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Effect of *Stevia rebaudiana*, sucrose and aspartame on human health: A comprehensive review

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Abstract
Consumption of sucrose is one of the dietary origins of some health concerns, such as dental caries, obesity and diabetes type 2. In Morocco, the statistics are alarming. Therefore, in order to reduce these major and growing problems of society, substituting sugar with low calorie sweeteners may be effective. Knowing that, the use of these sweetening compounds has increased seriously. Furthermore several experiments have questioned their lack of harmfulness to health, particularly aspartame. The revelation of a potential risk of synthetic sweeteners has led to the emergence of a new market, of intense sweeteners of natural origin, such as stevioside and rebaudioside A. The extracts from the leaves of *Stevia rebaudiana* Bertoni are natural, sweet-tasting and calorie free that may also be used as a sugar substitute or as an alternative to artificial sweeteners. Much progress has been made concerning their biological and pharmacological effects. This review article summarizes the current scientific researches about the actions and safety of sucrose Aspartame and *Stevia rebaudiana* extracts on human health.

Keywords: *Stevia rebaudiana* bertoni*;* sucrose; aspartame; diabetes type 2; stevioside; rebaudioside A.

Introduction
The attraction for sweet taste is present from birth, in humans as in many mammals, probably to guide us to a safe source of nutrients and guarantees the acceptance of breast milk with a slightly sweet taste by lactose. The attraction for sweetness is evident in the newborn and this from the first hours after birth [1]. Moroccans are big consumers of sugar. According to figures published by the Minister for General Affairs, they consume 1.211 million tons of sugar per year, or about 36 kilo per person per year. Which is, considerably higher than the world average consumption of natural sugar, so 25 grams or 6 teaspoons of sugar a day. This figure tends to increase considerably during the holy month of Ramadan. [2] This consumption can be dangerous for health, the main problem is that of obesity and the risk of diabetes later. In addition to culinary habits, the over consumption of sugars is mainly due to products manufactured today by the food industry that contain often huge amounts of sugars, for example a large glass of sweet soda drink contains on average 16 spoons of sugar and a large glass of juice type smoothie contains on average 22 spoons of sugar[2]. In Morocco, the statistics are alarming. According to the latest figures from the Ministry of Health issued on the occasion of World Diabetes Day, Morocco has more than 2 million diabetics in over 20 years [3]. Many studies have shown that excessive consumption of simple sugars has an adverse effect on health and it is accused of promoting obesity and diabetes type 2. In fact, the excess of simple sugar leads to excess energy intake which can lead to overweight and obesity, thus favor the occurrence of diabetes or cardiovascular diseases. This is strengthened by the fact that many foods rich in simple sugars are often associated with fats such as cookies, chocolate or ice cream. These foods provide a lot of energy in a small volume [2]. In order to reduce these two major and growing problems in today's society, agri-food industries are trying to develop low-fat products that are sweetened with sugar-free, non-caloric molecules, which are mostly chemical molecules. Use of these sweetening compounds has increased dramatically due to health concerns related to sucrose usage, such as dental caries, obesity and diabetes [4]. These artificial or chemical sweeteners such as aspartame, acesulfame K, saccharin or cyclamate, are currently the subject of much controversy. Although their current use, they are suspected of having adverse health effects after several years of consumption,

experiences have questioned their lack of harmfulness to health [4]. However, consumers are increasingly turning to the use of natural products to heal or maintain their health; the discovery of a potential risk of artificial sweeteners has led to the emergence of a new market of natural intense sweeteners. Much attention has been directed towards stevioside and rebaudiauside A, a sweet glycosides extracted from stevia (Stevia rebaudiana Bertoni). Native peoples in South America have been using stevia extract as sweetener and traditional medicine for several hundred years [5]. Due to the sweetness and supposed therapeutic properties of its leaf, stevia has attracted economic and scientific interests. Japan was the first country in Asia to market stevioside as a sweetener in food and drug industry. Given the high consumption of sucrose and sucrose-sweetened soft drinks, as well as the increasing consumption of food and beverages sweetened with intense sweeteners, many scientists studied the effects of different sweeteners on human health. The purpose of this review is to bring together a selection of essential basic data coming from numerous scientific researches on sucrose, aspartame and stevia. We are interested in the various properties of stevia extracts in order to compare it with other sweeteners of the market as well as the advantages of its use as sweetener.

Sucrose

White sugar contains at least 99.7% of sucrose. Which is a disaccharide that consists of 50% glucose and 50% fructose (figure 1) and it is absolutely not essential in our alimentation, because it is very refined therefore completely devoid of nutrients such as vitamins, minerals and trace elements. [6]

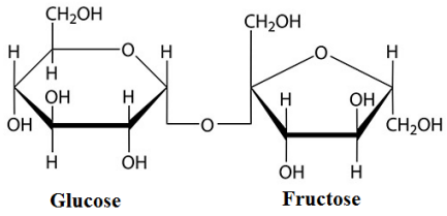

Fig 1: sucrose chemical structure

Sucrose and dental caries relationship

Dental carie, otherwise known as tooth decay, is one of the most prevalent chronic diseases of people worldwide. Individuals are susceptible to this disease throughout their lifetime. Dental carie forms through a complex interaction over time between acid-producing bacteria and fermentable carbohydrate, as well many host factors including teeth and saliva [7]. The composition of dental plaque is diverse, and includes a range of Gram positive and Gram negative bacteria [7]. Diet has a clear influence on caries development. The relation between the intake of refined carbohydrates, especially sugars, and the prevalence and severity of caries is so strong that sugars are clearly a major etiological factor in the causation of caries. Added sugars are the primary cause, although a limited degree of caries occurs in populations for whom the only sugars they consume are naturally occurring [8]. The high microbial density of dental plaque explains a number of the adverse effects of sucrose, particularly as a bacterial substrate [7]. Indirect evidence for the cariogenicity of sugar was obtained from studies on populations where sucrose consumption was highly variable from one individual to another. In countries such as China and Ethiopia, where the frequency of dental caries is very low, consumption of sucrose is very small. The other countries are represented by Australia, Hawaii and French Polynesia, where the overall intake of sucrose is high and the caries very responded [9]. The cariogenic power of sucrose is high if the ingestion is frequent and especially if sweet products are consumed in solid or pasty form between the principal meals. Under these conditions repeated ingestion, even very small amounts cause caries [7]. A study among low-income adults found that, 54% of their total energy intake came from several types of soft drinks and juices. High consumption of soft drinks when linked to poor oral hygiene was associated with higher caries levels [10]. There are more evidences showing that soft drink consumption is related to caries: the more often soft drinks are consumed, the greater the extent and severity of caries [11, 12, 13, 14]. Sugar in liquid form is cariogenic; it served well to demonstrate demineralization in landmark experimental caries studies [15]. The evidence is strong that consumption of sugars is a major risk factor for caries, also it has long been asserted that sugar–starch mixtures are more cariogenic than sugars alone. Studies of Bibby [16] and Firestone [17] on animal support that view.

Sucrose and obesity

Raben *et al* [18] investigated the effect of long-term supplementation with drinks and foods containing either sucrose or artificial sweeteners on ad libitum, food intake and body weight in overweight subjects. Overweight subjects who consumed fairly large amounts of sucrose (28% of energy), mostly as beverages, had increased energy intake, body weight, fat mass, and blood pressure after 10 weeks. These effects were not observed in a similar group of subjects who consumed artificial sweeteners. Diets consisting of high amounts of sucrose have been found to cause weight gain [19]. Moreover, excessive intake of high calorie and high glycemic food can result in exaggerated postprandial glucose and insulin levels and potentially lead to metabolic and hormonal changes that stimulate hunger levels and promote fat deposition [19]. In line with this, studies to date suggest that the consumption of sugar-sweetened beverages promotes positive energy balance, weight gain, and increases risk for Type 2 diabetes [20, 21].

Soft drinks seem to have replaced confectionery as the prime source of sugar in several populations. The subject therefore has serious health implications that go beyond dentistry, and is yet another example of a general public health problem having clear dental overtones. Soft drinks thus can be viewed as a ‘common risk factor’ in public health [22].

Based on accumulating evidence, sucrose sweetened beverages and high sucrose diets have adverse effects on body weight [23] and are associated with other medical complications, such as diabetes, cardiovascular disease, and cancer. The American Heart Association recently released a statement, recommending to limit sugar intake to just over 30 g (100 calories) per day for average-sized women and just over 45 g (150 calories) for average-sized men [24].

Sucrose and diabetes

Diets consisting of high amounts of sucrose have been found to cause adverse effects on glucose tolerance in healthy volunteers [25]. Overconsumption of fructose has also been found to cause dyslipidemia and ectopic lipid deposition in healthy subjects with and without a family history of Type 2 diabetes [26], as well as increase visceral adiposity and decrease insulin sensitivity in overweight individuals [27]. In animal models, high glycemic diets and high consumption of the natural sugar have been shown to induce a number of

metabolic complications including hyperinsulinemia, hyperglycemia, hypertension, and insulin resistance [28]. Moreover, recent studies in human demonstrate that fructose infusions can induce hepatic insulin resistance [29]. It is important to know that sugar diluted in water is very assimilable. The study of Sievenpiper *et al* [30] shows that sugar raises blood glucose much faster if it is diluted in water. Over consumption of sucrose have been found to cause weight gain [19], affects the development of diabetes [31], and to have adverse effects on glucose tolerance in healthy volunteers [25]. It is now common to find soft drinks and juices replacing formula and milk in children up to 2 years of age [14]. Soft drinks have also been implicated as part of the cause of the global epidemic of obesity in children [18].

Aspartame

Aspartame, a low calorie sweetener, discovered in 1961, is probably the most popular intense sweetener and is used in over 5000 foods, vitamins, some cough syrups and beverages in today's market. The use of aspartame by diabetic individuals is increasing, also it is widely used in the weight loss regime, and approximately 200 million people consume aspartame worldwide [32]. It is made up of an aspartic acid associated to phenylalanine (Figure 2), approximately 50% of the aspartame molecule is phenylalanine, 40% is aspartic acid (aspartate) and 10% is methanol. It's 200 time sweeter than sucrose, which means that 25 mg of aspartame can replace 5 g of sucrose, so a piece of standard sugar in terms of sweetness. If we consider the caloric intake, it's 20 kcal per piece of sugar, while it's almost negligible for 25 mg of aspartame. For this reason aspartame is called an intense sweetener. The acceptable daily intake (ADI) is limited to 40 mg/kg/day.[33]

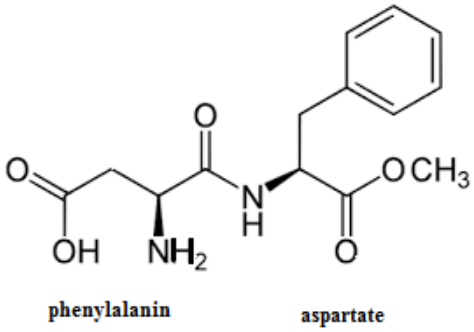

Fig 2: Chemical structure of aspartame.

Various neurochemical effects due to aspartame consumption have been reported such as headache [34]. Among the possible side effects of aspartame, seizures caught the attention of researchers. Besides the complaints of consumers collected in the United States, some studies suggest a relationship between the consumption of high doses of aspartame and the onset of epileptic seizures. Walton *et al* [35] report in a study of 13 patients with depression, that administration of 30 mg/kg/day of aspartame for 7 days caused serious side effects. That led researchers to conclude that individuals with mood disorders are particularly sensitive to this artificial sweetener. Thus the use of this sweetener in this population should be avoided. Also Wurtman *et al* [36] indicates that the administration of aspartame may affect the synthesis of catecholamines or serotonin, through an increase in phenylalanine uptake into the brain, and thereby cause seizures. Fernstrom *et al* [37] demonstrated very large increments in rate retinal phenylalanine concentration after aspartame administration. Furthermore Wurtman *et al* [36] reported that in a group of 505 aspartame reactors, eye pain or visual changes represented 35% of all complaints. Another potential harmful effect of aspartame that have been widely discussed in the scientific community, the possibility that aspartame is carcinogenic (especially for the brain). Olney *et al* [38] published an article on a possible relationship between the increase in the frequency of brain tumors in humans and the consumption of aspartame in the United States. Based on data from the National Cancer Institute (10% of the population) in the period from 1975 to 1992, the authors concluded a significant increase in the frequency of brain tumors in the mid 1980s, the period after aspartame market. Large doses of both aspartame and its individual metabolites have been tested in humans and animals, with controversial reports. It has been reported that not only the metabolites of methanol, but methanol as well, is toxic to the brain [40]. Methanol is gradually released in the small intestine when the methyl group of aspartame encounters the enzyme chymotrypsin. Methanol breaks down into formic acid and formaldehyde in the body. Formaldehyde is a deadly neurotoxin [41]. The primary metabolic fate of methanol is the direct oxidation to formaldehyde and then into formate. The toxic effects of methanol in humans are due to the accumulation of its metabolite formate [42,43]. The severity of clinical findings in methanol intoxication correlated better with formate levels [44]. Humans and non-human primates are uniquely sensitive to methanol poisoning because of their low liver folate content [45].

There are more recent scientific reports on aspartame revealing, that aspartame consumption affects the brain, Iyyaswamy and Rathinasamy [46] study deals with strengthening the toxic metabolite methanol released in the body after the consumption of aspartame. The alteration in the free-radical scavenging enzymes in the aspartame administered animals, indicates that, free radical generation may be due to the methanol which is one of the metabolic products of aspartame. Even after chronic aspartame administration, there was detectable blood methanol in the aspartame-treated animals. Exposure to methanol causes oxidative stress by altering the oxidant/antioxidant balance in lymphoid organs of rat [47]. The condition could also be associated with the abundance of redox active transition metal ions, and the relative death of antioxidant defense system [48]. Moreover, Mourad and Noor [49] have observed that the daily ingestion of aspartame induced oxidative stress which may depend on the duration of aspartame administration even within the acceptable daily intake dose. Furthermore this study reveals that aspartame administration in the body system persists for longer duration, which indicates the possible accumulation of methanol and its metabolite. Aspartame has biological effects even at the recommended daily dose. After chronic exposure of aspartame, methanol and its metabolites may be responsible for the generation of oxidative stress in brain regions, also detectable methanol continues to circulate in the blood.

Stevia

Stevia extracts contains steviol glycosides, a natural and non caloric sweeteners. Stevioside and rebaudiauside A are the major steviol glycosides isolated from stevia leaf; stevioside (5–10% of total dry weight), rebaudioside A (2–4% of total dry weight). The chemical structures of stevioside and rebaudioside A are shown in Figure 3. The sweetness of these major glycosides compared to sucrose is, rebaudioside A 250–450, and stevioside 300[50]. In addition to their sweetness,

stevia extract have therapeutic benefits. Stevia leaves have been used as a traditional medicine by local people in South America for several years [5]. The benefits associated with stevia leaf are principally due to their biochemical and nutritional composition, it's a good source of carbohydrates, protein, crude fiber [51], minerals, dispensable and indispensable amino acids, labdanes, flavonoids, sterols, triterpenoids, chlorophylls, organic acids, mono-disaccharides, and inorganic salts [52]. The most important of these bioactive compounds of plants are alkaloids, flavonoids, tannins and phenolic compounds [53], which promotes wellness and minimize the risk of certain diseases. This natural, acaloric product has the Generally Recognized as Safe (GRAS) status by the Food and Drug Administration (FDA) since 2009[54]. In 2010 the European Food Safety Authority (EFSA) established an acceptable daily intake of 4 mg/kg body weight. As a food additive, the E960 code has been assigned to it. In some countries, stevia has been consumed as a food and medicine for many years, including most notably Japan and Paraguay [55]. In addition, stevia sweetener extracts are suggested to exert beneficial effects on human health, such as anti-hyperglycemic, anti-hypertensive, anti-inflammatory, anti-tumor, anti-diarrheal, diuretic, and immunomodulatory effects [56].

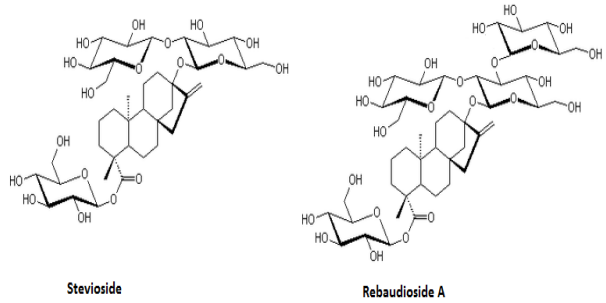

Fig 3: Stevioside and rebaudioside A, chemical structure

Interest of stevia in case of diabetes

Diabetes is more often associated with the release of a massive amount of toxic free radicals, which significantly decrease the level of antioxidant enzymes, increase lipid peroxidation, and worsen the disease state by causing further hyperglycemia. Antioxidants have been reported to prevent oxidative damage caused by free radicals. They can interfere with the oxidation process by reacting with the free radicals, chelating catalytic metals and also acting as oxygen scavengers [57]. Many plant extracts and plant-derived natural compounds have been reported to possess antioxidant activities, and useful in preventing the deleterious effects of oxidative stress. A recent study assessing the in vitro potential of ethanolic leaf extract of *S. rebaudiana* indicates that it has a significant potential for use as a natural antioxidant [58]. Moreover, many researchers have shown that stevia leaves extracts possess valuable biological effects on general health and glycemia in particular. Regular consumption of these compounds decreases the content of sugar in the blood [59], it exhibits a high degree of antioxidant activity and have significant antioxidant effect on diabetes pathology. These activities have been attributed to the scavenging of free radical electrons and superoxides [60]. Recent studies indicate that stevia extract is an important contributor to the development of insulin resistance and Type 2 diabetes [61]. In addition, stevioside has antihyperglycemic action [62, 63, 64]; and has been used as substitutes for saccharose in the treatment of diabetes [65, 66]. Also stevia extract improved the normal functioning of pancreatic ß-cells, which resulted in improving metabolism and glucose transport to cells [63].

At the seventh Congress of the International Diabetic Federation, a study was presented by Paraguayan doctors, proving that taking small amounts of stevia could normalize the blood sugar levels of diabetics and no cases of intolerance have been reported. According to their observations, unlike artificial sweeteners, prolonged consumption of stevia leaves extracts does not cause any side effects.

Stevia and overweight

Consumption of sugar-sweetened beverages may be one of the dietary causes of metabolic disorders, such as obesity. The sugar present in sweet products brings only energy and therefore unnecessary calories in our diet. We do not really need this added sugar in our alimentation (sucrose), only in case of hypoglycemia in the diabetics, or to promote weight gain.

Khiraoui *et al.* [67] analyzed stevia leaves on a dry weight basis and calculated an energy value of (3.05 - 3.17 kcal/g). This means that stevia may be granted the status of a low calorie sweetener. Therefore, substituting sugar with low calorie sweeteners may be an immense help in restricting or controlling calorie intake in the diet [55]. The stevia plant and its extracts have been used as substitutes for sucrose in the treatment of obesity [66, 68, 69]. Park and Cha [70], evaluated the effects of oral administration of stevia extract on diet induced obesity and related lipid abnormalities. This study has demonstrated that stevia extracts has beneficial metabolic effects, and sucrose diet had negative effects. Also it provided evidence that stevia extracts supplementation decreases weight gain, serum and liver triglyceride. The study of Park and Cha [70] suggests that stevia extracts may up regulate genes coding for enzymes of fatty acid oxidation in the liver. Finally, the study established the efficacy of stevia extract in preventing obesity and obesity-related symptoms, including hyperlipidemia and cardiovascular diseases.

Thus substituting stevia extract a no-calorie sweetener for sugar would help to reduce caloric intake and thus contribute to weight loss and weight management. Therefore *stevia rebaudiana* may be useful as a potential source of natural sweetener, on one side stevia has a higher sweetening power than sugar, on the other side does not have the disadvantages of sugar and chemical sweeteners on health.

Stevia and hypertension

The stevia plant and its extracts have been used as substitutes for sucrose in the treatment of hypertension [64, 68, 69, 70]. Several publications confirmed the antihypertensive properties of crude stevioside in rats [71] and in dogs [72].

Chan *et al* [68] conducted a study in humans for one year to investigate the effect of crude stevioside on systolic and diastolic blood pressure. His study involved administering 250 mg of stevioside three times per day to 60 hypertensive volunteers. After three months, systolic and diastolic blood pressures were significantly reduced, and this effect persisted throughout the year. Biochemical parameters of the blood, including lipid and glucose levels, have not shown significant changes. No adverse effects were observed. Within the treated group, mean arterial blood pressure at the start of the experiment was approximately 16.6/10.2, at the end of the study, it dropped to 15.3/9. Chan *et al* [68] found that stevioside has antihypertensive activity. Stevioside was used at higher doses (50, 100, 200 mg/kg) in the experiments and

no significant abnormalities were observed in the experimental animals. The study showed that the hypotensive effect was maximum when using 200 mg/kg stevioside. The maximal decrease of mean systolic blood pressure was 31% (200 to 137 mmHg) whereas the maximal decrease of mean diastolic blood pressure was 33% (149 to 100 mmHg) [68].

Stevia and oral health

Extract of stevia leaves and its major secondary metabolites, steviol, isosteviol, stevioside and rebaudioside A, B, C and E are non cariogenic, they can also act as an anti-cariogenic product [73, 74]. It has been found that these secondary metabolites inhibit glucan induced aggregation of cariogenic organism.

Blauth [75] suggested that development of dental caries in rat pups are triggered in presence of sucrose solution while it is not with stevioside. The major cariogenic organism, *S. mutans*, experiences growth suppression and secretes less acid when grown on media containing stevioside than when grown on sucrose, glucose or fructose media [75]. From experiments with albino rats, Das *et al* [76] conclude that neither stevioside nor rebaudioside A are cariogenic. High concentrations of stevioside and stevia extract are able to reduce the growth of bacteria. Nevertheless, the concentrations used as a sweetener are rather low, so the beneficial effect of stevioside is rather due to the substitution of sugar in the food by a non-cariogenic substance. In addition, stevioside is compatible with fluorine and significantly inhibits the development of dental plaque. Stevia can therefore help prevent cavities. Thus stevia have potential of providing oral health benefits.

Conclusion

Recent studies confirm the presence of toxic metabolite after aspartame administration and it affirm the need to caution the people who are using aspartame routinely. Since it is consumed more by diabetic people whose metabolism is already altered, it is essential to create awareness regarding the usage of this artificial sweetener. Contrarily, the use of stevia as a low-calorie sweetener could have an important role. It has been applied as a substitute for sucrose, treatment of diabetes mellitus, obesity, hypertension, and the reduction of calories. Thus stevia seems to have a dual beneficial quality in type 2 diabetes, with an antihyperglycemic and a blood pressure-lowering effect. Physiological and pharmacological experiments have suggested that stevia extracts have great effects on some metabolic diseases, such as obesity, diabetes type 2 and hypertension. In addition, in 2006, the World Health Organization conducted a thorough assessment of the steviol glycosides experiments on animals and humans and concluded that stevioside and rebaudioside A are not mutagenic (neither in vitro nor in vivo), also the report found no carcinogenic effects. Further, millions of Japanese people have been using stevia extracts for 30 years without any known or reported side effects. The toxicology of stevioside has been extensively studied, and related data, reassessed lately, indicated that it's non-toxic, non mutagenic, and non-carcinogenic. It was also clearly demonstrated that high concentrations of the sweetener rebaudioside A, administered in the diet of rats over 90 days, were not associated with any signs of toxicity and no allergic reaction have been observed when it is used as a sweetener.

Stevia rebaudiana is a plant of the future, with all the benefits it brings to our health. People do not usually know stevia, its extracts can be used as a natural alternative to sugar and chemical sweeteners for the diet of people with diabetes.

References

1. Philippe Reiser. 90 clés pour comprendre le sucre. Ed Quae. 2015, 176.
2. Paul Chambost. Chaque Marocain consomme 36 kilos de sucre par an. http://telquel.ma/2014/09/20/chauqe-marocain-consomme-36-kilos-sucre-par-an_1416482, 2017.
3. Hajjar El Haïti. Journée mondiale du diabète:Au Maroc, plus de 2 millions de personnes sont diabétiques. https://lematin.ma/journal/2017/au-maroc-plus-de-2-millions-de-personnes-sont diabetiques/281647. html. 13 Novembre 2017**.**
4. Marti N, Funes LL, Saura D, Micol V. An update on alternative sweeteners. International Sugar Journal. 2008; 110:425-429.
5. Kinghorn AD, Soejarto DD. Discovery of terpenoid and phenolic sweeteners from plants. Pure Appl Chem. 2002; 74(7):1169-1179.
6. Mathlouthi M, Reiser P. Sucrose: Properties and applications. Springer Science and Business Media, 1995 First Ed.1995, 294
7. Ole Fejerskov, Edwina Kidd. Dental Caries: The Disease and Its Clinical Management, 2nd Ed. 2008, 641.
8. Schamschula RG, Adkins BL, Barmes DE, Charlton G, Davey BG. WHO study of dental caries etiology in Papua New Guinea. WHO Offset Publication No. 40. Geneva: WHO, 1978.
9. Etude FAO. Alimentation et nutrition: Les glucides en nutrition humaine: rapport d'une réunion d'experts. Organisé par l'organisation des nations unies pour l'alimentation et l'agriculture et l'organisation mondiale de la santé. Genève 17-26 septembre 1979, 99
10. Burt BA, Kolker JL, Sandretto AM, Yuan Y, Sohn W, Ismail AI. Dietary patterns related to caries in a low-income adult population. Caries Res. 2006; 40:473-80.
11. Ismail AI, Burt BA, Eklund SA. The cariogenicity of soft drinks in the United States. J Am Dent Assoc. 1984; 109: 241-45.
12. Jones C, Woods K, Whittle G, Worthington H, Taylor G. Sugar, drinks, deprivation and dental caries in 14-year-old children in the north west of England in 1995. *Community* Dent Health. 1999; 16:68-71.
13. Watt RG, Dykes J, Sheiham A. Preschool children's consumption of drinks: implications for dental health. Community Dent Health. 2000; 17:8-13.
14. Marshall TA, Levy SM, Broffitt B, Eichenberger-Gilmore JM, Stumbo PJ. Patterns of beverage consumption during the transition stage of infant nutrition. J Am Diet Assoc. 2003; 103:1350-3.
15. Von der Fehr FR, Löe H, Theilade E. Experimental caries in man. Caries Res. 1970; 4:131-48.
16. Bibby BG. The cariogenicity of snack foods and confections. J Am Dent Assoc. 1975; 90:121-32.
17. Firestone AR, Schmid R, Mühlemann HR. Effect on the length and number of intervals between meals on caries in rats. Caries Res. 1984; 18:128-33.
18. Raben A, Vasilaras TH, Moller AC, Astrup A. Anne Raben, Tatjana H Vasilaras, A Christina Moller, and Arne Astrup, Sucrose compared with artificial sweeteners: different effects on ad libitum food intake and body weight after 10 wk of supplementation in overweight subjects. Am J Clin Nutr. 2002; 76(4):721-9.
19. O'Keefe JH, Bell DS. Postprandial hyperglycemia/hyperlipidemia (postprandial dysmetabolism) is a cardiovascular risk factor. The

American Journal of Cardiology. 2007; 100: 899-904.
20. Malik VS, Schulze MB, Hu FB. Intake of sugar-sweetened beverages and weight gain. A systematic review. The American Journal of Clinical Nutrition. 2006; 84:274-288.
21. Schulze MB, Manson JE, Ludwig DS, Colditz GA, Stampfer MJ, Willett WC *et al*. Sugar-sweetened beverages, weight gain, and incidence of type 2 diabetes in young and middle-aged women. The Journal of the American Medical Association. 2004; 292:927-934.
22. Sheiham A, Watt RG. The common risk factor approach: a rational basis for promoting oral health. Community Dent Oral Epidemiol. 2000; 28:399-406.
23. Johnson RJ, Segal MS, Sautin Y, Nakagawa T, Feig DI, Kang DH, *et al*. Potential role of sugar (fructose) in the epidemic of hypertension, obesity and the metabolic syndrome, diabetes, kidney disease, and cardiovascular disease. The American Journal of Clinical Nutrition. 2007; 86:899-906.
24. Mitka M. AHA. Added sugar not so sweet. The Journal of the American Medical Association. 2009; 302:1741-1742.
25. Cohen AM, Teitelbaum A, Balogh M, Groen JJ. Effect of interchanging bread and sucrose as main source of carbohydrate in a low fat diet on the glucose tolerance curve of healthy volunteer subjects. The American Journal of Clinical Nutrition. 1966; 19:59-62.
26. Le KA, Ith M, Kreis R, Faeh D, Bortolotti M, Tran C, *et al*. Fructose overconsumption causes dyslipidemia and ectopic lipid deposition in healthy subjects with and without a family history of type 2 diabetes. The American Journal of Clinical Nutrition. 2009; 89(6):1760-1765.
27. Stanhope KL, Schwarz JM, Keim NJ, Griffen SC, Bremer AA, Graham JL. Consuming fructose-sweetened, not glucose sweetened, beverages increases visceral adiposity and lipids and decreases insulin sensitivity in overweight/ obese humans. The Journal of Clinical Investigation. 2009; 119:1322-1334.
28. Barros CM, Lessa RQ, Grechi MP, Mouco TL, Souza MG, Wiernsperger N, *et al*. Substitution of drinking water by fructose solution induces hyperinsulinemia and hyperglycemia in hamsters. 2007; 62:327-334.
29. Wei Y, Wang D, Topczewski F, Pagliassotti MJ. Fructose-mediated stress signaling in the liver. Implications for hepatic insulin resistance. The Journal of Nutritional Biochemistry. 2007; 18:1-9.
30. John L, Sievenpiper Amanda J, Carleton Sheena Chatha, Henry Y, Jiang Russell J, de Souza Joseph Beyene, *et al*. Heterogeneous effects fructose on blood lipids in individuals with type 2 diabetes: systematic review and meta-analysis of experimental trials in humans. Diabetes Care. 2009; 32(10):1930-7.
31. Laville M, Nazare JA, Diabetes, insulin resistance and sugars. Obesity Research. 2009; 10:24-33.
32. Shapiro RB. Statement for the labor and human resources committee, US Senate (Washington, DC, Government Printing Office, 1988.
33. Amouyal C, Andreelli F. Effets métaboliques des édulcorants. Réalités en nutrition et en diabétologie. 2012; 41:25-28.
34. Johns DR. Migraine provoked by aspartame. New Engl. J. Med. 1986; 315-456.
35. Ralph G, Walton Robert Hudak, Ruth J. Green-Waite. Adverse Reactions to Aspartame: Double-Blind Challenge in Patients from a Vulnerable Population. BIOL PSYCHIATRY. 1993; 34:13-17.
36. Wurtman RJ. Aspartame: Possible effects on seizure susceptibility. Lancet. 1985; 2(8463):1060.
37. Femstrom JD, Femstmm MH, Massoudi MS. In vivo tyrosine hydmxylation in rat retina. Effect of aspartame ingestion in rats pretreated with p-chlorophenylaianine. Am J Clin Nutr. 1991; 53:923-929.
38. Olney JW, Price MT. Cholinergic Neurotoxicity: Mechanisms and Prevention. Washington University, St. Louis MO Dept of Psychiatry Annual Report, 1986.
39. Maher TJ, Wurtman RJ. Possible neurologic effects of aspartame, a widely used food additive. Environ. Health Perspect. 1987; 75:3-57
40. Jeganathan PS, Namasivayam A. Methanol induced biogenic amine changes in discrete areas of rat brain: Role of simultaneous ethanol administration. Indian J. Physiol. Pharmacol. 1998; 32:1-10.
41. Eells JT, Henry MM, Lewandowski MF, Seme MT, Murray TG. Development and characterization of a rodent model of methanol-induced retinal and optic nerve toxicity. Neurotoxicol. Rev. 2000; 21:321-330.
42. Tephly TR, McMartin KE. Methanol metabolism and toxicity; in Aspartame- physiology and biochemistry (eds) LD Stegink and LJ Filer Jr (New York: Marcel Dekker). 1984, 111-140.
43. Tephly TR. The toxicity of methanol. Life Sci. 1991; 48:1031-1041.
44. Osterloh JD, Pond SM, Grady S and Becker CE. Serum formate concentrations in methanol intoxication as a criterion for hemodialysis. Ann Intern Med. 1986; 104:2000-2003.
45. Johlin FC, Fortman CS, Nghiem DD, Tephly TR. Studies on the role of folic acid and folate-dependent enzymes in human methanol poisoning. Mol. Pharmacol. 1987; 31 557-561
46. Iyyaswamy A, Rathinasamy S. Effect of chronic exposure to aspartame on oxidative stress in the brain of albino rats. J. Biosci. 2012; 37:679-688.
47. Parthasarathy JN, Ramasundaram SK, Sundaramahalingam M, Rathinasamy SD. Methanol induced oxidative stress in rat lymphoid organs. J. Occup. Health. 2006; 48:20-27.
48. Samuel S, Ramanathan K, Tamilselvan J, Panneersevam C. Protein oxidative damage in arsenic induced rat brain: influence of DL-lipoic acid. Toxicol. Lett. 2005; 155:27-34.
49. Mourad IM, Noor NA. Aspartame (a widely used artificial sweetener) and oxidative stress in the rat cerebral cortex. Int. J. Pharm. Biomed. Sci. 2011; 2:4-10.
50. Crammer, B., & Ikan, R.Sweet glycosides from the stevia plant. Chem Br. 1986; 22:915-917.
51. Khiraoui A, Bakha M, Amchra F, Ourouadi S, Boulli A, Al-Faiz C, Hasib A. Nutritional and biochemical propertiesof natural sweeteners of six cultivars of Stevia rebaudianaBertonileavesgrown in Morocco J. Mater. Environ. Sci. 2017; 7:2028-2508.
52. Abou-Arab A, Abou-Arab A, Abu-Salem MF. Physico-chemical assessment of natural sweeteners steviosides produced from *Stevia rebaudiana* Bertoni plant. Afr. J. Food Sci. 2010; 4:269-281.
53. Edeoga H, Okwu D, Mbaebie B. Phytochemical constituents of some Nigerian medicinal plants. African Journal of Biotechnology. 2005; 4:685-688.
54. Rita Elkins MH, Stevia: Nature's Sweetener. Woodland,

Pleasant Grove, UT. 1997, 19-23.
55. Lemus-Mondaca R, Vega-Gálvez A, Zura-Bravo L, and Ah-Hen K. *Stevia rebaudiana* Bertoni, source of a high-potency natural sweetener: a comprehensive review on the biochemical, nutritional and functional aspects. Food Chemistry. 2012; 132(3):1121-1132.
56. Chatsudthipong V, Muanprasat C. Stevioside and related compounds: Therapeutic benefits beyond sweetness. Pharmacology and Therapeutics. 2009; 121:41-54.
57. Buyukokuroglu M, Gulcin I, Oktay M, Kufrevioglu, O. In vitro antioxidant properties of dantrolene sodium. Pharmacological Research. 2001; 44:491-494.
58. Shukla S, Mehta A, Mehta P, Bajpai, V. Antioxidant ability and total phenolic content of aqueous leaf extract of Stevia rebaudiana Bert. Experimental and Toxicologic Pathology. 2011; doi:10.1016/j.etp. 2011.02.002.
59. Atteh J, Onagbesan O, Tona K, Decuypere E, Geuns J, and Buyse J. 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. 2008; 92:640-649.
60. Thomas, J., and Glade, M. Stevia: It's not just about calories. The Open Obesity Journal. 2010; 2:101-109.
61. Viswanathan V, Clementina M, Nair BM, Satyavani K. Risk of future diabetes is as high with abnormal intermediate post-glucose response as with impaired glucose tolerance. The Journal of the Association of Physicians of India. 2007; 55:833-837.
62. Chen JG, Jeppesen PB, Abudula R, Dyrskog SEU, Colombo M, Hermansen K. Stevioside does not cause increased basal insulin secretion or h-cell desensitization as does the sulphonylurea, glibenclamide: studies *in vitro*. Life Sci. 2006; 78:1748-1753.
63. Jeppesen P, Gregersen S, Poulsen C, Hermansen K. Stevioside acts directly on pancreatic a cells to secrete insulin: Actions independent of cyclic adenosine monophosphate and adenosine triphosphate-sensitive K+ channel activity. Metabolism. 2000; 49:208-214.
64. Jeppesen P, Gregersen S, Gregersen S, Alstrupp K, Hermansen K. Stevioside induces antihyperglycaemic, insulinotropic and glucagonostatic effects in vivo: Studies in the diabetic Goto-Kakizaki (GK) rats. Phytomedicine. 2002; 9:9-14.
65. Jeppesen P, Gregersen S, Poulsen C, Hermansen K. Stevioside acts directly on pancreatic a cells to secrete insulin: Actions independent of cyclic adenosine monophosphate and adenosine triphosphate-sensitive K+ channel activity. Metabolism. 2000; 49:208-214.
66. Pól J, Hohnová B, Hyötyläinen T. Characterization of *Stevia rebaudiana* by comprehensive two-dimensional liquid chromatography time-of-flight mass spectrometry. Journal of Chromatography A. 2007; 1150:85-92.
67. Khiraoui A, Hasib A, Al Faiz C, Amchra FZ, Bakha M, Boulli A. *Stevia Rebaudiana* Bertoni (Honey Leaf): A Magnificent Natural Bio-sweetener, Biochemical Composition, Nutritional and Therapeutic Values. 2017; 7(14):2224-3186.
68. Chan P, Tomlinson B, Chen YJ, Liu JC, Hsieh MH, Cheng JT. Double-blind placebo-controlled study of the effectiveness and tolerability of oral stevioside in human hypertension. Br J Clin Pharmacol. 2000; 50:215-220.
69. Goyal S, Samsher, Goyal R. Stevia (*Stevia rebaudiana*) a bio-sweetener: a review. Int. J. Food Sci. Nutr. 2010; 61:1-10.
70. Jeong-Eun Park and Youn-Soo Cha. *Stevia rebaudiana* Bertoni extract supplementation improves lipid and carnitine profiles in C57BL/6J mice fed a high-fat diet. J Sci Food Agric. 2010; 90:1099-1105.
71. Hsu YH, Liu JC, Kao PF. *et al*. Antihypertensive effect of stevioside in different strains of hypertensive rats. Chin Med J. 2002; 65:1-6.
72. Liu JC, Kao PF, Chan P. *et al*. Mechanism of the antihypertensive effect of stevioside in anesthetized dogs. Pharmacology. 2003; 67:14-20.
73. Suanarunsawat T, Chaiyabutr N. The effect of steviosides on glucose metabolism in rat. Canadian Journal of Physiology and Pharmacology. 1997; 75:976-982.
74. Suanarunsawat T, Chaiyabutr N. The effect of steviosides on glucose metabolism in rat. Canadian Journal of Physiology and Pharmacology. 1997; 75:976-982.
75. Blauth de, Slavutzky S. Stevia and sucrose effect on plaque formation. Journal für Verbraucherschutz und Lebensmittelsicherheit. 2010; 5:213-216.
76. Grenby TH. Update on low-calorie sweeteners to benefit dental health. Int. J. Dent. 1991; 41:217-24.
77. Das S, Das AK, Murphy RA, Punwani IC, Nasution MP, Kinghorn AD. Evaluation of the cariogenic potential of the intense natural sweeteners stevioside and rebaudioside A. Caries Res. 1992; 26:363-366.