathway, measurement of reactive oxygen species (ROS) and assessment of mitochondrial transmembrane potential (MTP) were achieved. The research showed that stevioside was a potent inducer of apoptosis and it conveyed the apoptotic signal via intracellular ROS generation; thereby inducing change in MTP and induction of mitochondrial mediated apoptotic pathway. Taken together, the data indicated that stevioside induced the ROS-mediated mitochondrial permeability transition and resulted in the increased expression of apoptotic proteins such as Bax, Bcl-2 and Caspase-9. Effect of stevioside on stress-related transcription factors like NF-E2-related factor-2 opens up a new vista for further studies. This is a first report on the mechanism of the antibreast cancer (in vitro) activity of stevioside.
(**Paul, *et al.***, 2012).

Stevia and Cancer

"Seventeen steviol derivatives, i.e., 2-18, and 19 isosteviol derivatives, i.e., 19-37, were prepared from a diterpenoid glycoside, stevioside (1). Upon evaluation of the cytotoxic activities of these compounds against leukaemia (HL60), lung (A549), stomach (AZ521), and breast (SK-BR-3) cancer cell lines, nine steviol derivatives, i.e., 5-9 and 11-14, and five isosteviol derivatives, i.e., 28-32, exhibited activities

with single-digit micromolar IC(50) values against one or more cell lines. All of these active compounds possess C(19)-O-acyl group, and among which, ent-kaur-16-ene-13,19-diol 19-O-4',4',4'-trifluorocrotonate (14) exhibited potent cytotoxicities against four cell lines with IC(50) values in the range of 1.2-4.1 μM. Compound 14 induced typical apoptotic cell death in HL60 (leukaemia) cells upon evaluation of the apoptosis-inducing activity by flow-cytometric analysis. These results suggested that acylation of the 19-OH group of kaurane- and beyerane-type diterpenoids might be useful for enhancement of their cytotoxicities with apoptosis-inducing activity."
(**Ukiya, *et al*.,** 2013).

Stevia and Diabetes Mellitus

The prevalence of diabetes is rapidly rising all over the globe at an alarming rate. India shelters the highest number of diabetics and is thus known as the 'Diabetes Capital of the World'. The chemical management of diabetes has side effects and hence this study was undertaken to assess the hypoglycaemic and hypolipidaemic effect of Stevia rebaudiana in patients with type 2 diabetes, non-insulin dependent diabetes mellitus (NIDDM), its nutritional composition and use as a sweetener substitute.

Chemical analysis of dried Stevia leaf powder revealed it to be a nutritious herb with a good iron and fibre content. Intervention trials in diabetics revealed that it significantly lowered fasting and post-prandial blood glucose levels. The serum triglycerides and VLDL-C levels were also significantly reduced.

Hence it can be said that Stevia can safely be used as an anti-diabetic herb, as a sweetener substitute and may help to prevent cardiovascular diseases in patients with long-standing diabetes.
(**Ritu & Nandini**, 2016).

Therapeutic Effects of Stevia

Stevioside, an abundant component of Stevia rebaudiana leaf, has become well-known for its intense sweetness (250 to 300 times sweeter than sucrose) and is used as a non-kilojoule sweetener in several countries. A number of studies have suggested that, beside sweetness, stevioside along with related compounds, which include rebaudioside A (second most abundant component of S. rebaudiana leaf), steviol and isosteviol (metabolic components of stevioside) may also offer therapeutic benefits, as they have anti-hyperglycaemic (anti high blood sugar), anti-hypertensive, anti-inflammatory, anti-tumour, anti-diarrhoeal, diuretic, and immunomodulatory actions.

Other Health Benefits of Stevia

Additional health benefits of Stevia include:

- Herb parts of Stevia are very low in kilojoules. Part by part, its dry leaves possess roughly 40 times more sweetness than sugar. This sweetness quality in stevia is due to several glycoside compounds including stevioside, steviolbioside, rebaudiosides A-E, and dulcoside.
- *Stevioside* is a non-carbohydrate glycoside compound. Hence, it lacks the properties that sucrose and other carbohydrates possess. Stevia extracts, like rebaudioside-A, are found to be 250 to 300

times sweeter than sugar. Besides, being a near-zero kilojoule food ingredient, Stevia extracts have several unique properties such as long shelf life, high temperature tolerance, non-fermentative.

- Further, Stevia plants have many sterols and antioxidant compounds like *triterpenes, flavonoids,* and *tannins*. Some of flavonoid polyphenolic anti-oxidant phyto-chemicals present in Stevia are *kaempferol, quercetin, chlorogenic acid, caffeic acid, isoquercitrin,* and *isosteviol*. Studies found that kaempferol can reduce risk of pancreatic cancer by 23%
- Chlorgenic acid reduces enzymatic conversion of glycogen to glucose in addition to decreasing absorption of glucose in the gut. Thus, it helps reduce blood sugar levels. Laboratory studies also confirm a reduction in blood glucose levels and an increase in the liver concentrations of glucose-6-phosphate, and of glycogen.
- Certain glycosides in Stevia extract have been found to dilate blood vessels, increase sodium excretion, and urine output. In effect, Stevia, at slightly higher doses than as sweetener, can help lower blood pressure.
- Being a non-carbohydrate sweetener, Stevia would not favour the growth of *Streptococcus mutans* bacteria in the mouth which is attributed to be a causative agent of dental caries and tooth cavities. On the other hand, certain compounds in Stevia have been found to inhibit caries causing bacteria in the mouth.
- In addition, being a herb, Stevia contain many vitals minerals and vitamins that are selectively absent in the artificial sweeteners.

Palatnik, A., Moosreiner, A. & Olivier-Van Stichelen, S. 2020.
"In an effort to reduce sugar consumption to prevent diabetes mellitus and cardiovascular diseases, "sugar-free" or "no added sugar" products that substitute sugar with non-nutritive sweeteners (NNSs) (eg, Splenda, Sweet'N Low, and Stevia) have become increasingly popular. The use of these products during pregnancy has also increased, with approximately 30% of pregnant women reporting intentional NNS consumption. In clinical studies with nonpregnant participants and animal models, NNSs were shown to alter gut hormonal secretion, glucose absorption, appetite, kidney function, in vitro insulin secretion, adipogenesis, and microbiome dysbiosis of gut bacteria. In pregnant animal models, NNS consumption has been associated with altered sweet taste preference later in life and metabolic dysregulations in the offspring (eg, elevated body mass index, increased risk of obesity, microbiome dysbiosis, and abnormal liver function tests). Despite the accumulating evidence, no specific guidelines for NNS consumption are available for pregnant women. Furthermore, there are limited clinical studies on the effects of NNS consumption during pregnancy and postpartum and long-term outcomes in the offspring."

Medical Disclaimer

This Fact Sheet is intended to provide general information only and, as such, should not be considered as a substitute for advice, medically or otherwise, covering any specific situation. Users should seek appropriate advice before taking or refraining from taking any action in reliance on any information contained in this Fact Sheet. So far as permissible by law, the Cancer Association of South Africa (CANSA) does not accept any liability to any person (or his/her dependants/estate/heirs) relating to the use of any information contained in this Fact Sheet.

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