



STEVIA DERIVATIVE AND ITS POTENTIAL USES IN DIABETIC-DIRECTED FOODS. REVIEW

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ABSTRACT

Diabetes has been contextualized as pandemic, but market supplying their food does not seem to grow in parallel with the problem. There are many substances on the market that will be useful as ingredients to produce foods for diabetic consumers, focusing on the sweeteners, which can be used for food processing with low calories, and low glycemic index. Natural or synthetic sweeteners have received renewed attention with the toxicological acceptance and commercial development. However, many of them have little prospect of becoming commercial ingredients because, they do not meet some of the key criteria for commercial success. The stevia plant and its products have potential for commercial uses as sweetener or therapeutic. Beside the two known main molecules that are intense sweeteners that are occurring in stevia (stevioside and rebaudioside A), the plant contain other compounds of nutritional importance for therapeutic uses. The acceptable daily intake or ADI of 4 mg/kg bw/day to steviol glycosides have been regulated to glycosides of stevia. Moreover, there exists production of stevia worldwide, with established procedures for isolation and purification of its glycosides and one of them has been approved for food use. Then, a solid market of diabetes-oriented products must emerge, for satisfying demands from these consumers.

Keywords: Diabetes, Foods, Special regimes, Stevia, Rebaudioside A.

1. INTRODUCTION

According to WHO (OMS) [1] Diabetes has been contextualized as pandemic, and they have reported that Diabetic population will continue increasing to reaching quite high levels [2]. On the other hands, there is few processed food for diabetics at the shelves of the markets, and the increase of this population will also increase their need for food. Apparently the market supply of food for diabetic consumers, that this is in fact controlled by the diet, does not seem to grow in parallel with the problem, which shall induce to an increment levels of the disease. Then, a solid

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market for processed products is emerging, in order to meet the requirements of these consumers, and that in turn must fill properties as but these food must be autochthonous, versatile, easy to buy, and cheap.

There are many substances on the market, which will be useful as ingredients to produce foods for diabetic consumers, focusing on the sweeteners, which can be used for food processing with low calories, and low glycemic index. However, his selection in the context of food production and formulation must be carefully evaluated for their response during processing and in the body physiological of the consumer. These foods could serve not only for diabetics, but also to satisfy requirements of other consumers who suffer from diseases controlled by the diet or simply want to consume low calorie foods.

Our ancestors would have used their sense of taste to identify nutritious food items. The risks of making poor food selections when foraging not only entail wasted energy and metabolic harm from eating foods of low nutrient and energy content, but also the harmful and potentially lethal ingestion of toxins. They have learned consequences of ingested foods that have subsequently guided our future food choices. The evolved taste abilities of humans are still useful for the one billion humans living with very low food security by helping them identify nutrients. But for those who have easy access to tasty, energy-dense foods our sensitivities for sugary, salty and fatty foods have also helped cause over nutrition-related diseases, such as obesity and diabetes [3]. The innate sweet taste preference increase the pleasure of eating, therefore the added sugars have received considerable attention due to their association with weight gain. Higher intake of added sugars is associated with higher energy intake and lower diet quality, which can increase the risk for obesity, prediabetes, type 2 diabetes, and cardiovascular disease. [2, 4, 5].

At this context, sweeteners can be grouped as nutritive (NS) and nonnutritive (NNS). Sucrose (table sugar) is present naturally in a number of foods and is one of the most common natural NS added to the human diet. Adverse health effects associated with sucrose intake that have been proposed, include facilitation of excess caloric intake, excess weight gain, dilutional effects of essential nutrients, and increased risk for dental caries, type 2 diabetes, and cardiovascular diseases [4, 6-12]. By consensus, the sucrose was completely excluded from the diet or meal plan diabetics, and substituting it by alternative sweeteners, due that the increased sugar consumption may adversely affect glycemic control in patients with diabetes [13].

NNS are sugar substitutes, which are up to several hundreds of times sweeter than sucrose. They are also can be named as low calorie sweeteners (LCSs), and they are added to many foods and beverages, but their impact on beverages is potentially the most significant as they can reduce the energy content to zero, while maintaining palatability [14]. Seven NNS have been approved for use in the United States: acesulfame K, aspartame, Luo Han Guo fruit extract, neotame, saccharin, stevia, and sucralose. They have different functional properties that may affect

perceived taste or use in different food applications. All NNS approved for use in the United States are determined to be safe. [4, 15].

However, even after decades of scientific research demonstrating the safety of artificial sweeteners, some still remains unconvincing, main reason for searching for natural sweetener that can pass all tests of toxicity [10, 16] and many of them are not challenged, because they are unnatural or because they are less sweet, laxative [17] do not caramelize, expensive or leave an aftertaste [18, 19].

The plant of *Stevia rebaudiana* Bertoni; which produce around 30 steviol glycosides that have sweetener role, but the best known molecules from it, are the stevioside and rebaudioside A [19-24]. The goal of this review was to do a compilation of scientific and commercial literature that provides information in regards to the concerns about the food for diabetics and the use of by products from stevia in the formulation, production and commercialization of foods for diabetic consumers.

2. SWEETENERS: IMPORTANCE, DEFINITION, TYPES, REQUIREMENTS, SAFETY

The desirable taste for sugar is innate [25] related to the evolutionary survival mechanism [3] consequently consumers have psychological selective perception of the sweet taste, and it cannot be eliminated at all from the sweet food without bring a rejecting of it. On the other hand, its consumption is providing quick energy, and a concentrated source of calories. However, this benefit has its downside, because consuming too many calories, regardless of the source, contributes to obesity, and sugar is also a major contributor to tooth decay.

It is the position of the Academy of Nutrition and Dietetics [4] that consumers can safely enjoy a range of nutritive sweeteners and nonnutritive sweeteners (NNS) when consumed within an eating plan that is guided by current federal nutrition recommendations, such as the Dietary Guidelines for Americans and the Dietary Reference Intakes, as well as individual health goals and personal preference. Then, as a postulate, to eat sugar does not cause obesity, diabetes or even heart disease. But, the most common type of diabetes occurs in overweight adults, and among the primary risk factors for heart disease is the obesity. There is a solution to improve the problem above mentioned in regards to the sugar consumption and health of consumers and is the use of sweetener that do not contribute to the energy intake, because they are not absorbed by body. In this context the sweeteners from long time ago have been an important part of the global food, and beverage industry. They also act as seasonings for fresh vegetables, canned meat products, and seafood. Seasoning action was manifested as enhancement of total flavor, blending of flavor notes, replacement or intensification of sweetness, reductions of bitterness, sourness, and saltiness, and control of flavor factors of rawness [26].

With diverse sources and uses, sweeteners require a wide range of process technologies to manufacture it. North America has the highest demand accounting for over 60% of the total. Europe is the fastest growing region for the market followed by Asia-Pacific [27].

A sweetener is a substance that sweetens, as sugar or a low-calorie sugar substitute. A sugar substitute is a food additive that increases the effect of sugar in taste, usually with less energy. Then, the sugar and sugar substitute are sweeteners *per se*. Sweeteners could be classified as natural, nutritive, and intense. Two types of intense sweeteners are available: natural sweeteners of plant origin and artificial or synthetic sweeteners. Those that are not natural are, in general, called *artificial sweeteners*. The natural sweeteners include perillaldehyde, stevioside, rebaudioside, glycyrrhizin, osladin, thaumatococin, hennamycin, monellin. The compound miraculin, although not sweet, has the property of modifying the taste of sour food into a delightfully sweet taste. The artificial sweeteners currently in use are saccharin, aspartame, and acesulfame K, sucralose [28].

The use of sugar substitutes have progressively increased over the past three decades, to permit too many patients suffering mainly of obesity and/or diabetes to restore a certain level of food palatability [29]. Sugar-containing foods are traditionally strongly restricted in the diabetic diet despite some sugars such as sucrose or fructose induces no more or less hyperglycemia, than the white bread. While the specific taste is an important component of food palatability, several sugar substitutes were used by diabetic patients with the aim to maintain a high palatability food and to better control their weight. Some bulk sweeteners such as maltitol are involved in “sugar free” manufactured food (chocolate, jelly, candies). Overall, polyol-based foods have a lower glycemic index and a low cariogenic potential, but provided roughly the same amount of energy as the food of reference. These “sugar free” products present no significant advantages and should be weakly recommended in overweight diabetic patients [30].

3. GLYCOSIDES AS SWEETENER FROM STEVIA PLANTS

Natural sugar substitutes have received renewed attention with the toxicological acceptance and commercial development. Excluding the simple sugars and polyols, there are 100 or more sweet compounds found in nature. However, the majority of these have little prospect of becoming commercial ingredients because they fail to meet one or more key criteria for commercial success [21].

Among the natural plants having medicinal and commercial importance as sweetener is found Stevia. *Stevia rebaudiana* Bertoni an herbaceous plant from the Asteraceae (compositae) family is a small perennial shrub native to Paraguay, Brazil, and Argentina. Indians of the Guarani tribe appear to have used the leaves as a sweetener since pre-Columbian times, with the name of Ka'a He'e, but it was not until 1887 that Moisés Santiago Bertoni, an European scientist have “discovered” the plant for the "new world" [20, 31]. The Guarani have used the leaf mainly as a sweetener particularly in their green tea, branded as mate. Later on in 1931, some French

chemists extracted the stevioside, the main component in the form of an extremely sweet, white and crystalline compound [31]. Later the final structure elucidation of the glycosides was done by Mosettig, et al. [32]. The leaves of *Stevia* accumulate at least eight steviol glycosides (SGs), the concentrations of which vary quite widely depending on the genotype and production environment [33]. The metabolism of stevioside leads to the formation of steviol. Steviol glycosides are tetracyclic diterpenes derived from the same *kaurenoid* precursor as gibberellic acid and their intense sweetness has made them of significant scientific, and of commercial interest as sweeteners [33]. Thirty of these compounds have been reported to date among them, the best known molecules are the stevioside and rebaudioside A (Figure 1).

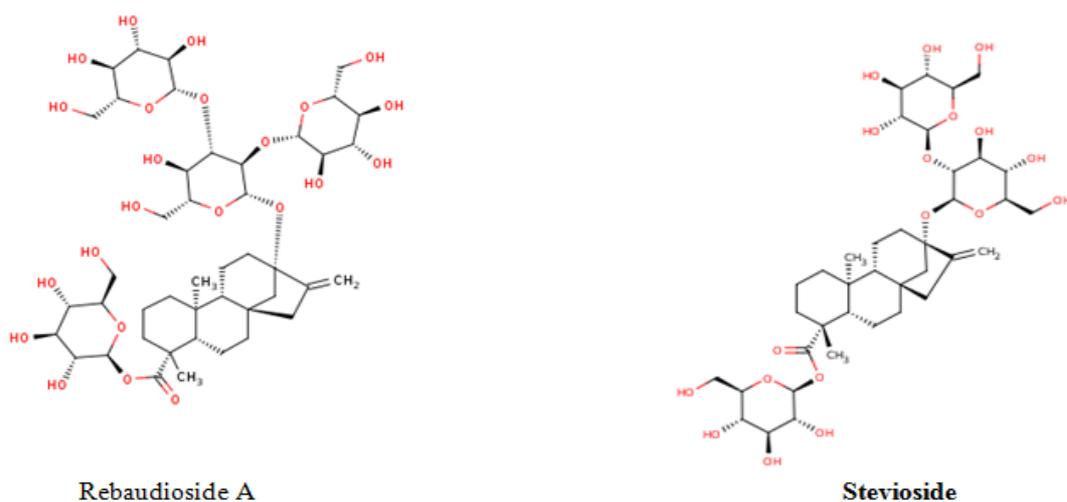


Figura-1. Chemical structure of glycosides found in *Stevia rebaudiana*

Source: METLIN Metabolite Database

Stevioside is normally found in greater quantities than the other compounds, between 4% and 20% weight of the dried leaves, and it is known that stevioside is 143 times sweeter than sucrose on a weight basis, but rebaudioside A is 242 times sweeter [23]. The steviol glycosides consumption is permitted in many countries around the world, even FAO/WHO in 2008 have concluded that they are safe for use as general purpose sweeteners [8, 20] however at high concentrations, they have a bitter aftertaste. The taste quality of rebaudioside A is better, than those of the stevioside [34] and it has been shown that the stevioside is which has the bitter aftertaste, so it must be separated from the rebaudioside A, to obtain a pure sweet product. [18, 24].

Rebiana is the common name for high-purity rebaudioside A, a natural non-calorie sweetener 200–300 times more potent than sucrose isolated from the stevia leaf. It provides zero calories and has a clean, sweet taste with no significant undesirable taste characteristics. Several investigations have demonstrated the stability of Stevioside and rebaudioside A under normal temperature, pH and sunlight conditions, [19] which makes them functional in a wide array of

beverages and foods and can be blended with other non-calorie or carbohydrate sweeteners. They are stable under dry conditions, and have much better stability than aspartame or neotame in aqueous food systems [35]. Rebiana is used as the primary sweetness in the Truvia brand [25, 26]. 3.5 g of rebiana provides the same sweetness as two teaspoons of sugar, which produced to food-grade specifications and according to Good Manufacturing Practices is safe for human consumption under its intended conditions of use as a general purpose sweetener [36-38]. All the above mentioned approach leads us to suggest the use of steviol glycoside for diabetic consumption. Maki 2008b have pointed out that chronic use of 1000 mg rebaudioside A does not alter glucose homeostasis or blood pressure in individuals with type 2 diabetes mellitus [39].

4. CHEMICAL COMPOSITION OF STEVIA

It has been reported [40, 41] that stevia is nutrient-rich, containing substantial amounts of protein, calcium, phosphorous, folic acid, vitamin C and all of the indispensable amino acids with the exception of tryptophan. González, et al. [18] have reported the composition of Stevia cultivar grown at Venezuela, Colombia and France. The crude protein, crude fat, and ash contents (dm) have shown ranges varying from 9.9-11.3; 1.2-1.8; and 6.3-7.6% respectively. Also the authors have reported a polyphenolic content of 50.5-62.6 as mg gallic acid/g sample. Other research works have reported the chemical composition of essential oils and fatty acids of *Stevia rebaudiana Bertoni* leaves grown in Bangladesh [42, 43]. They have identified 62 compounds with the major compounds the α -cadinol, carvacrol caryophyllene oxide, (-)-spathulenol and β -guaiene, α -pinene, limonene, isopinocarveol, ibuprofen, quercetin dihydrate, protocatechuic acid and quercetin glucosyl. The fatty acid analysis by GLC showed palmitic acid (86.50%) as the most abundant fatty acid in the leaves of *Stevia Rebaudiana Bertoni*. In regards to its glycosides contents, besides some authors [18, 23, 33, 35] have reported 20-40, and 20-70, mg/g sample of stevioside and rebaudioside A, respectively in varieties of stevia grown in Venezuela, Colombia and France. The authors have also shown that the variety Morita II (Venezuelan and Colombian cultivars) have the highest proportion of rebaudioside A, as compared with its proportion of stevioside. On the other hand, Erkucuk, et al. [44] using supercritical fluid extraction (SFE) in stevia leaves, have reported a inverse yields of 36.66 mg/g stevioside and 17.79 mg/g rebaudioside A. Total glycosides composition were close to those obtained using conventional water extraction (64.49 mg/g) and a little higher than ethanol extraction (48.60 mg/g) demonstrating challenges for industrial scale application of SFE. Stevia have also been associated with bioactive compound content and antioxidant activity. Kim, et al. [45] results, showed that the leaf and callus extracts from stevia contained high radical scavenging activities against free radicals of hydroxyl and superoxide anion. The authors also report that folic acid (52.18 mg/100 g) was a major component, followed by vitamin C, and that the total phenolic and flavonoid contents were found to be 130.76 μ g catechin and 15.64 μ g quercetin for leaves and

43.99 µg catechin and 1.57 µg quercetin for cellus at mg of water extracts, respectively. Pyrogallol was the major material among the phenolic compounds in both leaf and callus extracts.

5. STUDIES ON SAFE CONSUMPTION OF THE STEVIA AND ITS USE BY CONSUMERS WITH REGIMEN ESPECIAL FEEDING

At the first time there was some discrepancy for consumption safety of the stevia, [Geuns, et al. \[46\]](#) have pointed out that stevia and stevioside have no effect on mammalian reproduction or fertility, and they are safe for use as sweeteners and acceptable for both diabetic and phenylketonuria patients. Posterior research performed by [Geuns, et al. \[46\]](#) have shown that steviol or related metabolites do not accumulate in the human body, and that at least in healthy human subjects pure stevioside taken at a dose of 750 mg/day had no effect on either blood pressure or insulin levels. Following those reviews, clinical evidence emerged that suggested stevioside can be used by diabetics and hypertensive patients and they may also offer therapeutic benefits, as they have anti-hyperglycemic, anti-hypertensive, anti-inflammatory, anti-tumor, anti-diarrheal, diuretic, and immuno-modulatory actions [\[38, 47-54\]](#). Stevia extracts, besides having therapeutic properties, contain a high level of sweetening compounds, known as steviol glycosides, which are thought to possess antioxidant, antimicrobial and antifungal activity. Stevioside and rebaudioside A are the main sweetening compounds of interest. Moreover the glycoside from stevia are thermostable even at temperatures of up to 200 °C, changes of pHs, and fluorescence, even during long storage periods, making them suitable for use in cooked foods [\[19, 41, 55, 56\]](#). As [González, et al. \[19\]](#) have reported stevioside and rebaudioside A have multiple advantages as dietary supplements. They are non-metabolizable (non-caloric) [\[57-59\]](#) non acidogenic, and do not cause dental caries [\[60\]](#). Another notable benefit is that the consumption of both steviol glycosides is safe for human health and there are no restrictions on their use by people suffering from diabetes [\[46, 48-50, 52, 53\]](#). In fact, high doses of stevioside (750–1500 mg per day) have been used with favorable results for the treatment of hypertension and type 2 diabetes [\[48\]](#). The therapeutic value of stevioside consists of the fact that it substitutes sugar whilst at the same time stimulating the secretion of insulin in the pancreas during the treatment of diabetes and other carbohydrate metabolism disorders [\[44, 46\]](#).

6. REGULATIONS

Current findings have documented that sweeteners are safe for consumption in a normal diet [\[4\]](#). These conclusions are consistent with recommendations from both the American Diabetes Association and the Academy for Nutrition and dietetics [\[61\]](#). On the other hand, [Cook, et al. \[14\]](#) have postulated that the evidence reviewed suggests that low calories sweeteners are an appropriate tool for weight management with few, if any, discernible negative effects and some potential benefits. However, even after decades of scientific research demonstrating the safety of

artificial sweeteners, some still remains unconvincing, main reason for searching for natural sweetener that can pass all tests of toxicity. In regards to stevia many government authorities around the world have concluded that this intense sweetener are safe for the general population, including children, people with diabetes, and women who are pregnant or nursing. Stevia sweeteners are permitted for use in many countries, including the European Union, Japan, China, Australia, Brazil, and the U.S. In the U.S., stevia sweeteners are GRAS, based on published research and expert opinions that have been reviewed by the FDA [62]. In addition, the FAO/WHO (Food and Agriculture Organization/World Health Organization) Joint Expert Committee on Food Additives (JECFA) completed a review of all available scientific data on stevia sweeteners in June 2008 and concluded that they are safe for use as general purpose sweeteners (See sidebar on Global Safety Recognition of Stevia sweeteners) [63]. In addition, to being an approved sweetener in many countries, the World Health Organization has now recognized that stevioside is not genotoxic and have assigned a temporary acceptable daily intake for steviol glycosides of 0–2 mg/kg body weight [64]. Since, the steviol glycosides have been permitted in numerous countries [65] they can be used as ingredients or dietary supplement in food for special regimes. Several reports [19] have also shown that daily oral consumption at a reasonable level of stevioside (5 mg•kg of body weight) is safe and is also guaranteed to be neither carcinogenic nor mutagenic. According to Parent-Massin in 2011 Parent-Massin [66] assessing by European Food Safety Authority (EFSA) of the new natural sweetener, steviol extracts that is obtained from stevia plant, have showed that no adverse effects can be induced by these extracts as well as on genotoxicity, cancerogenicity, long term exposure, fertility and development. EFSA allocated an Acceptable daily intake or ADI of 4 mg/kg bw/day to steviol glycosides.

7. DIABETES CONSIDERATION

According to WHO (OMS) [1] Diabetes has been contextualized as pandemic and it is often considered a "disease of civilization". Indeed, it has been set the "World Diabetes Day" because it is very serious and increasingly brings to the state, the family and the patient high costs of purchasing power in treatment. WHO in 2013 WHO (OMS) [1] have reports that 347 million people worldwide suffer from diabetes Type 2. In an interview with the Bulletin, it has been reported that Type 2 diabetes, which accounts for over 90% of cases of diabetes, is a product of "modern technology", and it will continue increasing, and it shows a wide range of variation in prevalence around the world, and it is expected to affect around 600 millions of people by the year 2035 [67-72]. It is why, the IDF [73] in its introduction reports several keys messages as follows:

- **382 million** people have diabetes; by 2035 this will rise to **592 million**
- The number of people with type 2 **diabetes is increasing** in every country
- **80%** of people with diabetes live in **low- and middle-income countries**

- The **greatest number** of people with diabetes are between **40 and 59** years of age
- **175 million** people with diabetes are **undiagnosed**
- Diabetes caused **5.1 million deaths** in 2013; Every six seconds a person dies from diabetes
- Diabetes caused at least **USD 548 billion dollars** in health expenditure in 2013 – **11% of total spending** on adults
- More than **79,000 children** developed **type 1 diabetes** in 2013
- More than **21 million live births** were affected by diabetes during pregnancy in 2013.

This Federation also report, the Diabetes prevalence in the regions:

- In **Africa**, 76% of deaths due to diabetes are in people under the age of 60
- **Europe** has the highest prevalence of type 1 diabetes in children
- In the **Middle East and North Africa**, 1 in 10 adults has diabetes
- More was spent on healthcare for diabetes in **North America and the Caribbean** than in any other region
- In **South and Central America**, the number of people with diabetes will increase by 60% by 2035
- In **South-East Asia**, almost half of people with diabetes are undiagnosed
- In the **Western Pacific**, 138 million adults have diabetes—the largest number of any region.

While, the type 1 diabetes (T1DM) is associated with the complex insulin regimens [74] in the type 2 diabetes (T2DM), the improvement in blood glucose control is based primarily on behavioral changes (reduced calorie and carbohydrate intakes, increased physical activity) [75].

Consumption of sugar-sweetened food may be one of the dietary causes of metabolic disorders, such as obesity. Since the World Health Organization (WHO) in 1997 **WHO World Health Report** [76] have declared obesity as a major public health problem, diabetic prevalence has been documented during the last two decades [77-85]. Therefore, substituting sugar with low calorie sweeteners may be an efficacious weight management strategy. In view of these postulates previously discussed, strategies involving the use of steviol glycosides in the development of food for the consumption of diabetics must be applied, and these foods should be validated through large-scale population trials, considering validated surrogate end points to evaluate its effect in prevention of chronic diseases such as type 2 *Diabetes Mellitus*.

8. STEVIA PROCESSING

Several derivatives products from stevia plant are today commercialized. They include the dry leaf, leaf extract (from highest quality leaves extracted with cool, purified water), purified dry extract, blend of stevia with other sweeteners or cane sugar, and rebaudioside A [66, 86, 87].

In a patent **Parent-Massin** [66] have pointed out that the process for the production of steviosides from *Stevia rebaudiana* Bertoni includes extraction of comminuted plant material by

directly injecting steam into the extractor followed by filtration to get aqueous extract and alkali treatment to remove unwanted compounds in the form of precipitate. The treated aqueous extract was filtered and the filtrate was first treated with gel or macroporous strong acid cation exchange resin and then with gel or macroporous weak base anion exchange resin. The aqueous eluant containing steviosides was concentrated to obtain purified steviosides [88]. The rebaudioside A is obtained in two stages. First, steviol glycosides are extracted from the leaves with water and the extract dried. In the second stage, further purification via alcohol/water crystallization yields pure rebiana [25].

Since, the conventional methods of isolation of steviosides involve long extraction and purification procedures; therefore optimization of product yields is a challenging problem. The application of tailor-made membranes in a multi-stage process for the purification of sweeteners from *Stevia rebaudiana* was recently investigated by Vanneste, et al. [89] and Rao, et al. [90]. The studies, establishes a new process of extraction of steviosides in which the dry treated leaves were grounded, defatted, and extracted through pressurized hot water extractor (PHWE), followed by purification and concentration of the sweet glycosides through ultra (UF) and nano (NF) membrane filtration in obtaining high (98.2%) purity steviosides. The authors have concluded that this process should be seen as a useful pretreatment for other purification steps, with for instance crystallization. Other patent [91] and researching on the extraction, separation and modification have been performed by using novels technologies; such as, microwave-assisted extraction [92] Ultrasonic-assisted extraction [93] enzymes treatments [91, 93] and high-speed counter-current chromatography [94].

9. USING STEVIA: CONTROVERSY

Some research that today have not been yet well confirmed, are promoting three ideas: 1.- that due to that intense sweeteners, that by itself do not induce to significant metabolic effects, but they stimulate the sweet sensorial perceptor could induce early insulin liberation, called cephalic phase, increasing the hunger sensation and the subsequent food intake, thus promoting weight gain. 2. Its anorexigenic properties. 3. - Its direct stimulation of of incretins secretion [95]. Other Critically examination of evidences for effects of non caloric of the nonnutritive sweeteners on compensatory appetite and food intake concluded, that the available evidence; either refuted or was insufficient to refute or support each of these potential mechanisms or hypotheses for nonnutritive sweeteners increasing appetite, hunger, or energy intake [96]. Indeed, studies of Anton, et al. [97] in regards to stevia effects on the body metabolism have shown that stevia preloads, significantly has reduced postprandial glucose levels as compared to sucrose preloads ($p < 0.01$), and postprandial insulin levels compared to both aspartame and sucrose preloads ($p < 0.05$). When consuming stevia and aspartame preloads, participants did not compensate by eating more at either their lunch or dinner meal and reported similar levels of

satiety, compared to when they consumed the higher calorie sucrose preload. Although leaves or crude stevia extracts are not absolutely approved by the FDA, its refined products are in the inventory Generally Regarded as Safe (GRAS) notices of FDA [62]. The rebaudioside A is now considered on the trade market and is supplanting other sweeteners in the food industry.

As Parent-Massin [66] previously established the steviol extracts obtained from stevia have potential to be used as a sweetener or flavoring ingredient in the formulation of foods for special regimens, due to there are world production, established procedure and industrial patent from extraction and purification, and no legal objection for its use.

10. STEVIA AND THEIR POTENTIAL USES DIABETIC-DIRECTED PROCESSED FOOD

There exist in the market only a limited diabetic-directed processed foods, those available generally are non autochthonous, versatile, and expensive. Several researching have been done for to use the stevia refined products, Narayanan, et al. [98] in sensorial studies of the appropriated concentration of stevia used for yogurt, underline the importance of careful selection of stevia type and concentration as well as optimizing yogurt cultures and fermentation conditions before product launch. Other authors [36, 99, 100] have shown that stevioside and rebaudioside A isolated from stevia leaves are sweetening compounds of interest for promoting healthy foods. On the other hand, stevia with 97% rebaudioside A did not show off-flavor and presented similar acceptance and sensory profile in relation to control of mango nectar [101] formulated chocolates containing stevia leaves and peppermint exhibited the best sensory properties (especially with regard to mouth feel, sweetness and herbal aroma), as well as the highest polyphenolic content and antioxidant capacity [102]. Melo, et al. [103] studies have shown the crucial attributes which determine consumer acceptability of chocolate using stevia. They have found the sweet aroma, melting rate, and sweetness as attributes of acceptance; whereas the bitterness, bitter aftertaste, adherence, and sandiness were drivers of disliking. In order to analyze the ideal and relative sweetness of a prebiotic chocolate milk dessert, Morais, et al. [104] have studied the of sweetness level in this product with different types of artificial and natural sweeteners. They have concluded that estevia was the lower with sweetening power as compared to neotame, saccharose, sucralose and aspartame.

Lothrop [105] had conducted a research to determine the physicochemical and sensory effects of replacing a mixture of rebaudioside-A and erythritol for sucrose at varying levels (0, 25, 50, 75 and 100%) in chiffon cake. The author has concluded that functional properties specific gravity, cake volume) some chemical (moisture content) and physical properties (crumb and crust color) were not affected by the sucrose substitution. However, there are impacts on the water activity of the chiffon cake, and nutrition analysis showed a decrease in both calories and sugars as the sucrose replacement level increased. All other nutrient levels remained constant among

treatments. These findings suggest a chiffon cake formulated with 50% sucrose and 50% rebaudioside-A and erythritol results in a product with high overall consumer acceptability and 20% fewer calories than one formulated with 100% sucrose. Kienle in 2014, of Universität Hohenheim [106] have recommend stevia natural sweetener for use in different food stuff, providing different recipes and concentrations of the sweetener. Prakash, et al. [107] have studied the degradation of rebaudioside A under acidic conditions, they author have concluded that rebaudioside A yielded six minor degradation compounds.

At industrial level there several products strictly directed to diabetic consumers, such as: dessert, cookies, jam, and the sweeteners, but the most common use of the non caloric sweeteners in the carbonated beverages Mattes and Popkin [96]. ChromaDex [108] is a company that offers a large number presentation of stevia and its derivatives for use in different food products. Trini SA [109] in Argentina commercialize a group of product for diabetic with stevia as sweetener, among they there are a powder for preparing diet ice with stevia, in three flavors: Chocolate, Strawberry and Vanilla, which provide in average 31.7 Kcal /133 KJ (unprepared product), and Papaphilippou & Patisserie Panayiotis Ice Cream LTD [110] is sold the fat free ice cream with Paraguayan stevia. Truvia Company offer Truvia® sweetener and baking blends products and also provide its product to their partner to produce a gamma of products such beverages (sodas, vitaminwater, juices, tea), yogurt, bars and iSKream. The Truvia® natural sweetener commercialized in USA [111] is safe and recommended for use by people with diabetes, because in the label it is declared stevia leaf extract and erythritol. Truvia® stevia leaf extract and erythritol have both been studied in short and long term clinical studies to evaluate safety for use by people with diabetes. Truvia® stevia leaf extract and erythritol have both been studied in short and long term clinical studies to evaluate safety for use by people with diabetes. This Truvia® natural sweetener has little or no effect on blood glucose or insulin. However, the Truvia® sweetener commercialized in Venezuela contains sucrose (azúcar morena), and then it cannot be recommended for diabetic uses.

11. CONCLUSION

The evolved taste abilities of humans are useful for identify nutrients, but those who have easy access to tasty, energy-dense foods our sensitivities for sugary, salty and fatty foods have also helped cause over nutrition-related diseases, such as obesity and diabetes. This is one of the causes that affect the increased diabetes population. Indeed, Diabetes has been contextualized as pandemic, and it will continue increasing next coming years. The diabetes is controllable or reduced by diet, and by consensus it has been attributed an adverse effects to the sucrose intake. The role of sweeteners in this context is extremely important, but some on them despite they are approved are questioned by consumers, and stevia comes to be a solution. Moreover, the glycosides from stevia can be used other patients because offer other important therapeutic

benefits. There exists production of stevia worldwide, with established procedures for isolation and purification of its glycosides and one of them has been approved for food use. Then, a solid market for processed products must emerge, in order to meet the requirements of these consumers, for reducing or controlling the disease.

REFERENCES

- [1] WHO (OMS), "Organización Mundial de la Salud. Diabetes. Día Mundial de la Diabetes. E. Available <http://who.int/diabetes/es/index.html> [Accessed 6/12/14]," 2013.
- [2] C. A. Johnston, B. Stevens, and J. P. Foreyt, "The role of the low-calories sweeteners in diabetes," *US Endocrinology*, vol. 9, pp. 13-21, 2013.
- [3] P. A. S. Breslin, "An evolutionary perspective on food and human taste," *Current Biology*, vol. 23, pp. R409-R418, 2013.
- [4] ADA American Dietetic Association, "Position of the academy of nutrition and dietetics: Use of nutritive and nonnutritive sweeteners," *Journal of the American Dietetic Association*, vol. 1112, pp. 739-758, 2012.
- [5] A. Sylvetsky, K. I. Rother, and R. Brown, "Artificial sweetener use among children: Epidemiology, recommendations, metabolic outcomes, and future directions," *Pediatric Clinics of North America*, vol. 58, pp. 1467-1480, 2011.
- [6] A. M. Coulston, C. B. Hollenbeck, C. C. Donner, R. Williams, Y. A. Chiou, and G. M. M. Reaven, "Metabolic effects of added dietary sucrose in individuals with noninsulin dependent diabetes mellitus NIDDM," *Metabolism*, vol. 34, pp. 962-966, 1985.
- [7] A. M. Coulston, C. B. Hollenbeck, A. L. M. Swislocki, Y. D. I. Chen, and G. M. Reaven, "Deleterious metabolic effects of high-carbohydrate, sucrose-containing diets in patients with non-insulin-dependent diabetes mellitus," *American Journal of Medicine*, vol. 82, pp. 213-220, 1987.
- [8] C. Fitch and K. S. Keim, "Position of the academy of nutrition and dietetics: Use of nutritive and nonnutritive sweeteners," *Journal of the Academic of Nutrition and Dietetics*, vol. 112, pp. 739-758, 2012.
- [9] B. Caballero, *Sucrose: Dietary sucrose and disease. Encyclopedia of human nutrition*, 3rd ed. Amsterdam: Elsevier, 2013.
- [10] P. Shankar, S. Ahuja, and K. Sriram, "Non-nutritive sweeteners: Review and update," *Nutrition*, vol. 29, p. 12931299, 2013.
- [11] D. Michael, M. D. Kendig, S. Candy, C. S. Lin, J. E. Beilharz, K. B. Rooney, and R. A. Boakes, "Maltodextrin can produce similar metabolic and cognitive effects to those of sucrose in the rat," *Appetite*, vol. 77, pp. 1-12, 2014.
- [12] G. A. Mohamed, S. R. M. Ibrahim, E. S. Elkhayat, and R. S. El Dine, "Natural anti-obesity agents," *Bulletin of Faculty of Pharmacy, Cairo University*, vol. 53, pp. 269-284, 2014.

- [13] J. H. Yu, M. S. Shin, J. R. Lee, J. H. Choi, E. H. Koh, W. J. Lee, J. Y. Park, and M. S. Kim, "Decreased sucrose preference in patients with type 2 diabetes mellitus," *Diabetes Research and Clinical Practice*, vol. 104, pp. 214-219, 2014.
- [14] D. Cook, D. Haslam, and C. Weir, "The role of low calorie sweeteners in weight management: Evidence and practicalities," *Supplement to Diabetes Digest*, vol. 12, pp. 1-4, 2013.
- [15] M. O'Mullane, B. Fields, and G. G. Stanley, "Food additives: Sweeteners," *Encyclopedia of Food Safety*, vol. 2, pp. 477-484, 2014.
- [16] K. Rosenman, "Benefits of saccharin: A review," *Environmental Research*, vol. 15, pp. 70-81. M. Sánchez, M. Luna, Y. Villarreal, Y. Zerpa and A. Bermúdez. Manejo de la hiperglucemia en el paciente hospitalizado con Diabetes Mellitus. Guía práctica del servicio de endocrinología del Instituto Autónomo Hospital Universitario de Los Andes. Revista Venezolana de Endocrinología y Metabolismo, vol. 12 pp. 34-40, 2014, 1978.
- [17] T. Oku and M. Okazaki, "Laxative threshold of sugar alcohol erythritol in human subjects," *Nutrition Research*, vol. 16, pp. 577-589, 1996.
- [18] C. González, M. S. Tapia, E. Pérez, M. Dornier, and G. Morel, "Caracterización de cultivares de stevia rebaudiana bertonii de diferentes procedencias," *Bio. Agro.*, vol. 26, pp. 79-88, 2014a.
- [19] C. González, M. Tapia, E. Pérez, D. Pallet, and M. Dornier, "Main properties of steviol glycosides and their potential in the food industry: A review," *Fruits*, vol. 69, pp. 127-141, 2014b.
- [20] A. D. Kinghorn, Y. W. Chin, L. Pan, and Z. Jia, "Natural products as sweeteners and sweetness modifiers," *Comprehensive Natural Products II*, vol. 3, pp. 269-315, 2010.
- [21] J. C. Fry, *Natural low-calorie sweeteners. Natural food additives, ingredients and flavourings*, Ed. D. Baine and R. Cambridge, UK: Seal Woodhed Pub, 2012.
- [22] D. D. Kinghorn, *Stevia medicinal and aromatic plant / industrial profile*. UK: Taylor and Francis, Co, 2002.
- [23] R. Mehrotra, D. Singh, and A. Tiwari, "Steviol glycosides and their use in food processing: A review," *Innovare Journal of Food Science*, vol. 2, pp. 7-13, 2014.
- [24] A. E. Abou-Arab, A. A. Abou-Arband, and M. F. Abu-Salem, "Physico-chemical assessment of natural sweeteners steviol glycosides produced from stevia rebaudiana bertonii plant," *African Journal of Food Science*, vol. 4, pp. 269- 281, 2010.
- [25] G. K. Beauchampa and J. A. Mennella, "Early flavor learning and its impact on later feeding behavior," *Journal of Pediatric Gastroenterology and Nutrition*, vol. 48, pp. S25-30, 2009.
- [26] L. B. Sjöström and S. E. Cairncross, *Chapter 15 role of sweeteners in food flavor. In: Use of sugars and other carbohydrates in the food industry*. Cambridge, Mass: Arthur D. Little, Inc, 1955.
- [27] T.M.R Transparency Market Research, "Non sugar sweeteners market - global industry analysis, size, market share, growth, trends and forecast, 2012-2018. Available <http://www.transparencymarketresearch.com/non-sugar-sweeteners.html>." 2013.

- [28] V. M. Sardesai and T. H. Waldshan, "Natural and synthetic intense sweeteners," *Journal of Nutritional Biochemistry*, vol. 2, pp. 236-244, 1991.
- [29] L. Monnier and C. Colette, "Les édulcorants: Effets métaboliques et sur la santé: Sweeteners: Metabolic effects and health considerations," *Médecine Des Maladies Métaboliques*, vol. 4, pp. 537-542, 2010.
- [30] J. L. Schlienger, "Les édulcorants de masse ou de charge ont-ils leur place dans l'alimentation chez le patient diabétique," *Médecine Des Maladies Métaboliques*, vol. 7, pp. 483-487, 2013.
- [31] B. Ahmed, M. Hossain, R. Islam, A. Kumar Saha, and A. Mandal, "Review on natural sweetener plant—stevia having medicinal and commercial importance," *Agronomski Glasnik*, vol. 1-2, pp. 75-92, 2011.
- [32] E. Mosettig, U. Beglinger, F. Dolder, H. Lichti, and P. P. Quitt, "The absolute configuration of Steviol and Isosteviol waters," *Journal of the American Chemical Society*, vol. 85, pp. 2305–2309, 1963.
- [33] J. E. Brandle and P. G. Telmer, "Steviol glycoside biosynthesis," *Phytochemistry*, vol. 7, pp. 1855–1863, 2007.
- [34] G. E. DuBois and R. A. Stephenson, "Diterpenoid sweeteners. Synthesis and sensory evaluation of stevioside analogues with improved organoleptic properties," *Journal of Medical Chemistry*, vol. 28, pp. 93–98, 1985.
- [35] I. Prakash, G. E. DuBois, J. F. Clos, K. L. Wilkens, and L. E. Fosdick, "Development of rebiana a natural, non-caloric sweetener," *Food and Chemical Toxicology*, vol. 46, pp. S75–S82, 2008.
- [36] M. C. Carakostas, L. L. Curry, A. C. Boileau, and D. J. Brusick, "Overview: The history, technical function and safety of rebaudioside a, a naturally occurring steviol glycoside, for use in food and beverages," *Food and Chemical Toxicology*, vol. 46, pp. S1-S10, 2008.
- [37] L. L. Curry, A. Roberts, and N. Brown, "Rebaudioside a: Two-generation reproductive toxicity study in rats," *Food Chemical Toxicology*, vol. 46, pp. S21-S30, 2008.
- [38] K. C. Maki, L. L. Curry, M. C. Carakostas, S. M. Tarka, M. S. Reeves, M. V. Farmer, J. M. McKenney, P. D. Toth, S. L. Schwartz, B. C. Lubin, M. R. Dicklin, A. C. Boileau, and J. D. J. C. Bisognano, "The hemodynamic effects of rebaudioside a in healthy adults with normal and low-normal blood pressure," *Food and Chemical Toxicology*, vol. 46, pp. S40-S46, 2008.
- [39] K. C. Maki, L. L. Curry, M. S. Reeves, P. D. Toth, J. M. McKenney, M. V. Farmer, S. L. Schwartz, B. C. Lubin, A. C. Boileau, M. R. Dicklin, M. C. Carakostas, and S. S. M. Tarka, "Chronic consumption of rebaudioside a, a steviol glycoside, in men and women with type 2 diabetes mellitus," *Food and Chemical Toxicology*, vol. 46, pp. S47-S53, 2008.
- [40] A. M. Viana and J. Metivier, "Changes in the levels of total soluble proteins and sugars during leaf ontogeny in *Stevia rebaudiana* Bert," *Annals of Botany*, vol. 45, pp. 469–475, 1980.

- [41] R. Lemus-Mondaca, A. Vega-Gálvez, L. Zura-Bravo, and K. Ah-Hen, "Stevia rebaudiana Bertoni, source of a high-potency natural sweetener: A comprehensive review on the biochemical, nutritional and functional aspects," *Food Chemistry*, vol. 132, pp. 1121-1132, 2012.
- [42] A. B. Siddique, S. M. Mizanur Rahman, and M. Amzad Hossain, "Chemical composition of essential oil by different extraction methods and fatty acid analysis of the leaves of Stevia rebaudiana Bertoni," *Arabian Journal of Chemistry*, pp. 1-5, 2012.
- [43] F. N. Muanda, R. Soulimani, B. Diop, and A. Dicko, "Study on chemical composition and biological activities of essential oil and extracts from Stevia rebaudiana Bertoni leaves," *LWT - Food Science and Technology*, vol. 44, pp. 1865-1872, 2011.
- [44] A. Erkucuk, I. H. Akgun, and O. Yesil-Celiktas, "Supercritical CO₂ extraction of glycosides from stevia rebaudiana leaves: Identification and optimization," *Journal of Supercritical Fluids*, vol. 51, pp. 29-35, 2009.
- [45] I. S. Kim, M. Yang, O. H. Lee, and S. N. Kang, "The antioxidant activity and the bioactive compound content of Stevia rebaudiana water extracts," *LWT - Food Science and Technology*, vol. 44, pp. 1328-1332, 2011.
- [46] J. M. C. Geuns, J. Buyse, A. Vankeirsbilck, and E. H. M. Temme, "Metabolism of stevioside by healthy volunteers," *Experimental Biology and Medicine*, vol. 232, pp. 164-173, 2007.
- [47] B. Chan, Y. J. Tomlinson, J. C. Chen, M. H. Liu Hsieh, and J. T. Cheng, "A double-blind placebo-controlled study of the effectiveness and tolerability of oral stevioside in human hypertension," *British Journal of Clinical Pharmacology*, vol. 50, pp. 215-220, 2000.
- [48] P. B. Jeppesen, S. Gregersen, S. E. D. Rolfsen, M. Jepsen, M. Colombo, A. Agger, J. Xiao, M. Krühoffer, T. Ørntofta, and K. Hermansen, "Antihyperglycemic and blood pressure-reducing effects of stevioside in the diabetic Goto-Kakizaki rat," *Metabolism*, vol. 52, pp. 372-378, 2003.
- [49] R. J. Huxtable, *Pharmacology and toxicology of stevioside, rebaudioside a, and steviol*. In *Stevia: The genus Stevia*. London, U.K. / New York, U.S.A: Taylor and Francis, 2002.
- [50] S. Gregersen, P. B. Jeppesen, J. J. Holst, and K. Hermansen, "Antihyperglycemic effects of stevioside in type 2 diabetic subjects," *Metabolism*, vol. 53, pp. 73-76, 2004.
- [51] C. Boonkaewwan, C. Toskulkao, and M. Vongsakul, "Anti-inflammatory and immuno-modulatory activities of stevioside and its metabolite steviol on THP-1 cells," *Journal of Agricultural and Food Chemistry*, vol. 54, pp. 785-789, 2006.
- [52] V. Chatsudhipong and C. Muanprasat, "Stevioside and related compounds: Therapeutic benefits beyond sweetness," *Pharmacology & Therapeutics*, vol. 121, pp. 41-54, 2009.
- [53] G. Brahmachari, L. C. Mandal, S. Mondal, and A. K. Brahmachari, "Stevioside and related compounds – molecules of pharmaceutical promise: A critical overview," *Archiv Der Pharmazie*, vol. 344, pp. 5-19, 2011.
- [54] S. K. Yadav and P. Guleria, "Steviol glycosides from Stevia: Biosynthesis pathway review and their application in foods and medicine," *Critical Reviews in Food Science and Nutrition*, vol. 52, pp. 988-998, 2012.

- [55] V. Prakash, J. Clos, and I. Prakash, "Stability study of steviol glycoside in mock beverage using fluorescent light exposure under ICH guidelines," *International Journal of Pharmacy and Pharmaceutical Science*, vol. 3, pp. 316-323, 2011.
- [56] Q. Gong and I. N. Bell, "Degradation kinetics of rebaudioside a in various buffer solutions," *International Journal of Food Science and Technology*, vol. 48, pp. 2500-2505, 2013.
- [57] P. B. Jeppesen, S. Gregersen, C. R. Poulsen, and K. Hermansen, "Stevioside acts directly on pancreatic beta cells to secrete insulin: Actions independent of cyclic adenosine monophosphate and adenosine triphosphate-sensitive K⁺-channel activity," *Metabolism*, vol. 49, pp. 208-214, 2000.
- [58] J. M. C. Geuns, P. Augustijns, R. Mols, J. G. Buyse, and B. Driessen, "Metabolism of stevioside in pigs and intestinal absorption characteristics of stevioside, rebaudioside a and steviol," *Food and Chemical Toxicology*, vol. 41, pp. 1599-160, 2003.
- [59] J. O. Atteh, O. M. Onagbesan, K. Tona, E. Decuypere, J. M. Geuns, and J. Buyse, "Evaluation of supplementary stevia (*Stevia Rebaudiana*, Bertoni) leaves and stevioside in broiler diets: Effects on feed intake, nutrient metabolism, blood parameters and growth performance," *Journal of Animal Physiology and Animal Nutrition Berl*, vol. 92, pp. 640-649, 2008.
- [60] E. Brambilla, M. G. Cagetti, A. Ionescu, G. Campus, and P. Lingström, "An in vitro and in vivo comparison of the effect of *Stevia rebaudiana* extracts on different caries-related variables: A randomized controlled trial pilot study," *Caries Research*, vol. 48, pp. 19-23, 2014.
- [61] A. Craig, C. A. Johnston, B. Stevens, P. John, and J. P. Foreyt, "The role of low-calorie sweeteners in diabetes," *US Endocrinology*, vol. 9, pp. 13-15, 2013.
- [62] FDA, "Agency response letter GRAS Notice No. GRN 000348. Re: GRAS Notice No. GRN 000348 2014. Available <http://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm267232.htm>," 2014.
- [63] U.S., "U.S. Food and drug administration: GRAS notice inventory. Available <http://www.accessdata.fda.gov/scripts/fdcc/?set=GRASNotices>," 2014.
- [64] D. J. Beneford, M. DiNovi, and J. Schlatter, *Steviol glycosides. Safety evaluation of certain food additives. In: WHO food additive series*. Geneva: WHO, 2006.
- [65] R. S. McQuate, "Ensuring the safety of sweeteners from Stevia," *Food Technology*, vol. 65, pp. 42-49, 2011.
- [66] D. Parent-Massin, "Édulcorants intenses: Point d'actualité sur leur sécurité d'emploi et les dernières innovations," *Cahiers De Nutrition et De Diététique*, vol. 46, pp. H27-H34, 2011.
- [67] H. King, R. E. Aubert, and W. H. Herman, "Global burden of diabetes, 1995-2025: Prevalence, numerical estimates, and projections," *Diabetes Care*, vol. 21, pp. 1414-1431, 1998.
- [68] P. Zimmet, J. Shaw, S. Murray, and R. Sicree, "La epidemia de diabetes en crecimiento: Predecir el futuro," *Diabete Voice*, vol. 48, pp. 12-16, 2003.

- [69] S. Wild, G. Roglic, A. Green, R. Sicree, and H. King, "Global prevalence of diabetes estimates for the year 2000 and projections for 2030," *Diabetes Care*, vol. 27, pp. 1047-1053, 2004.
- [70] S. Valdés, G. Rojo-Martínez, and F. Soriguer, "Evolución de la prevalencia de la diabetes tipo 2 en población adulta española," *Medicina Clínica*, vol. 129, pp. 352-355, 2007.
- [71] WHO OMS, "Organización mundial de la salud," *Diabetes Consultado. Available* <http://www.who.int/mediacentre/factsheets/fs312/es/index.html>. [Accessed 6/12/14], 2013.
- [72] R. Sicree, J. Shaw, and P. Zimmet, "The global burden diabetes and impaired glucose tolerance." *IDF Diabetes Atlas 4th edi*, pp. 1-105, 2014.
- [73] IDF, "Diabetes atlas Sixth edition. Available" <http://www.idf.org/diabetesatlas/introduction>," 2013.
- [74] G. I. Kourtoglou, "Insulin therapy and exercise," *Diabetes Research and Clinical Practice*, vol. 93, pp. S73-S77, 2011.
- [75] J. L. Sievenpiper and P. D. N. Dworatzek, "Food and dietary pattern-based recommendations: An emerging approach to clinical practice guidelines for nutrition therapy in diabetes," *Canadian Journal of Diabetes*, vol. 37, pp. 51-57, 2013.
- [76] WHO World Health Report, *Conquering suffering, enriching humanity*. Geneva: World Health Organization, 1997.
- [77] Y. Wang and M. A. Beydoun, "The obesity epidemic in the United States—gender, age, socioeconomic, racial/Ethnic, and geographic characteristics: A systematic review and meta-regression analysis," *Epidemiologic Reviews*, vol. 29, pp. 6-28, 2007.
- [78] C. L. Ogden, S. Z. Yanovski, M. D. Carroll, and K. M. Flegal, "The epidemiology of obesity," *Gastroenterology*, vol. 132, pp. 2087–2102, 2007.
- [79] M. D. Nguyen and H. B. El-Serag, "The epidemiology of obesity," *Gastroenterology Clinics of North America*, vol. 39, pp. 1–7, 2010.
- [80] WHO, "Global health observatory (GHO). Available" http://www.who.int/gho/ncd/risk_factors/obesity_text/en/," 2008.
- [81] M. A. Charles, "Obesity: What epidemiology tells us?," *Cahiers De Nutrition et De Dietetique*, vol. 46, pp. 167-172, 2011.
- [82] M. Mello, "Legal and policy approaches to the obesity epidemic. Surgery for obesity and related," *Diseases*, vol. 8, pp. 507-513, 2012.
- [83] R. N. Haththotuwa, C. N. Wijeyaratne, and U. Senarath, *1 - worldwide epidemic of obesity. In: Obesity*. Oxford: Elsevier, 2013.
- [84] J. L. Kraschewski, K. O. Hwang, D. R. George, E. B. Lehman, and C. N. Sciamann, "Feasibility of utilising an all-volunteer workforce as a disruptive innovation for the US obesity epidemic," *Obesity Research & Clinical Practice*, vol. 8, pp. e488-e496, 2014.
- [85] F. J. Santonja and L. Shaikhet, "Probabilistic stability analysis of social obesity epidemic by a delayed stochastic model," *Nonlinear Analysis: Real World Applications*, vol. 17, pp. 114-125, 2014.

- [86] J. Liu, J. Li, and J. Tang, "Ultrasonic-assisted extraction of total carbohydrates from Stevia rebaudiana and identification of extracts," *Food and Bioproduct Process*, vol. 88, pp. 215-221, 2010.
- [87] M. Puri, D. Sharman, and C. J. Barow, "Downstream processing of stevioside and its potential applications," *Biotechnology Advances*, vol. 29, pp. 781-791, 2012a.
- [88] K. Jonnala, B. G. D. Kiran, V. Kaul, and P. Ahuja, "Patent process for production of steviosides from stevia rebaudiana bertonii." Patent. US 20060142555 A1, 2006.
- [89] J. Vanneste, A. Sotto, C. M. Courtin, V. Van Craeyveld, K. Bernaerts, J. Van Impe, S. Taes, B. Van Der Bruggen, and J. Vandeur, "Application of tailor-made membranes in a multi-stage process for the purification of sweeteners from Stevia rebaudiana," *Journal of Food Engineering*, vol. 103, pp. 285-293, 2011.
- [90] A. B. Rao, E. Prasad, G. Roopa, S. Sridhar, and Y. V. Lakshmi Ravikumar, "Simple extraction and membrane purification process in isolation of steviosides with improved organoleptic activity," *Advances in Bioscience and Biotechnology*, vol. 3, pp. 327-335, 2012.
- [91] V. H. Abelyan, V. T. Ghochikyan, A. A. Markosyan, M. O. Adamyan, and L. A. Abelyan, "Extraction separation and modification of sweet glycosides from Stevia rebaudiana plant." US Patent No. 7838044B2, 2010.
- [92] V. Jaitak, B. Bikram Sinh, and V. K. Kaul, "An efficient microwave-assisted extraction process of stevioside and rebaudiose-A from Stevia rebaudiana Bertoni," *Phytochemical Analysis*, vol. 20, pp. 240-245, 2009.
- [93] M. Puri, D. Sharman, and C. J. Barow, "Optimization of novel method for the extraction of stevioside from S rebaudiana leaves," *Food Chemistry*, vol. 132, pp. 1113-1120, 2012b.
- [94] X. Y. Huang, J. F. Fu, and D. L. Di, "Preparative isolation and purification of steviol glycosides from Stevia rebaudiana Bertoni using high-speed counter-current chromatography," *Separation and Purification Technology*, vol. 71, pp. 220-224, 2010.
- [95] M. Fantino, "Effets nutritionnels et métaboliques des édulcorants intenses," *Cahiers De Nutrition et De Diététique*, vol. 46, pp. H35-H39, 2011.
- [96] R. D. Mattes and B. M. Popkin, "Nonnutritive sweetener consumption in humans: Effects on appetite and food intake and their putative mechanisms," *American Journal of Clinical Nutrition*, vol. 89, pp. 1-14, 2009.
- [97] S. D. Anton, C. K. Martin, H. Han, S. Coulon, W. T. Cefalu, P. Geiselman, and D. A. Williamson, "Effects of stevia, aspartame, and sucrose on food intake, satiety, and postprandial glucose and insulin levels," *Appetite*, vol. 55, pp. 37-43, 2010.
- [98] P. Narayanan, B. Chinnasamy, J. Jin, and S. Clark, "Use of just-about-right scales and penalty analysis to determine appropriate concentrations of stevia sweeteners for vanilla yogurt," *Journal of Dairy Science*, vol. 97, pp. 3262-3272, 2014.
- [99] V. K. Tejo, S. Karsodihardjo, and V. K. Ananingsih, "Stevia rebaudiana: An excellent natural alternative for sugar replacer faculty of agricultural technology," presented at the The Third International Congress on Interdisciplinary Research and Development, Thailand, 2013.

- [100] G. Jones, "Stevia, G1634, university of Nebrask –Lincoln Extension, Institute of Agriculture and Natural Resources." [Accessed April 8, 2014]. Available <http://extensionpublications.unl.edu/assets/html/g1634/build/g1634.htm>, 2014.
- [101] R. Silva Cadena, A. Gomes Cruz, R. Rolim Netto, W. Freitas Castro, J. A. Fonseca Faria, and H. M. André Bolini, "Sensory profile and physicochemical characteristics of mango nectar sweetened with high intensity sweeteners throughout storage time," *Food Research International*, vol. 54, pp. 1670-1679, 2013.
- [102] A. Belščak-Cvitanović, D. Komes, M. Dujmović, S. Karlović, M. Biškić, M. Brnčić, and D. Ježek, "Physical, bioactive and sensory quality parameters of reduced sugar chocolates formulated with natural sweeteners as sucrose alternatives," *Food Chemistry*, vol. 167, pp. 61-70, 2015.
- [103] L. L. M. Melo, H. M. A. Bolini, and P. Efraim, "Sensory profile, acceptability, and their relationship for diabetic-reduced calorie chocolates," *Food Quality and Preference*, vol. 20, pp. 138-143, 2009.
- [104] E. C. Morais, A. R. Morais, A. G. Cruz, and H. M. A. Bolini, "Development of chocolate dairy dessert with addition of prebiotics and replacement of sucrose with different high-intensity sweeteners," *Journal of Dairy Science*, vol. 97, pp. 2600-2609, 2014.
- [105] R. S. Lothrop, "Physicochemical and sensory quality of chiffon cake prepared with rebaudioside-a and erythritol as replacement for sucrose," Thesis for Requirement of the Degree of Doctor of Philosophy, Department of Food Science and Human Nutrition, Colorado State University Fort Collins, Colorado, USA, 2012.
- [106] U. Kienle, "Formulas for the use of stevia natural sweetener in foodstuff. Available <https://stevia.uni-hohenheim.de>," 2014.
- [107] I. Prakash, J. F. Clos, and V. Prakash, "Stability of rebaudioside A under acidic conditions and its degradation products," *Food Reserch International*, vol. 48, pp. 65-75, 2012.
- [108] ChromaDex, "Chromadex® acquires spherix consulting - spherix consulting." Available <https://www.chromadex.com/Detailsp.aspx?Aid=693>, 2014.
- [109] Trini SA, Available <http://www.steviatrini.com.ar/>, 2014.
- [110] Papaphilippou, "Papaphilippou & patisserie panayiotis ice cream LTD." <http://www.pandpicecream.com/>, 2014.
- [111] Truvia Company, Available <http://truvia.com/products>, 2014.

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