Scope of natural sweeteners over artificial sweeteners in diabetes mellitus

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Abstract
Diabetes is very much prevalent due to the poor lifestyle choices made by people today. Diabetes treatment does not only include taking oral hypoglycaemic drugs but it also includes lifestyle and diet modification. Studies have proved that some of the artificial sweeteners are carcinogenic. They also have calories and are a mediator of obesity as they increase hunger. Other prominent side effect is the dental caries caused by artificial sweeteners. Natural sweeteners which were not very much in light before have started to gain the attention of various researchers. These sweeteners are obtained from natural sources and have remarkable sweetness when compared with sugar. This review article aims to highlight the scope of natural sweeteners and their benefits in diabetes care.
Keywords: Artificial Sweeteners, Saccharin, Sucralose, *Glycyrrhiza glabra*, Stevia

Introduction
Diabetes, characterized by hyperglycaemia is a chronic lifestyle disorder. The metabolic disorder results in elevated blood glucose due insufficient insulin secretion or action. Insulin is a hormone produced by the beta cells of pancreas responsible for regulation of the blood glucose. [1]

Type 1 diabetes is also known insulin independent diabetes mellitus. In type 1 diabetes there is no insulin secretion due to destruction of beta cells in the pancreas. It is also known as juvenile diabetes and is less prominent as compared to type 2 diabetes. The genetic component responsible for autoimmune reaction is HLA complex. However, some environmental triggers are also responsible for altering the immune function and thereby resulting in the destruction of β cells. [2] Type 1 diabetes was considered more prevalent in children and adolescents however this opinion has changed with progress in studies. The classic symptoms include polyuria, polyphagia and polydipsia along with hyperglycaemia. [3]

Type 2 diabetes is known as non-insulin dependent diabetes mellitus is a progressive disease. The major factors responsible for the disease are insulin resistance or the β cell dysfunction.

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A defect in insulin signalling leads to insulin resistance whereas due to amyloid deposition in the islets cells, excessive fatty acids, oxidative stress leads to β cell dysfunction. [4]

The use of oral hypoglycaemic drugs and lifestyle modifications is very important in the management of type 2 diabetes mellitus. The macro complications of diabetes include diabetic retinopathy, diabetic neuropathy and diabetic nephropathy. In diabetic retinopathy, the small retinal blood vessels are damaged resulting in blindness. It is observed that patients with long term diabetes often develop severe visual impairment. Up to 50% of the diabetes patients suffer from diabetic neuropathy causing nerve damage with the common symptoms of pain, tingling, weakness, numbness in the feet and hands. There are chances of increased foot ulcers eventually leading to limb amputation. A diabetes patient is also often prone to kidney failure and cardiovascular diseases primarily stroke. (WHO)

Artificial Sweeteners

The development of artificial sweeteners began in the late 19th century. The first one to be synthesized was saccharin having a sweetening property of about 300- 600 times than sugar. Aspartame (AS), acesulfame-K and sucralose are other artificial sweeteners. Recent studies have indicated that artificial sweeteners contribute to weight gain despite their lack of calories. [5, 6] The different types of artificial sweeteners are

discussed in the next sections.

Aspartame (AS)

Discovery of AS took place in the year 1965. Since 1974 it has been used as a novel sweetener in the U.S. There were many studies which proved that there was a relationship between AS and brain toxicity and was also responsible for causing cancer. Further studies failed to prove the same and it was marketed for solid food. [7]

Phenylalanine is an amino acid which is essential and it should be obtained from the diet as our body cannot metabolize it. Excess of it is broken and forms fumarate and acetoacetate, both are a part of energy metabolism. There are people who cannot convert phenylalanine to tyrosine due to enzyme inactivity or absence and are unable to metabolize phenylalanine normally. There is a name for such a condition, phenylketonuria. In this disease phenylalanine appears in the urine and hence the name. If this condition is not taken care of in time, then it can lead to problems in the brain. There are concerns related to brain toxicity in many studies. It is a genetic disease and routine tests became important. People with this disease are at a high risk after consuming phenylalanine so the products with aspartame come with a warning. [8]

When methanol is taken in excess the body is overwhelmed, the liver cannot metabolise it properly. The higher side can cause systemic acidosis. The systemic acidosis is because of the formic acid which is a breakdown product of methanol. [9] Aspartic acid is a class of excitotoxins which in extremely high quantity can lead to a variety of chronic diseases as it can cross the blood brain barrier. [10]

A study carried out at San Antonio showed a positive relation between obesity and use of artificial sweeteners. Use of AS is related to the increase in weight. Intake of this does not cause a sense of satiety which is basically the cause of cravings later. The feeling of fullness at the time of intake makes a person feel full although later there is need of fats and proteins because of which there is overeating. This leads to obesity in diabetic patients who have been taking the aspartame on a regular basis as a substitute. [11]

Acesulfame K

It was first discovered in the year 1967. Acesulfame K is sweeter than normal table sugar (almost 200 times sweeter) and is very low in calories. [12] It is a potassium salt of 6-methyl-1,2,3-oxathiazin-4(3H)-one-dioxide.

As it is not metabolized in the body it does not affect the potassium level even though it contains potassium. In the year 1988 USFDA approved the use of Acesulfame K in food and non-caloric beverages. A product formed due to the breakdown of ace-k is acetoacetamide which is known to be toxic if taken in large amount. [13]

Exposure to the sweetener has caused irritation of the eye in animals. A test conducted in New Zealand has proved that the eye turns red on exposure to acesulfame-K. [14] Many animal studies have proved the fact that AS causes increase in weight. A taste which is sweet causes insulin response but AS does not increase blood sugar level. [15, 16]

Saccharin

Saccharin was the first artificial sweetener discovered as serendipity by Constantine Fahlberg in 1997. It was discovered during clinical trials that saccharin is linked to bladder cancer in rats. Saccharin is also known to cause allergic reactions and symptoms such as headache, skin problem, and diarrhoea. [18]

The exposure study on saccharin proved its potential to induce cancer in animals (rats and dogs) and also in humans. The study included two generation bioassay and such bioassays are useful for finding the potential effects of substances. The study was done on a group of rats by exposing them to saccharin during their development. [19] Due to the above results saccharin was banned in Canada and a ban was proposed in the U.S. [20] [21]

Sucralose

It was discovered in the year 1976 and came to be known in the markets as Splenda, Sukrana, Candys, Nevella. Sucralose is a molecule containing sucrose where chlorine atoms replace three of its hydroxyl groups. [6]

Research on animals like mice, rats, rabbits have shown that sucralose causes problems like

shrunken thymus gland (40%), lymph follicles in thymus and spleen atrophy, decreased RBC count, enlarged liver and kidney, reduced growth rate and migraines etc. [22] The chemical structure of the sucralose contains 6-chloro-6-deoxyglucose which is responsible for causing infertility in rats. It was claimed in Japan that ingested sucralose leads to induction of DNA damage in gastrointestinal organs. [23]

Erythritol

Erythritol is a polyol that can be found in small quantities in vegetables, fruits, mushrooms and fermented foods. Chemically named 1,2,3,4-butaneterol, it can also be found in human tissues such as semen, lens, serum and cerebrospinal fluid. Erythritol is used widely as a bulk sweetener which is low in calories and also not causing dental problems. It has no after taste is 70% sweet when compared with sucrose. It also shows low caloric properties and has high digestive tolerance. Due to this it is highly beneficial for diabetic patients. It has antioxidant properties due to its ability to scavenge free radicals. [26]

Clinical trials

A feeding experiment consisting of albino rats weighing 40g was carried out for a period of 3 months. The test group of 20 rats received 35% dextrose and 5% of sugar alcohol i.e. sorbitol and mannitol in their balanced diet. The control group received 40% of dextrose in their balanced diet. The body weight of rats receiving sugar alcohol along with carbohydrate in their diet was found to be less than the control group receiving only carbohydrate.

Macacus rhesus monkeys were administered with 8 g per body weight of sugar alcohol after fasting for 24 hours to study the glycogen storage. After 3 hours of administration, the liver of the monkeys was extracted to estimate the glycogen storage. It could be found from the results that mannitol was incapable of glycogen storage in the liver of the fasted animal. However, sorbitol was capable of glycogen storage to some extent.

Chronic toxicity studies of sorbitol and mannitol were carried out in the rhesus monkey. Two feeding experiments were carried out each lasting for 3 months. 3 g of sugar alcohol was administered to each monkey in their daily diet. During the feeding periods, the blood sugar and nitrogen urea were continuously monitored. The results obtained showed no toxic indications or histopathological findings in case of both mannitol and sorbitol.

To study the toxicity of mannitol and sorbitol in man, normal individuals were administered 10 grams of these sugar alcohols every day for a month. Urine analysis, blood test and kidney function test were carried out during the experiments. There was no change in the blood count after 24 hours and no kidney damage in man reported at the end of the experiment.

On administering normal individuals with dextrose, sorbitol and mannitol 25 grams each it was found that mannitol and sorbitol did not significantly influence the blood sugar levels. [28]

A study was done to understand the effect of xylitol and erythritol on gastric acid and gut hormone secretion. The trial was carried out using 10 lean i.e. 5 men and 5 women having a BMI of 21.7 ± 0.5 kg/m^2 and age of 24.6 ± 0.2 year and 10 obese i.e. 5 men and women having a BMI of 40.0 ± 1.4 kg/m^2 and age of 27.2 ± 2.8 years. The diet of the subjects was restricted and a simple carbohydrate dinner before 8 pm. The fasting was from 12 am onwards. 50 grams of xylitol in 300 ml of water, 75 g of erythritol in 300 ml of water and 75 g of glucose in 300ml of water was administered to the subjects.

Various feedback mechanisms regulate gastric emptying including the release of cholecystokinin (CCK) and glucagon like peptide (GLP-1). Satiety is promoted by prolonged gastric emptying and results in meal termination. The results obtained from the trial showed glucose compared to xylitol and erythritol lead to gut hormone release thereby slowing the speed of gastric emptying. [27] Some more clinical trials in progress are briefed in table 2.

Natural sweeteners

Natural sweeteners are sugar substitutes which provide sweet taste as an alternative to sugar. They are obtained naturally from plants and hence shows very less or no side effects. Natural sweeteners can be used in the pharmaceutical and food industry. In pharmaceutical industries natural sweeteners can be used in oral and liquid

preparations to prepare the syrup base which maintains the consistency of the preparation. They are also used in lozenges, tablets and pills. These liquid preparations also help to mask the bitter taste of the drug. Sugar is helpful in coating of the tablet. In food industry, sweeteners are used for the preparation of jams, ice- creams and chocolates etc. They are effective when used in small concentrations and are stable at a wide range of temperatures. [35]

Glycyrrhiza glabra

The usage of natural plant extracts has tremendously increased in recent times. In the present context, the complications relating to treatment/control of diabetes mellitus using artificial sweeteners have been discussed. About 80% of the population on earth, now depends on the traditional medications followed since years for their first-hand heath cure. These traditional remedies involve majorly the use of the active components from the various plant parts. One of these drugs is *Glycyrrhiza glabra* (GG) /Licorice of family Fabaceae/Papilionaceae. The plant is also believed to fight low blood pressure related complications. The root of the plant is mainly used to obtain the active components such as triterpene saponins, glycerrhizhin and glycyrrhetic acid which are responsible for the above activities. The present article focuses upon the antidiabetic activity of *Glycyrrhiza glabra* and its use as a natural sweetener is under study. [29, 30] The active component responsible for imparting the sweet taste in the liquorice is an oleanane type called the triterpene saponin. The flavonoids- liquirtin, isoliquiritin, present in the plant are responsible for the yellow color of the plant. The isoflavones include glabridin, hispaglabridins A and B possess remarkable antioxidant property. [31]

Karthikeson et al. [31] investigated the *in vitro* anti diabetic action of *Glycyrrhiza glabra* using alpha amylase enzyme. In the study, a control extract of drug was compared with the test solutions of different concentrations and using different reagents. In the first extract, 100 µl of test solution was reacted with 200 µl of alpha amylase enzyme and 100 µl of 2mM Phosphate buffer. Then, this solution was allowed to incubate for 20 minutes and 100 µl of starch was added. Similar procedure was applied to prepare the controlled extract by replacing amylase enzyme with buffer. The solutions were incubated for 5 minutes followed by addition of 500 µl of di nitro salicylic acid reagent added to both the controlled and test solutions. The absorbance of these solutions was recorded at 540 nm in the spectrophotometer. The % inhibition of alpha amylase is obtained from the following formula: % inhibition = 100 * (Control-test) / Control. It was observed from the experiment that the alpha amylase enzyme showed an inhibition of about 80.78%. The inhibition results in disaccharide hydrolysis which reduces the risk of post prandial hyperglycemia.

Gupta et al. [32] concluded that the *Glycyrrhiza glabra* possesses potent therapeutic effect in glucose uptake. In this study, the role of *Glycyrrhiza glabra* in the mechanism of glucose transport was compared with metformin. The experiment was done on Swiss albino rats weighing 150-200g. These rats were maintained in standard conditions of the environment i.e. 12 hours in the day light (or artificial light) and 12 hours in the dark. Food and water were given in sufficient amounts. The effects of the extract of *Glycyrrhiza glabra* and metformin on the glucose transport mechanism and fluid absorption is shown in table 1. From table 3, it can be observed that the extract of *Glycyrrhiza glabra* is remarkably more in terms of glucose transport than metformin. Thus, there is high potency seen in the action of the *Glycyrrhiza glabra*.

Another important component of the *Glycyrrhiza glabra* named as Grz was found to show glucose suppressant action. A study carried out by Hiroshi Takii et al. [34] on the "KK-A^y" mice affected by the 'non-insulin dependent diabetes' showed that there was a notable increase in the blood insulin levels and hence the increase in the fasting blood glucose levels to normal levels after the administration of Grz. The study was performed for about 9 weeks on mice. Grz was administered in 4 different doses to mice. The doses and its effect on the body weight and appetite were recorded as shown in table 4.

Thus, a daily supplement of 0.41% Grz is highly potent to reduce or prevent the NNIDM and its complications. The higher doses may be used in case of obese patients suffering from diabetes. However, the mechanism of action by which Grz acts is still not clearly known. One possibility is Grz might act by raising the blood glucose level

remarkably after the meals, thereby reducing the insulin sensitivity in the mice. More studies are yet to be carried out to know the clear mechanism of the component. The study on mice clearly indicates the therapeutic effect of the Grz on the NNIDM affected mice as well as for the treatment of hyperglycemia.

Stevia

Stevia also known as sweat leaf, sweat herb; is obtained from *Stevia rebaudiana plant*, from the chrysanthemum family, subgroup of Asteracea family is a semi-humid subtropical plant. It is used since ancient times throughout the world. It grows 60-80cm tall and has oppositely arranged leaves. Stevia has different species and each contains potent sweetening constituents. Stevia can be grown at home with pH 6.5-7.5. It is cultivated in many Indian states. [37]

Stevia contains glycosides such as stevioside (3-10%), rebaudisoerder, dulcoside-A, rebaudiosides A, D, E and F, stevioside and rebaudioside A (Reb-A). Stevioside is a glycoside in which the aglycon moiety has glucosyl and sophorosyl residue attached to it. It is a cyclo pentanoperhydrophenanthrene skeleton.

Stevia sold on grocery stores does not contain stevia leaf as it is made by refining the extract of stevia leaf which is called as Reb-A, a novel sweetener which 200 times sweeter when compared to table sugar. It has no added chemicals but has nutritional value. It is mainly produced in Thailand, Malaysia, Japan, and Brazil. Stevia is a non-caloric sweetener and is used in many parts of world. It has little bitter after taste along with its sweetness. It has a high potency as compared to other herbal sweeteners. [37]

Leaves and its extract are safe for use. Its extract is often used for investigation as an IV infusion in rats. It affects metabolism of glucose and the functioning of the endocrine system. This extract acts as antioxidant and shows anti-androgenic activity, relieves blood pressure and hypertension. Traditionally stevia is used to sweeten tea by drying the leaves, used regularly without any side effects, though it had an unpleasant aroma. This aroma can be removed by processing it appropriately. [38]

Health Benefits

Alternate to sucrose, Stevia has potential health benefits and the sweetness occurs naturally. Stevia is considered as safe and effective for diabetic patients as it shows no effect on blood glucose. However, the raw form of the herb might harm kidney, reproductive and cardiovascular system. It may also interact with medicines that help in lowering the blood sugar as it drops blood pressure. The powdered leaf lowers cholesterol and triglycerides and also decreases calorie by providing food and beverages that contains Stevia. Hence, it is helpful in weight control and obesity. In pregnancy, glycoside Reb-A can be used in moderation. Stevioside prevents cancer by boosting death of cancer cells in breast cancer. Also, it decreases mitochondrial pathways. Steviol glycoside does not cause allergic reactions. [37] Stevia can be used instead of table sugar; its pinch is equal to one teaspoon of table sugar. Raw Stevia replaces half of the total amount of sugar. There is no calorie in the pure form of stevia. Reb-A is considered safe for all patients. [36, 37] As it does not affect the blood sugar levels, stevia is considered safe for diabetes. It has no neurological side effect and also possesses anti-fungal and anti-bacterial properties. [37]

Several trials revealed that there are no changes observed on blood pressure and blood sugar levels when steviol glycoside is administered in high doses for months. Two clinical trials conducted on hypertensive patients concluded that there was decrease in blood pressure after the patient was treated for long term with Stevioside. Its beneficial effects were seen on using steviol on the post-prandial glucose homeostasis amongst type II diabetic patients. The effects of Reb-A were examined on blood pressure of healthy individuals or subjects.

In type II diabetes, glucose homeostasis using Reb-A 1000mg/day had no marked changes in blood pressure or blood lipid or glucose homeostasis. The patients were tested in catabolic and anabolic phase. [40]

The test is performed before and after the extract is administered. Glucose tolerance is increased due to the extract and it decreases plasma glucose after an overnight fast of all the volunteers. [39]

Safety evaluation

Studies show that, absorption of small amount of stevioside undergoes degradation to give steviol via metabolism. Stevioside does not get degraded to steviol by any of the digestive enzymes present in GIT of man and animals but gets metabolized into steviol in caecum due to presence of bacterial flora when feeding of rats is done. Stevioside in rat and mouse have oral toxicity in acute amounts. According to the study on rats, there is an action seen on Na- glucose renal tubular transport system when glucose is excreted renally. It was concluded that, steviol is mainly secreted by the renal tubule epithelium which causes fall in renal tubular reabsorption, diuresis and natriuresis. Experimental studies conducted on humans and animals from stevia extract, stevioside and Reb-A reported no genotoxicity. [40]

Table 1. Toxicity of artificial sweeteners (1, 19)

Artificial sweeteners	**Metabolites**	**Minor disorders**	**Major disorders**
Aspartame	Phenylalanine, methanol, aspartic acid	Nausea and vomiting, acute seizures, dizziness, dry mouth, headache & thrombocytopenia	Leukaemia and lymphomas in rats
Acesulfame-K	--	Headache	In rats, it was found to cause tumour of thyroid gland. It is genotoxic and clastogenic at high doses.
Saccharin	O-sulfamoylbenzoic acid	Diarrhoea, nausea and vomiting	Found to cause cancer in breast fed animal offspring's. Other complications include bladder cancer, hepatotoxicity and low birth weight.
Sucralose	--	Diarrhoea	In rats, thymus shrinkage was observed.
Neotame	Methanol and neotame	Hepatotoxic at high doses and headache	Weight loss and low birth rate.

Table 2. Clinical Trial in progress

Animal used	**Time period and numbers of Animal taken**	**Amount administered**	**Results**
Rats- White male	3 months, 20 Rats	5% Control- diet consisting of 40% dextrose	The increase in body weight when compared to dextrose was less in animals administered with sugar alcohols
Macacus Rhesus Monkey	Fasting- 24 hours; 3 hours	8 g. per body weight	Sorbitol does not cause glycogen deposition in the liver of the monkeys.
Man	24 hour evaluation of urine sample, blood count and renal function test	10 g	No changes in the blood count and no kidney damage was observed.
Man	3 hours	25 g	No significant increase in blood sugar levels

*Fred W Ellis, John Krantz, [28]

Table 3. Effect of G. Glabra and Metformin on Glucose transport mechanism and fluid absorption

Glucose transport mechanism and fluid absorption	Glycyrrhiza Glabra	Metformin
Mucosal absorption	79.04 %	68.55 %
Serosal appearance	59.87 %	22.50 %
Gut wall content	19.17 %	16.05 %

Table 4. Effect on the body weight and appetite of mice with different doses of G. Glabra

Dose of Grz	Effect on the body weight and appetite of mice
2.5% daily	Decrease after a week
1%	Decrease after a week
0.41%	No change
0.27%	No change

Conclusion

Based on the studies carried out by the researchers, it can be concluded that *Glycyrrhiza glabra* is a potent natural sweetener and its consumption by the diabetic patients can be taken into consideration. Although these studies prove its activity but more research needs to be carried out in order to bring up this natural sweetener to the diabetic patients. There is no data of the clinical trials performed on human beings to support its safe use in humans. Therefore, further detailed research is must in this field to provide complete information.

Artificial sweeteners are widely used whereas the natural sweeteners are yet out of reach. Diabetes is also co morbid with conditions like obesity and hypertension. From the studies it is proved that the artificial sweeteners play a huge part in obesity development as they do not promote satiety whereas increase hunger. The major side effect of concern is the carcinogenic effect of these sweeteners on prolonged use. Sweeteners being an important part of diabetes regimen cannot be avoided. But the use of the artificial sweetener with numerous health risks is more dangerous. Sugar alcohols are also proven to have reduced or side effects when compared with artificial sweeteners. Xylitol and sorbitol are widely used and have proven dental care benefits. On the other hand, the natural sweeteners which have good health benefits for the diabetes patients are not much focused on. With the use of natural sweeteners, the co- morbid conditions can be avoided. They are known to promote satiety and do not cause an increase in body weight. They are non-carcinogenic and hence provide additional health benefits. The major drawback of natural sweeteners is that they are not easily available and there is very less information known to people. From the study it can be concluded that more research in the area of natural sweeteners is required in order to increase awareness about its benefits and increase its use.

Conflict of Interest

The authors declare no conflict of interest.

Disclaimer

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