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### NOVEL APPROACH IN DIABETES MELLITUS: SAY NO TO SUGAR AND YES TO ARTIFICIAL SWEETENERS

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**Abstract:** In current scenario Chronic diseases such as coronary heart disease, obesity, diabetes, and hypertension are closely related to excessive consumption of sugar. Obesity is a risk factor for heart disease, cancer, diabetes, and some other diseases. The most restricted item in the diets of both noninsulin-dependent and insulin-dependent diabetic individuals is refined carbohydrate. So there is growing need for substitution of sugar for prevention of macro and micro vascular disorders associated with diabetes. In this condition artificial sweeteners play important role in management of blood sugar level. Five artificial sweeteners Acesulfame K, Aspartame, Neotame, Saccharin, and Sucralose are approved for use in the U.S. All are chemically manufactured molecules that do not be present in nature. Sugar alcohols like xylitol, sorbitol, mannitol, erythritol also helpful in diabetic patient. Natural sweeteners are sugar substitutes that are often promoted as healthier options than processed table sugar or other sugar substitutes. Stevia Sweeteners, Date sugar, Grape juice concentrate, Honey, Maple sugar, Maple syrup, Molasses, and Agave nectar are safe natural sugar. Artificial sweeteners may be a good alternative to sugar for diabetes. Unlike sugar, artificial sweeteners generally do not raise blood sugar levels because they are not carbohydrates.

**Keywords:** Diabetes, Artificial Sweeteners, Natural sweeteners, Sugar alcohol



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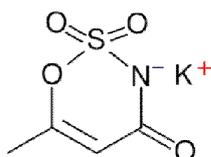
## INTRODUCTION

Preference for sweet taste at a variety of intensities is characteristic of the human kind. Embryonic people may have developed the wish for sweet taste as a means of existence because they considered sweetness a determinant of food safety. Berries and other plant foods which were sweet tasting were usually found to be harmless; while bitter tasting foods were typically toxic. In current scenario increased obesity associated mortality has resulted in a flow of weight loss diets and products, and various fitness routines. Chronic diseases such as coronary heart disease, obesity, diabetes, and hypertension were linked to excessive consumption of sugar. Obesity is a risk factor for heart disease, cancer, diabetes, and some other diseases.<sup>1</sup> The most restricted item in the diets of both noninsulin-dependent and insulin-dependent diabetic individuals is refined carbohydrate.<sup>2</sup>

Low-calorie sweeteners are ingredients added to foods and yogurt and sugar-free pudding. In addition, many low beverages to provide sweetness without adding calorie sweeteners do not contribute to cavities or tooth significant amount of calories. They also play an important role in a weight management program that includes both good nutrition choices and physical activity.<sup>3</sup> Artificial sweeteners are synthetic sugar alternatives but may be derived from naturally occurring substances, with herbs or sugar itself. Artificial sweeteners are also known as intense sweeteners because they are many times sweeter than regular sugar. Two types of intense sweeteners are available: Natural sweeteners of plant origin and Synthetic sweeteners. The sweeteners from ordinary sources with potential for commercial use include perillaldehyde, stevioside, rabadioside, glycyrrhizin, osladin, thaumatins, and monellin.

Low calorie sweeteners are sugar replacements that have zero calories and do not raise blood glucose levels through eating them, which makes them a preferable choice for diabetic people over sugar. Five artificial sweeteners Acesulfame K, Aspartame, Neotame, Saccharin, and Sucralose are approved for use in the U.S. All are chemically manufactured molecules that do not be present in nature. Artificial sweeteners are used in one of two ways. They may be used directly in commercially processed foods, or they are mixed with one or more starch based sweeteners before deal to consumers.

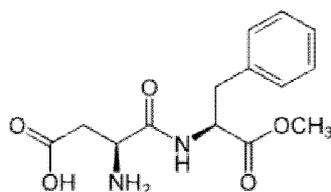
### Acesulfame K



Acesulfame K, also known as acesulfame potassium or ace K. It was discovered accidentally in 1967 by German chemist Karl Claus.<sup>4</sup> In chemical structure, acesulfame potassium is the potassium salt of 6-methyl-1,2,3-oxathiazine-4(3*H*)-one-2,2-dioxide. It is approximately 200 times sweeter than sugar. Acesulfame K has no calories because it is not metabolized by the body. Ace-K is not broken down by the body and is eliminated unchanged by the kidneys. It has no effect on serum glucose, cholesterol or triglycerides and people with diabetes may safely include products containing ace-K in their diet.

Furthermore to tabletop products, Acesulfame K can be found in thousands of a wide diversity of oral hygiene and pharmaceutical products, as well as foods and beverages. Acesulfame K is approved as a general purpose sweetener in the U.S., and is used in such diverse products as dry beverage and dessert mixes, hard and soft candies, chocolate confections, chewing gum, baked goods, dairy products, carbonated drinks and alcoholic beverages. Acesulfame K has the advantage that it is stable at temperatures below 400°F. Acesulfame K is commonly blended with other healthful and artificial sweeteners.

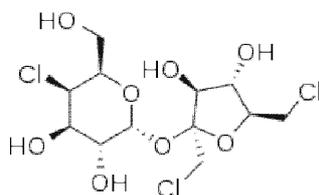
### Aspartame



Aspartame was discovered in 1965 by James M. Schlatter at the G.D Seale Company. Aspartame is a low calorie intense artificial sweetener. It is a white odorless powder, 200 times sweeter than sugar. Aspartame is approximately 200 times sweeter than sugar.

Aspartame is a molecule consisting of two amino acids-phenylalanine and aspartic acid. People who have a rare hereditary that condition called phenylketonuria (PKU) cannot metabolize phenylalanine; Prior to aspartame must carry a statement warning PKU of the presence of aspartame on the label.<sup>5,6</sup> Aspartame is completely broken down by the body into its two component amino acids aspartic acid and phenylalanine and a small amount of methanol which is wood alcohol. Although aspartame therefore has four calories per gram, its intense sweetness means so little of aspartame is used that essentially no calories are provided. Aspartame has been well studied, and it hasn't shown any serious side effects.

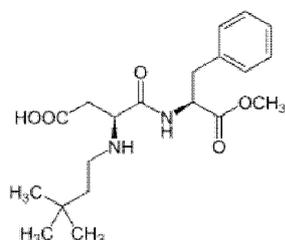
## Sucralose



Sucralose is made from sucrose by a multistep patented manufacturing process that selectively replaces three hydroxyl with chlorine atoms. This molecular change makes sucralose 600 times sweeter than sugar.

Sucralose is a chlorinated sugar that is about 600 times as sweet as sugar. It is produced from sucrose when three chlorine atoms substitute three hydroxyl groups. It is used in beverages, frozen desserts, chewing gum, baked goods and other foods. Sucralose incidentally is not a natural product; sucralose is prepared in the laboratory from sucrose by a chemical reaction that substitutes three chloride groups for three hydroxyl groups. This cannot be construed as natural, sucralose contains chlorine. It is heat stable, meaning that it does not break down when cooked or baked. It is used in many diet foods and drinks.

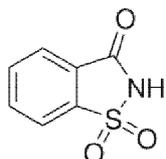
## Neotame



Neotame is the newest of the artificial sweeteners approved for general use in the U.S. Like aspartame, it is composed of aspartic acid and phenylalanine.

Neotame is also a derivative of aspartic acid and Phenylalanine. It is approximately 7,000 to 8,000 times sweeter than sugar, although some report a sweetening Power of up to 13,000 times that of sugar. While structurally different, neotame is still metabolized like aspartame. It is completely broken down into aspartic acid and phenylalanine. Since only trace amounts of neotame are required to mimic the sweetness of sugar, it contributes no calories. Use as a tabletop product and packaged food ingredient is anticipated. Neotame can be used in the same foods and beverages as both aspartame and acesulfame K.

## Saccharin

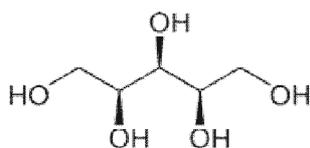


Saccharin was discovered more than 100 years ago, which makes it the oldest of the artificial sweeteners. Its sweetness depends on how it is used, and ranges from 200 to 700 times sweeter than sugar. It is used to sweeten products such as drinks, candies, cookie, medicines and toothpaste. In the 1960s saccharin was proven to cause cancer by many research groups. In 1977, the Food and Drug Administration (FDA) proposed a ban on saccharin, but since saccharin was the only artificial sweetener in that era, the ban was met with great opposition.

The U.S congress placed a moratorium on the ban; but required the product to display a warning label saying that the use of saccharin may be carcinogenic. Research has indicated that saccharin was not carcinogenic after all. As a result, in 1991 the Food Administration withdrew its proposed ban on saccharin. Saccharin however, is another synthetic chemical intended to fool the body into thinking it is consuming something that it has not. It is not broken down by in our bodies and is eliminated without providing any calories. Saccharin is heat stable, therefore making it suitable for tastes and looks exactly like sugar and is really sugar's cooking and baking.

## Sugar alcohol

### Xylitol

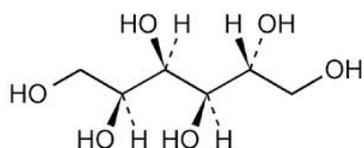


Xylitol is a sugar alcohol that is used as a sugar substitute. It occurs naturally and it is found in the fibrous vegetables and fruit, as well as in corn cobs and various hardwood trees such as birch. In fact, it is produced naturally in our bodies. It is roughly as sweet as sucrose but only has two thirds of the energy. It is used in cooking, baking, in beverages, chewing gum, mints, and other products such as nasal and mouth washes.

Research has confirmed that plaque is reduced when xylitol is consumed as it attracts and then starves harmful microorganisms allowing the mouth to demineralize damaged teeth with less interruption. Xylitol is a five-carbon sugar, which means it is an antimicrobial, preventing the growth of bacteria.<sup>7</sup> Xylitol is safe for teeth as it does not encourage tooth decay, and may actively aid in repairing minor cavities. Xylitol does not contribute to high blood sugar levels or

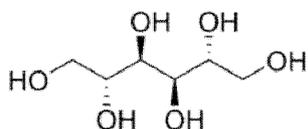
the resulting hyperglycaemia caused by insufficient insulin response. It may also have potential as a treatment for osteoporosis. Xylitol based chewing gum can help to prevent ear infections as the act of chewing and swallowing helps with the disposal of earwax and clearing the middle ear, while the xylitol prevents the growth of bacteria in the Eustachian tubes.

### Sorbitol



Sorbitol, also known as glucitol, is a sugar alcohol that is slowly metabolized by the body. It is mainly used in sugar free mints and various cough syrups, and is usually listed under the inactive ingredients. It is also used in diet foods, and sugar-free chewing gum. Sorbitol also occurs naturally in many stone fruits and berries from trees of the Sorbus genus. It does not promote tooth decay and is helpful for people with diabetes. Consuming large amounts of sorbitol can lead to abdominal pain, gas, and mild to severe diarrhea. It can also intensify irritable bowel syndrome and fructose malabsorption.

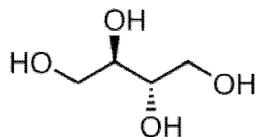
### Mannitol



Mannitol is a polyol or sugar alcohol that was originally isolated from the secretions of the Flowering Ash, called Manna after their resemblance to the biblical food. Chemically, it is similar to xylitol and sorbitol.

Mannitol is used as a sweetener for people with diabetes, and is commonly used as a sweetener in breath freshening candies as it has a cooling effect. It is about 50 percent as sweet as sucrose. It does not promote tooth decay and has a low caloric content. Mannitol does not pick up moisture and for this reason it is often used as a dusting powder for chewing gum. Due to its high melting point, it is also used in chocolate flavored coating agents for ice cream and sweets.

### Erythritol

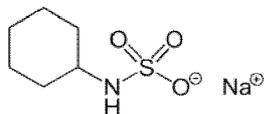


Erythritol, sorbitol and xylitol are natural sugar alcohols found in fruits and vegetables. They can be made commercially by catalytic hydrogenation from the corresponding sugars. Xylitol is produced from xylose, sorbitol also known as glucitol is produced from glucose.

Erythritol is about 60-80% as sweet as sucrose and has a calorie value of 0.2 calories per gram. It is used primarily in chewing gum, baked goods and beverage and occurs naturally in pears, soy sauce, watermelon and grapes. In fact, Erythritol has even been found to exist naturally in human tissues and body fluids. Erythritol is a sugar alcohol that has been approved for used as a food.

Erythritol is produced commercially by fermentation of glucose. Erythritol does not promote tooth decay and does not cause gastric side effects like other sugar alcohols.

### Sodium cyclamate

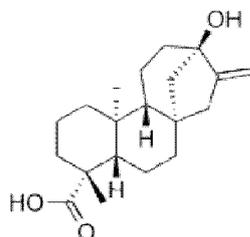


**Sodium cyclamate** (sweetener code 952) is an artificial sweetener. It is 30–50 times sweeter than sugar (depending on concentration; it is not a linear relationship), making it the least potent of the commercially used artificial sweeteners. Some people find it to have an unpleasant aftertaste, but, in general, less so than saccharin or acesulfame potassium. It is often used with other artificial sweeteners, especially saccharin; the mixture of 10 parts cyclamate to 1 part saccharin is common and masks the off-tastes of both sweeteners. It is less expensive than most sweeteners, including sucralose, and is stable under heating.<sup>8</sup>

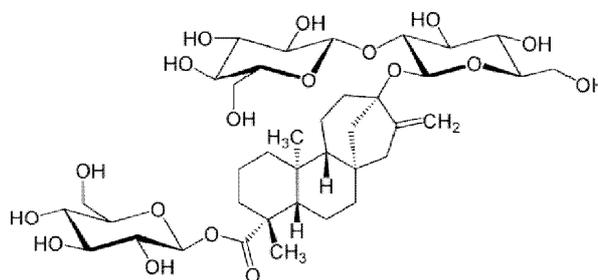
### Natural sweeteners

Natural sweeteners are sugar substitutes that are often promoted as healthier options than processed table sugar or other sugar substitutes. Stevia Sweeteners, Date sugar, Grape juice concentrate, Honey, Maple sugar, Maple syrup, Molasses, and Agave nectar are safe natural sugar.

## Stevia Sweeteners



Steviol



Stevioside

Stevia has a negligible effect on blood glucose it is attractive to people on carbohydrate-controlled diets. The stevia plant is native to South America and today, it can be found mounting in various countries including China, Brazil, Argentina, Paraguay, India and South Korea. Hundreds of foods and drinks consumed around the world are sweetened with stevia sweeteners. Stevia sweeteners are highly purified steviol glycosides, which make up the sweetest part of the stevia plant. In December 2008, the FDA stated it had no questions regarding the conclusion of an expert panel that steviol glycosides are generally recognized as safe (GRAS) for use as general purpose sweeteners.



Stevia was only permitted for use as a dietary supplement in the U.S. Stevia sweeteners are natural, contain zero calories and are 200-300 times sweeter than sugar. Stevia sweeteners are approved for food and beverage use in several countries and can be found in the U.S. in many food and beverage products, including some juice and tea beverages, as well as some tabletop sweeteners.<sup>9</sup> A review study found that stevioside and related compounds may have anti-hyperglycemic, anti-hypertensive, anti-inflammatory, anti-tumor, anti-diarrheal, diuretic, and immunomodulatory actions.<sup>10</sup> The use of stevia sweeteners as replacements for sugar would likely benefit diabetic patients.<sup>11</sup> Chemical constituent of stevia rebaudiana Over 100 photochemical have been discovered in Stevia now. It is rich in terpenes and flavonoids. It consists of eight glycosides named as stevioside, steviolbioside, rebaudiosides A-E, and dulcoside A. total sweet glycoside concentration as stevioside (5-10%), rebaudioside(1-2%),

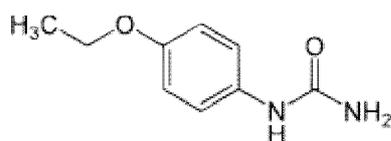
pulcoside-A(0.4-0.7%). Of these eight glycoside one called stevioside which is 300 times sweeter than sugar.<sup>12</sup> It is a cardio tonic, for obesity, hypertension and heartburn and also to help lower uric acid level.

Furthermore to being a sweetener, Stevia is considered to be hypoglycemic, diuretic, cardio tonic and tonic. The leaf is used for diabetics, obesity, hypertension, fatigue, depression, sweet cravings and infection. The leaves of the stevia shrub contain specific substances (glycosides), which produce a sweet taste but have no caloric value, apart from protein, fibers, carbohydrates, phosphorus, iron, calcium, potassium, sodium, magnesium, rutin (flavonoid), zinc, vitamin C and vitamin A.<sup>13</sup> A number of animal studies have been conducted to investigate the effects of stevioside, having antihyperglycemic, insulinotropic, and glucagon static actions in diabetic rat.<sup>14,15</sup>

### Functional Use

1. It is used as a natural sweetener, for diabetics, for high blood pressure.
2. It is used for cavity prevention, as a weight loss aid.
3. It also shows antibacterial, antifertility, anti-inflammatory, antiseptic properties.
4. It has similarly digestive tonic properties and also shows good results in cleaning up skin difficulties like acne, seborrhea, dermatitis, eczema etc.

### Dulcin



Dulcin is an artificial sweetener about 250 times sweeter than sugar discovered in 1884 by Joseph Berlinerbau. It was first mass-produced about seven years later. Despite the fact that it was discovered only five years after saccharin, it never enjoyed the latter compound's market success. Still, it was an important sweetener of the early 20th century and had an advantage over saccharin in that it did not possess a bitter aftertaste.<sup>16</sup>

### Honey



Honey is a sweet food made by bees using nectar from flowers. Honey bees transform nectar into honey by a process of regurgitation and evaporation. They store it as a primary food source in wax honey combs inside the bee hive. This alternative approach to diabetes therapy includes the use of herbal preparations, dietary components or supplements and other natural products such as honey.<sup>17</sup> Honey has been shown to scavenge reactive oxygen species, ameliorate oxidative stress and reduce hyperglycemia.<sup>18,19</sup> While honey supplementation in diabetic rats ameliorates renal oxidative stress independent of the dose, its hypoglycemic effect is dose-dependent.<sup>20</sup>

Honey gets its sweetness from the monosaccharides, fructose and glucose and has approximately the same relative sweetness as that of granulated sugar. Honey is a mixture of sugars and other compounds. To explain this surprising finding, it is hypothesized that the fructose and oligosaccharides present in honey might in some way contribute to the observed hypoglycemic effect.<sup>21,22</sup> A study, the first of its kind, reported the beneficial effects of combining anti-diabetic drugs with honey in diabetes mellitus. Honey administration was found to increase serum levels of insulin while it reduced serum concentrations of glucose and fructose amine in diabetic rats.<sup>23</sup> Furthermore, the combination of antidiabetic drugs with honey also enhanced antioxidant defenses and reduced oxidative damage in the kidney and pancreas of diabetic rats.<sup>24-26</sup>

In brief, though data from *in vivo* studies are still limited, these studies reveal that honey could be used as an adjunct to diabetes therapy to achieve better glycemic control, improve metabolic derangements and mitigate oxidative stress-linked diabetic complications. In a recent study, metformin combined with honey markedly produced lower levels of hyperglycemia, bilirubin, triglycerides, total cholesterol, VLDL and LDL and increased high density lipoprotein (HDL) cholesterol. On the other hand, metformin alone neither reduced bilirubin and triglycerides nor increased HDL in diabetic rats.<sup>27</sup>

### **Uses for natural sweeteners**

Natural sweeteners have a variety of uses both at home and in processed foods. They are sometimes known as added sugars because they're added to foods during processing. They may be used to sweeten drinks such as tea and cocktails, in desserts, as pancake and waffle toppings, on cereals.

### **Artificial Sweeteners and Diabetes**

Artificial sweeteners may be a good alternative to sugar if you have diabetes. Unlike sugar, artificial sweeteners generally don't raise blood sugar levels because they are not carbohydrates. But because of concerns about how sugar substitutes are labeled and

categorized, always check with your doctor or dietitian about using any sugar substitutes if you have diabetes. Sugars are naturally occurring carbohydrates. These include brown sugar, cane sugar, confectioners' sugar, fructose, honey, and molasses. They contain calories and raise your blood glucose levels. Reduced calorie sweeteners are sugar alcohols. The FDA has approved the following low calorie sweeteners for people with diabetes, and the American Diabetes Association also recommends them. No sugar or sugar-free. The product does not contain sugar at all, though it may contain sugar alcohols or artificial sweeteners. During processing, no extra sugar was added. However, the original source might have contained sugar, such as fructose in fruit juice. Additional sweeteners such as sugar alcohols or artificial sweeteners also might have been added.

### **Additional Health benefits**

#### **Artificial Sweeteners and Weight Loss**

Xylitol, sorbitol, and mannitol are all sugar alcohols that have a lower caloric value than sugars. In this way, they can help people to achieve their weight goals. They are incompletely absorbed by the body and what is absorbed is metabolised by insulin-independent mechanisms or excreted via the urine. A significant amount of what is not absorbed is metabolised to short chain fatty acids and gases in the large intestine. Xylitol has 2.4 calories per gram; sorbitol 2.6 calories per gram; and mannitol 1.6 calories per gram. This is compared to the traditional 4 calories per gram that sugar has. All sugar alcohols have a low GI, and they can be used to completely or partially replace traditional sugars such as sucrose and glucose. This helps to reduce the overall glycemic load of the diet, thus assisting with weight loss.

Still, some studies have shown that products that contain artificial sweeteners can actually help to promote weight gain. The theory is that when the body tastes sweetness, it prepares itself for a calorie load. If the sweetness occurs without the related calories, such as when artificial sweeteners are used, we either keep on eating or reduce our calorie-burning metabolic activity. It is currently recommended that foods and drinks that contain artificial sweeteners be used in moderation. Do not use them as an excuse to indulge in other high calorie foods or to skip physical activity that is important to weight control and health.

One of the most appealing aspects of artificial sweeteners is that they are non-nutritive they have virtually no calories. In contrast, each gram of regular table sugar contains 4 calories. A teaspoon of sugar is about 4 grams. For perspective, consider that one 12-ounce can of a sweetened cola contain 8 teaspoons of added sugar, or about 130 calories. If you're trying to lose weight or prevent weight gain, products sweetened with artificial sweeteners rather than with higher calorie table sugar may be an attractive option. On the other hand, some research

has suggested that consuming artificial sweeteners may be associated with increased weight, but the cause is not yet known.

### Dental cavities

Unlike sugar, artificial sweeteners don't contribute to tooth decay. It's no secret that sugar is not good for your teeth. High fructose corn syrup, a type of artificial sugar, isn't good for them, either. The creators of some brands of artificial sweeteners kept this in mind when creating their products. You can use some artificial sweeteners that will not harm your teeth. Some are even designed to help rebuild your teeth. This can be incredibly beneficial for you if you've suffered from problems with your teeth in the past.

### Uses for artificial sweeteners



Artificial sweeteners are attractive alternatives to sugar because they add virtually no calories to your diet. In addition, you need only a fraction compared with the amount of sugar you would normally use for sweetness.

Artificial sweeteners are widely used in processed foods, including baked goods, soft drinks, powdered drink mixes, candy, puddings, canned foods, jams and jellies, dairy products, and scores of other foods and beverages.

### CONCLUSION

Diabetes, obesity and cardiovascular disorders are associated with high sugar intake directly or indirectly. Consumption of more sugar having several difficulties on human health which diminishes quality of life. In this situation artificial sweeteners are play beneficial role in controlling blood sugar level. They also have several health benefits like they have zero calories, they do not have any adverse effect on Dental cavities. They are supportive in controlling body weight. Therefore artificial sweeteners are decent alternatives of glucose. Honey and stevia like natural sweeteners are helpful in diabetes and cardiovascular complication.

## REFERENCES

1. Bray GA: In Present Knowledge in Nutrition. Nutritional Foundation, Washington, D.C. 1990: 23-38.
2. Endres J, Poon SW, and Welch P: Diabetics in long-term care. Effect of sweetness on dietary intake. *Annals of the New York Academy of Sciences* 1989; 561: 157–161.
3. Blackburn GL, Kanders BS, Kanders PT, Lavin SD: Keller and J. Whatley. The effect of aspartame as part bacteria that eat hemicellulose in corn fiber and other. *The American Journal of Clinical Nutrition* 1997; 65: 409-418.
4. Clauss K.; Jensen H: "Oxathiazinone Dioxides - A New Group of Sweetening Agents". *Angewandte Chemie International Edition* 12 (11): 869–876.
5. Soffritti, M. and F. Belpoggi, F. Tibaldi, E.D.D. Esposti and M. Lauriola: Life-Span Exposure to Low Doses of Aspartame Beginning during Prenatal Life Increases Cancer Effects in Rats. *Environ Health Perspect* 2007; 115:1293-1297.
6. Soffritti, M F. Belpoggi, DD. Esposti and xylitol L. Lambertini: Aspartame induces lymphomas and leukemias in rats. *European journal of oncology* 2005; 10: 107-116.
7. Charu G, Dhan P, Sneha G and Sudha G: Role of Low Calorie Sweeteners in Maintaining Dental Health. *Middle-East Journal of Scientific Research* 2012; 11 (3): 342-346.
8. Packard, Vernal S: Processed foods and the consumer: additives, labeling, standards, and nutrition. Minneapolis: University of Minnesota Press 1976; 332.
9. Carakostas, M.C., 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 Toxicological* 2008; 46: S1-S10.
10. Chatsudthipong, V.; Muanprasat, C: "Stevioside and related compounds: therapeutic benefits beyond sweetness". *Pharmacological Therapeutics* 2009; 121 (1): 41–54.
11. Goyal, S. K.; Samsher; Goyal, R. K: "Stevia (*Stevia rebaudiana*) a bio-sweetener: a review". *International Journal of Food Science and Nutrition* 2010; 61 (1): 1–10.
12. R. Ranjan, J. Jaiswal and Jitendra Jena: Stevia as a Natural Sweetener. *International Journal of Research in Pharmacy and Chemistry* 2011; 1 (4): 1199-1202.
13. Kim J, Choi, C.H, & Choi, CH: Stevia, the genus *Stevia*. Medicinal and aromatic plants industrial profiles. In A. D. Kinghorn (Ed.), *Use of Stevioside and Cultivation* 2002.

14. Jeppesen, PB, Gregersen S, Alstrup, K K: Stevioside induces antihyperglycaemic, insulinotropic and glucagonostatic effects in vivo: Studies in the diabetic Goto-Kakizaki (GK) rats. *Phytomedicine* 2002; 9: 9–14.
15. Jeppesen, PB, Gregersen S, Poulsen, CR: Stevioside acts directly on pancreatic beta cells to secrete insulin: Actions independent of cyclic adenosine monophosphate and adenosine triphosphate-sensitive K<sub>v</sub>-channel activity. *Metabolism* 2000; 49: 208–214.
16. Goldsmith, R.H: "A tale of two sweeteners". *Journal of Chemical Education* 1987; 64 (11): 954–955.
17. Chawla R, Thakur P, Chowdhry A, Jaiswal S, Sharma A, Goel R, Sharma J, Priyadarshi SS, Kumar V, Sharma RK: Evidence based herbal drug standardization approach in coping with challenges of holistic management of diabetes: a dreadful lifestyle disorder of 21st century. *Journal of Diabetes Metabolite Disorders* 2013; 12: 35.
18. Beretta G, Orioli M, Facino RM: Antioxidant and radical scavenging activity of honey in endothelial cell cultures (EA.hy926). *Planta Med* 2007, 73: 1182–1189.
19. Erejuwa OO, Sulaiman SA, Wahab MS, Sirajudeen KN, Salleh MS, Gurtu S: Antioxidant protection of Malaysian tualang honey in pancreas of normal and streptozotocin-induced diabetic rats. *Ann Endocrinol (Paris)* 2010; 71: 291–296.
20. Erejuwa OO, Gurtu S, Sulaiman SA, Ab Wahab MS, Sirajudeen KN, Salleh MS: Hypoglycemic and antioxidant effects of honey supplementation in streptozotocine-induced diabetic rats. *International journal of vitamin and nutrition Research* 2010; 80: 74–82.
21. Erejuwa OO, Sulaiman SA, Wahab MS: Fructose might contribute to the hypoglycemic effect of honey. *Molecules* 2012; 17: 1900–1915.
22. Erejuwa OO, Sulaiman SA, Wahab MS: Oligosaccharides might contribute to the antidiabetic effect of honey: a review of the literature. *Molecules* 2011; 17: 248–266.
23. Erejuwa OO, Sulaiman SA, Wahab MS, Sirajudeen KN, Salleh MS, Gurtu S: Glibenclamide or metformin combined with honey improves glycemic control in streptozotocin-induced diabetic rats. *International Journal of Biological Science* 2011; 7: 244–252.
24. Erejuwa OO, Sulaiman SA, Wahab MS, Salam SK, Salleh MS, Gurtu S: Effect of glibenclamide alone versus glibenclamide and honey on oxidative stress in pancreas of streptozotocin-induced diabetic rats. *International Journal of Applied Research Nat Prod* 2011; 4: 1–10.

25. Erejuwa OO, Sulaiman SA, Wahab MS, Salam SK, Salleh MS, Gurtu S: Antioxidant protective effect of glibenclamide and metformin in combination with honey in pancreas of streptozotocin-induced diabetic rats. *International Journal of Molecular Sciences* 2010; 11: 2056–2066.

26. Erejuwa OO, Sulaiman SA, Wahab MS, Salam SK, Salleh MS, Gurtu S: Comparison of antioxidant effects of honey, glibenclamide, metformin, and their combinations in the kidneys of streptozotocin-induced diabetic rats. *International Journal Molecular Sciences* 2011, 12: 829–843.

27. Abdulrhman MM, El-Hefnawy MH, Aly RH, Shatla RH, Mamdouh RM, Mahmoud DM, Mohamed WS: Metabolic effects of honey in type 1 diabetes mellitus: a randomized crossover pilot study. *Journal of Medicinal Food* 2013; 16: 66–72.