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Non-nutritive Sweeteners and Their Role in Health Care System

Komal Dohra,* Madhuri Hinge

Pharmaceutical Quality Assurance, ROFEL, Shri G.M. Bilakhia College of Pharmacy, Vapi, Gujarat, India

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For Correspondence:

Komal Dohra

Pharmaceutical Quality Assurance, ROFEL, Shri G.M. Bilakhia College of Pharmacy, Vapi, Gujarat, India.

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ABSTRACT:

There are two main categories of sweeteners: artificial or synthetic sweeteners and natural sweeteners derived from plants. Sweetening substances either provide a sweet flavour or enhance the perception of a sweet taste. More sugar is consumed at a higher risk of gaining weight and developing ailments like diabetes, obesity, and cardiovascular issues. These days, foods with no added sugar have a considerably better reputation because of their low or no calorie counts. As a result, numerous food manufacturers replace sugars with other low-calorie artificial sweeteners, also called non-nutritive sweeteners (NNS). NNS are dietary supplements that mimic the sweet flavour effects of sugar with lower caloric intake. As a result, NNS is now used more frequently worldwide. FDA has accepted the use of eight artificial sweeteners (saccharin, acesulfame-K, aspartame, sucralose, stevia, neotame, advantame, luo ha guo). These artificial sweeteners or sugar substitutes are widely used in the dairy, medicinal, and processed food industries. The primary goal of this review is to discuss the various artificial sweetener and how they can be used to avoid various ailments within the healthcare system.

KEYWORDS: Non-nutritive sweeteners, Artificial sweeteners, Obesity, Dental health, Diabetes, Metabolic syndrome, Reactive hypoglycemia.

INTRODUCTION [1-10]

Natural sweeteners such as fructose and sucrose give sweetness to a substance, but they also contain calories that may be harmful to humans when taken in excess quantities. Sugar is a natural sweetener with 4 calories per gramme. It is known that consuming too much sugar results in consuming more calories, which can cause weight gain and chronic disorders linked to obesity and tooth caries. Therefore, there is a demand for sugar alternatives that can aid in calorie reduction, especially in overweight people. Worldwide, there is a growing need for innovative, "low calorie," substitute sweeteners for diabetic and dietetic applications.

On the other hand, artificial sweeteners are substances used as substitutes for natural sugar (sucrose). They consist of fewer calories. These are many times sweeter compared to regular sugar, so they are also known as intense sweeteners. Due to the low metabolic rate of the human body, non-nutritive sweeteners (NSSs) have a reasonable sweetness but do not raise the calorie count.[1] Other names of non-nutritive sweeteners are artificial sweeteners, sugar substitutes, and high-intensity sweeteners.

Non-nutritive sweeteners (NNS) are also called as artificial sweeteners as they provide a sweet taste like that of sugar while containing less food energy than sugar-based sweeteners thus, making them zero-calorie or low-calorie sweeteners. As compared to sucrose, NNS are at least 13 to 13,000 times sweeter in taste.[2] NNS is used by obese and diabetic people to lower calorie and carbohydrate consumption for weight management and glycaemic control. Artificial sweeteners may be derived through the manufacturing of plant extracts or processed by chemical synthesis. For instance, whereas stevia and its extract stevioside are obtained from natural sources, aspartame, acesulfame potassium, and sucralose are chemically generated. These sweeteners are widely used in baked

goods, carbonated beverages, powdered drink mixtures and dairy products.

This non-nutritive sweetener is normally referred as sugar substituent. Sugar substitutes have been classified as natural sweeteners and artificial sweeteners (table no 1). Natural sugar substitutes and sugar alcohols occur naturally in fruits and vegetables and can be manufactured industrially. They are not considered as intense sweeteners as they are less sweet than sugar. Brazzein, Erythritol, Curculin, Lactitol, Maltitol, Glycerol, Glycyrrhizin, Mannitol, Sorbitol, Xylitol, Stevia, Tegatose, and Trehalose are a few significant natural sweeteners. Artificial sweeteners are sweeteners that do not occur naturally. These Artificial sweeteners can be consumed safely up to an Acceptable Daily Intake (ADI). The main benefits of using artificial sweeteners are reducing obesity, dental care, diabetes mellitus, reactive hypoglycemia and low cost. Non-nutritive sweeteners are commercially available in various forms, such as small pills, powders, and packets.

Table no. 1: Various forms of sugar substituent

Nutritive sweeteners	Non-nutritive sweeteners
➢ Monosaccharide polyols • Sorbitol • Xylitol • Mannitol • Erythritol ➢ Disaccharide polyols • Isomalt • Maltilol • Isomaltulose ➢ Polysaccharide polyols • Hydrogenated glucose syrup(lycasin)	• Saccharin • Acesulfame-K • Aspartame • Sucralose • Stevia • Monk fruit • Neotame • Advantame

OVERVIEW OF NON-NUTRITIVE SWEETENERS

FDA has approved the use of the following non-nutritive sweetener: saccharin, acesulfame-K, aspartame, sucralose, stevia, neotame, advantame.

Saccharin

Saccharin is approved for use in food as a non-nutritive sweetener. It is the oldest artificial sweetener. Saccharin brand names include Sweet and Low®, Sweet Twin®, Sweet'N Low®, and Necta Sweet®. Benzoic sulfilimine is the basic constituent of saccharin which is sweeter as compared to sucrose and gives no calories. It is 200 to 700 times sweeter than table sugar (sucrose), and it does not contain any calories. It is a true “non-caloric” food additive because it is resistant to degradation and thus excreted by body intact. Saccharin is very effective in diabetic population because it does not get absorbed and digested in gastrointestinal tract, thus not affect insulin level.[3] Saccharin is often used in baked goods, jams, jelly, chewing gum, canned fruit, candy, dessert toppings, and salad dressings. It can also be found in cosmetic products, including toothpaste and mouthwash. Additionally, it’s a common ingredient in medicines, vitamins, and pharmaceuticals.

Metabolism and health aspects:

In 1977, the FDA tried to ban saccharin after rat cancer in animal experiments (mainly bladder cancer). Saccharin has since been the subject of numerous studies. Saccharin consumption and health hazards in people at normal dosages have never been causally linked in any study. An interim regulation that limits the maximum amounts of saccharin that can be used in processed foods, beverages and sugar substitutes is now in effect. This law also mandates that the product level must list saccharin in the ingredient declaration and identify the amount used.

Saccharin has no nutritional value and no food energy. For individuals who have diabetes, it is safe to consume.[4] Saccharin is a sulfonamide derivative and can cause allergic reactions in people who are sensitive to sulfonamides. For those who are sensitive, the saccharin in toothpaste might result in mouth and lip rashes, swelling and burning sensations. Excess consumption or ingestion of saccharin severe headaches, difficulty in breathing and eruption of skin and diarrhoea.

Aspartame

Aspartame is a non-saccharide artificial sugar substitute, first synthesized in 1965. It is the methyl ester of the dipeptide of natural amino acids L-aspartic acid and L-phenylalanine. However, it cannot be called a non-caloric sweetener because it is absorbed and metabolized after being broken down in the gut.[5] Aspartame brand names include Nutrasweet®, Equal®, and Sugar Twin®. It is about 200 times sweeter than table sugar. FDA approved aspartame in 1981 for uses, under certain conditions, as a tabletop sweetener, in chewing gum, cold breakfast cereals, and dry bases for certain foods (i.e., beverages, instant coffee and tea, gelatins, puddings, and fillings, and dairy products and toppings). In 1983, FDA approved the use of aspartame in carbonated beverages and carbonated beverage syrup bases, and in 1996, FDA approved it for use as a "general purpose sweetener". It is not heat stable and

loses its sweetness when heated, so it typically isn't used in baked goods.

Metabolism and health aspects:

After consumption, aspartame disintegrates into natural residual components including aspartic acid, phenylalanine, and methanol. It also further breakdown into formaldehyde, formic acid, and diketopiperazine. Each of which is safe when ingested in a typical diet since it is digested exactly as it would be if it were derived from other food sources. Aspartame disintegrates into a compound Diketopiperazine which may be accountable for these adverse effects.[6]

Since the U.S. Food and Drug Administration (FDA) first approved aspartame in 1974, there has been debate about the substance's safety. For persons born with the rare hereditary condition phenylketonuria (PKU), high levels of the naturally occurring essential amino acid phenylalanine pose a health risk. Because people with phenylketonuria cannot metabolize phenylalanine, aspartame is contraindicated in these patients, and items containing aspartame should be labelled accordingly.[7] Nalt Toxicological Programme (NTP) conducted investigations on the carcinogenicity of aspartame in 2 strains of transgenic mice, and they came to the conclusion that aspartame exposure was linked to an increase in either male or female mice's risk of developing cancer. More than 90 nations around the world have determined that aspartame is safe for consumption by people based on reviews of government research and recommendations from advisory bodies such as European Commissions Scientific Committee on Food and joint FAO/WHO expert committee.

Acesulfame potassium (Ace-K)

Acesulfame potassium is combination of an organic acid and potassium and is named on food label as acesulfame K, acesulfame potassium or Ace-K. Is is about 200 times sweeter than table sugar and is often combined with other sweeteners. Acesulfame potassium is sold under the brand names Sunett® and Sweet One®. FDA approved acesulfame potassium for use in specific food and beverage categories in 1981 and in 2003 approved it as a general-purpose sweetener and flavour enhancer in food, except in meat and poultry, under certain conditions of use. It is heat stable, meaning that it stays sweet even when used at high temperatures during baking, making it suitable as a sugar substitute in baked goods. Acesulfame potassium is typically used in frozen desserts, candies, beverages, and baked goods.

Metabolism and health aspects:

Acesulfame-K is not metabolized in the human body, thus mite provides no calories and does not influence potassium intake despite its potassium content.[8] One breakdown product of ace-k is acetoacetamide known to be toxic if consumed in very large doses because human exposure to this breakdown product would be negligible.

The Ace-k constituent methylene chloride is carcinogenic and causes cancer in humans. This might induce serious headaches, sadness, nausea, mental disturbances, liver, and kidney issues if used in excess. When ace-k is metabolised in the human body, it produces acetoacetamide, a very poisonous compound that induces tumours in the thyroid glands of rats, dogs, and rabbits.

Sucralose

Sucralose, the most used artificial sweetener in the world, is a chlorinated sugar that is 600 times sweeter than table sugar. Splenda® is the trade name for the brand of sucralose. Three chlorine atoms replace three hydroxyl groups to create it from sugar. Sucralose is approximately 3.3 times sweeter than aspartame, twice as sweet as saccharin and 600 times sweeter than table sugar. It can be used as an additive in products requiring a longer shelf life because of its stability under extreme temperatures and over a wide range of pH.[9] In addition to other foods, it is utilized in beverages, frozen desserts, chewing gum, and baked goods. It is stable when heated, unlike other artificial sweeteners, and can therefore be used in baked and fried items. Sucralose was discovered in 1976, and the FDA approved its usage in 1998.

Metabolism and health aspects:

Despite being manufactured from sugar, sucralose has no calories since it is not metabolized by the body and is not recognized as a sugar human body. While 11- 27% of the sucralose that is consumed is absorbed, the majority of it is directly expelled in the faeces without passing through the digestive tract. The kidneys primarily remove the quantity received from the gastro intestinal tract from the bloodstream and discard it in the urine. Sucralose is not known to be harmful despite being an organo chloride since some of which are known to have high toxicity. Sucralose also doesn't degrade or dechlorinate.

The FDA examined information from more than 110 studies on humans and animals to determine the safety of sucralose. Numerous research sought to find

potential hazardous effects, such as neurological and reproductive effects that could be cancerous, however none of these effects were discovered. Sucralose approval

by the Food and Drug Administration (FDA) is based on research showing that it is safe for human consumption.

Neotame

Neotame is a derivative of dipeptide phenylalanine and aspartic acid. It is approximately 7,000-13,000 times sweeter than table sugar. Neotame is sold under the brand name Newtame®. This substance is rapidly metabolized and completely eliminated from the body, reducing the availability of phenylalanine. In 2002, the FDA approved neotame to be used as a general purpose sweetener and as a flavor enhancer in foods, except in meat and poultry. It is heat stable, meaning that it stays sweet even when used at high temperatures during baking, making it suitable as a sugar substitute in baked goods.

Metabolism and health aspects:

Neotame is quickly broken down, entirely removed, and does not build up in the body. Esterase, which is found throughout the body, hydrolyzes the methyl ester, which is the main metabolic pathway for neotame. The main metabolite, de esterified neotame, is produced along with a significant amount of methanol. The 3,3-di-methylbutyl group peptide link between the aspartic acid and phenylalanine moieties. This decreases the availability of phenylalanine. The amount of methanol obtain from neotame is extremely small.[10]

Neotame consumption affects the liver when consumed in excess. Other harmful effects of neotame include changes in body weight, moderate headaches, and appetite reduction. It is safe for those who suffered phenylketonuria.[11]

Advantame

Advantame is the most recent NNS to receive FDA approval for use as a multipurpose sweetener and flavour enhancer. It shares a structural similarity with aspartame but is sweeter (approximately 20,000 times sweeter than sucrose). It can be used as a sugar substitute in various items, including baked foods, as it is stable to low pH and high temperature. Advantame can be ingested by those who have phenylketonuria and is used in very tiny amounts due to its great sweetness and low-calorie content.

Metabolism and health aspects:

Advantame is poorly absorbed, and rapidly metabolized and only small amounts of it and its metabolites can be detected in blood shortly after ingestion. 52% of the ingested dose is excreted in feces as de-esterified advantame and 30% as N-(3-(3- hydroxy-4-methoxyphenyl)) propyl-L-aspartic acid and as an equivalent molar amount of phenylalanine. In the body, aspartame is broken down into phenylalanine. For most people, this in turn is broken down into tyrosine. However, for persons with the congenital disease phenylketonuria, phenylalanine is not broken down but concentrated in the blood. Eventually, that leads to damage. The European Food Safety Authority (EFSA) has concluded that aspartame-derived sweetener advantame is safe for human consumption.

Stevia

It is a generic term used for food ingredients derived from the herb Stevia rebaudiana, a plant native to South America. Steviol glycosides, is the term used to refer to a group of intensively sweet compounds extracted and purified from leaves of this plant. Steviol glycoside is nonnutritive sweeteners which are 200-400 times sweeter than table sugar. The FDA has categorized steviol glycoside of high purity (95% minimum purity) as generally recognized as safe. In August 2019, the FDA placed an import alert on stevia leaves and crude extracts – which do not have GRAS(generally recognized as safe) status – and on foods or dietary supplements containing them due to concerns about safety and potential for toxicity. Stevia is a genus of around 240 species of shrubs and herbs in the Asteraceae family. [12]

Metabolism and health aspects:

The steviol is transported via the blood to the liver where it reacts with glucuronic acid to form steviol glucuronide. The steviol glucuronide ends up in the kidneys and is excreted in the urine. There is no accumulation in the body of steviol glycosides. The steviol glycosides pass through the body untouched (as opposed to sugar) down to the colon where the glycoside is gradually eliminated by hydrolysis to produce steviol. The liver receives the steviol through the blood, where it is transported and combined with glucuronic acid to create steviol glucuronide. The steviol glucuronide is eliminated in the urine after passing through the kidneys. The body does not accumulate steviol glycosides. It is suited for diabetic and obese person. It may be advantageous in the later of type 2 diabetes. Due to its additional benefit of reactivating pancreatic beta cells that secrete insulin, it is advantageous as a food additive for the diabetic population and improves glucose tolerance.[13] It can substitute for of sugar in toothpaste because it also helps prevent tooth decay. It also showed antibacterial, antiseptic, anti-inflammatory, anti-fertility, hypotensive, diuretic and cardiotonic properties. It has shown good results in clearing up skin problems like acne, dermatitis,

eczema etc. Steviol regulate blood glucose level by enhancing not only insulin secretion but also insulin utilization in insulin deficient animal. It is also used as digestive tonic.

Luo Han Guo

The Siraitia grosvenorii Swingle fruit extract, usually known as Luo Han Guo or monk fruit, is an extract with sweet taste containing different non-nutritive mogrosides (mostly mogroside V) obtained from a plant native to Southern China, and it recently received the "generally recognized as safe" status by the FDA. Mogrosides, a kind of triterpene glycosides that make up roughly 1% of the fresh fruit's flesh, are primarily responsible for the fruit's sweetness. It is about 100-250 times sweeter than sucrose.

Others sweeteners

Xylitol: Xylitol is a lower-calorie sugar substitute with a low glycemic index. Xylitol is a natural sugar alcohol found in plants, including many fruits and vegetables. It has a sweet taste and is often used as a sugar substitute. Xylitol has recognized glycemic index of 8 and caloric value of 2.4 calories/gm. The joint expert committee on food additives (JECFA) confirmed the safety of xylitol for human use and allocated an ADI of 'Not specified'. It is a common ingredient in sugar-free chewing gums, candies, mints, diabetes-friendly foods and oral-care products.

Cyclamates: Cyclamates include three similar compound namely sodium cyclamate, calcium cyclamate and cyclamic acid and are about 30 times sweeter than natural sugar. It is a salt of cyclohexylsulfamic acid. Sodium cyclamate is used as non-nutritive sweetener and the analogues calcium salt used specially in low sodium diets. Cyclamate is used together with other NNS because of their low potency among artificial sweeteners available in market.

Alitame: Alitame is a potent sweetener with 200 times more sweetness potential than sucrose. It is a dipeptide of L-aspartic acid and D-alanine with a terminal N- substituted tetra methylthietanyl-amine moiety. Alitame is easily absorbed in the GI tract, rapidly metabolized, and then quickly eliminated. Aspartic acid and alanine amide are its two primary constituents. The aspartic acid component is routinely digested, and the alanine amide moves through the body with few metabolic modifications.

Rare sugar: Recently, a lot of interest has been focused on rare sugars, which are defined as monosaccharides and their derivatives that are rare in nature. Due to its low caloric content, this can offer an alternative to the other sweetener. Rare sugars are either not digested by the body at all or just partially metabolised compared to natural sugar. Due to these Patients with diabetes can easily tolerate these. The absence of any unfavourable aftertaste is another benefit of rare sugar.

Table no. 2: Characteristics of non-nutritive sweetener

Non-nutritive sweetener	Acceptable Daily Intake(ADI), FDA (mg/kg body weight)	Times sweeter than sucrose	Uses
Saccharin	15	200-700	Soft drinks, beverages, fruit drinks, powdered dessert mixes, Chewing gum, Baked goods, canned fruits
Aspartame	50	200	Tabletop sweetener (in packets), chewing gums, instant coffee and tea, gelatins, puddings, Yoghurt
Acesulfame-K	15	200	Tabletop sweeteners (in packets), carbonated beverages, desserts which are frozen, Candies, Chewing gum, Dairy products, syrups and sauces
Sucralose	5	600	Tabletop sweetener (in packets), baked foods, Frozen desserts and dairy products, Fruits juices, Chewing gum
Neotame	0.3	7000-13000	Baked goods, Soft drinks, Chewing gum, Jams, Jellies, Puddings, Processed fruit and fruit juices
Stevia	4	200-400	Ice cream, sauces, yogurts, pickled food, chewing gums
Advantame	32.8	20000	Bubble gums, flavoured product, milk products
Luo Han Guo	-	100-250	Coffee, sauces, smoothies, yogurt

EFFECT OF NON-NUTRITIVE SWEETENERS ON HEALTH

Obesity

Obesity is a condition in which excess body fat has accumulated to such an extent that it may have a negative effect on health. Obesity is a major cause of disability and is correlated with various diseases and conditions,

particularly cardiovascular diseases, type 2 diabetes, obstructive sleep apnea, certain types of cancer and osteoarthritis. For persons who are attempting to lose weight or maintain their present weight, non-nutritive sweeteners may be helpful. Compared to the 16 calories in 1 teaspoon (4 grams) of sugar, non-nutritive sweeteners have less or no calories. They can mimic the sweetness of sugar without the calories when used as tabletop sweeteners, in cooking, or in baking. The American Dietetic Association suggested that, if added sugars are replaced with NNS an average of 360 fewer calories will be ingested per day, resulting in weight loss of approximately one pound over 10 days.[14]

Regarding weight control, some observational studies report a link between consuming artificially sweetened beverages and obesity. NNS consumption is associated with higher body weight and metabolic disease in observational studies. In contrast, randomized controlled trials demonstrate that NNS may support weight loss, particularly when used alongside behavioral weight loss support. Additional long-term, well-controlled intervention studies in humans are needed to determine NNS effects on weight, adiposity and chronic disease under free-living conditions.[15] These studies also show that replacing regular soft drinks with sugar-free versions can decrease body mass index (BMI) by up to 1.3–1.7 points. However, a high-quality study that analyzed all the evidence about artificial sweeteners and how they affect food intake and body weight determined that replacing sugar with zero- or low-calorie sweeteners does not cause weight gain.

Dental health

Caries or tooth decay, commonly referred to as dental cavities, result from the bacteria in your mouth fermenting sugar. The creation of acid can harm tooth enamel. Artificial sweeteners do not interact with the microorganisms in your mouth like sugars do. This implies that they don't produce acids or lead to tooth decay.[16] Non-nutritive sweeteners do not increase the chances of developing dental cavities. That is why they are used in oral hygiene products, such as mouthwash and toothpaste. Stevia also has a role in reduction of tooth decay, therefore can act as a substitute for sugar in tooth pastes. Studies have shown that xylitol may help prevent dental cavities.

Xylitol is used as an additive in consumable items, medicines and oral hygiene products such as toothpaste, mouthwashes and fluoride tablets, it has a well- studied role in preventing demineralization of tooth enamel, retardation of progression of plaques & dental cavities, increasing saliva production and protecting salivary proteins.[17] Sucralose is less likely than sugar to contribute to tooth decay, according to research. Because of this, the Food and Drug Administration (FDA) permits sucralose-containing products to make the claim that they lessen tooth decay. According to the European Food Safety Authority (EFSA), all artificial sweeteners neutralize acid and aid in preventing tooth decay when used in place of sugar.

Diabetes

Artificial sweeteners may be advantageous for diabetics because they provide a sweet flavour without causing a spike in blood sugar levels. Saccharin is very effective in the diabetic population because it does not get absorbed and digested in the gastrointestinal tract, thus not affecting insulin levels. Stevia is beneficial as a food additive for diabetic population because of its added benefit in reactivating insulin-secreting pancreatic beta cells, thus boosting glucose tolerance.[18] However, some studies report that drinking diet soda is associated with a 6–121% greater risk of developing diabetes. On the other hand, many controlled studies show that artificial sweeteners do not affect blood sugar or insulin levels. Grotz conducted a randomised, double-blind research in 128 subject with type II diabetes, that showed the advantages of NNS in this population.[19] The findings revealed that sucrose consumption of 667 mg/day for 13 weeks had no impact on fasting plasma glucose, fasting serum C.peptide, or glycosylated (HbA 1C). Based on each participant's body weight, it was estimated that they consumed 7.5: 0.2 mg/kg/day of sucralose daily, which is about three times more than the daily dosage of 2.4 mg/kg/day. According to this study's findings, sucralose-sweetened meals and beverages are advantageous for diabetic patients. Type II diabetics who consumed 7.5 mg of sucralose per kilogram of body weight per day for 13 weeks did not experience any changes in their glucose homeostasis.

Metabolic Syndrome

Metabolic syndrome refers to a cluster of medical conditions, including high blood pressure, high blood sugar, excess belly fat, and abnormal cholesterol levels. These conditions increase your risk of chronic disease, such as stroke, heart disease, and type 2 diabetes. A review was conducted which discuss the role of non nutritive sweeteners in metabolic syndrome, which focus on three main potential mechanism: NNS interacting with sweet taste receptors, NNS interfering with gut microbiota composition, and NNS interfering with learned responses

to sweetness.[20] Some study suggest that, consumption of diet soda at least daily was associated with significantly greater risks of select incident metabolic syndrome components and type 2 diabetes.[21] Many studies were conducted which shows that, risk of developing metabolic syndrome is probably not increased by artificial sweeteners.

Reactive hypoglycemia

Reactive hypoglycemia (RH) is the condition of post prandially hypoglycemia occurring 2-5 hours after food intake. RH refers to low blood sugar that occurs after a meal- usually within 4 hours after eating. Reactive hypoglycemia causes an excess of insulin to be produced by the body after glucose is swiftly absorbed into the bloodstream. Their blood glucose levels thus drop below the level required for physiological activity. Because of this, they must avoid eating high-glycemic items like white bread, just like diabetics, and frequently opt for artificial sweeteners as a substitute.

HEALTH HAZARDS

Depression, anxiety and mood disorders

Researchers have discovered a link between depression and irritability and diets heavy in artificial sweeteners.[22] According to a different study, people who suffer from mood disorders should stay away from artificial sweeteners since they make them particularly sensitive.[23]

Weight gain

Artificial sweeteners slow down your metabolism by interfering with your body's insulin and glucose levels. The body interprets this as becoming more hungry, which might result in overeating. Artificial sweeteners have long been marketed as low-calorie options that are safe for those trying to reduce weight. However artificial sweeteners are now recognised for changing the gut microbiota and causing weight gain.[24]

Headache and migraine

It's crucial to stay away from artificial sweeteners if you experience frequent headaches or migraines (especially aspartame). Recent research have discovered nutritional correlations between prolonged use of artificial sweeteners and headaches or migraines.[25]

Cancer

Consuming artificial sweeteners has been shown to increase the size of cancerous tumors. Researchers have called aspartame—one of the most dangerous artificial sweeteners—a 'multi-potent carcinogenic compound'. Another study even referred to America's consumption of aspartame as an 'urgent matter'.[26, 27, 28]

Risk for pregnant women

According to studies, children whose mothers consumed artificial sweeteners when they were pregnant and lactating had an increased risk of developing obesity and metabolic syndrome diseases.[29] Two commonly used artificial sweeteners, aspartame and sucralose, which can be found in diet soda and sugar- free candies and gum, have been the subject of years of research and controversy concerning their safety when consumed while pregnant.[30] Artificial sweeteners have been related to premature delivery and can make newborns gain weight before birth, according to evidence.[31, 32]

Increased risk of Irritable Bowel Syndrome and Crohn's disease

The gut flora, which is the centre of your digestion and immune system, has been found to change when artificial sweeteners like Splenda, another name for sucralose, are consumed in large quantities. Additionally, artificial sweeteners have been associated with gut irritability and, in certain situations, can set off Crohn's disease and Irritable Bowel Syndrome (IBS) in vulnerable patients.[33]

Table no.3: Toxic potential of artificial sweeteners

Sweeteners	Known metabolite	Acute effect	Chronic effect
Aspartame	Methanol, aspartic acid, phenylalanine	Headache, dry mouth, dizziness, nausea, vomiting, thrombocytopenia, mood swings	Lymphomas and leukemia in rodents
Saccharin	Sulfamoylbenzoic acid	Nausea, vomiting, diarrhea	Cancer in offspring of breast-fed animals, low birth rate ,bladder cancer, hepatotoxicity
Neotame	De-esterified neotame, methanol	Headache, hepatotoxic at high dose	Lower birth rate, weight loss
Sucralose	-	Diarrhoea	Thymus shrinkage and enlargement in rats
Acesulfame-K	Acetoacetamide	Headache	Clastogenic, genotoxic at high dose,

			thyroid tumors in rats
Cyclamate	Cyclohexylamine	_	Bladder cancer in mice, testicular atropy in mice

Conflict of interest:

There was no conflict of interest between the authors and co-authors regarding the content and the review work.

CONCLUSION:

The risk due to the most common disease like obesity, diabetes and cardiovascular risk are increasing nowadays. People's concern for their health has increased as a result of an increase in sugar consumption from processed foods, sweets and soft drinks. For this reason, artificial sweeteners or sugar substitutes are becoming more popular. The use of non-nutritive sweeteners has several benefits and drawbacks, therefore the physician should suggest proper usage of these sweeteners based on the patient's clinical profile. Thus, patients can have a healthy and prosperous life without sacrificing taste by using artificial sweeteners wisely.

REFERENCES

1. Miller, P.E. and Perez. Low-calorie sweeteners and body weight and composition: a meta-analysis of randomized controlled trials and prospective cohort studies, The American Journals of Clinical Nutrition, 2014, 100(3): 765-777.

2) Zygler A, Wasik A, Kot-Wasik AK, etal. Determination of nine high- intensity sweeteners in various foods by high-performance liquid chromatography with mass spectrometric detection, Anal Bioanal Chem, 2011,400: 2159–2172.

3) Mukherjee M, Sarkar A. etal. Sugar content in artificial sweeteners, Adv Appl Sci RES, 2011, 2: 407-409.

4) Low-Calorie Sweeteners: What's News, What's New, American Diabetes Association. Archived from the original on 2016-03-04.

5) Deepak jain, Pulkit Chhabra, etal. Non nutritive sweeteners– Current perspective, Romanian Journal of Diabetes Nutrition & Metabolic Diseases , Vol. 24, 2017; 58-64.

6) Prodolliet J, Bruelhart M. Determination of aspartame and its major decomposition products in foods. JAOAC Int, 1993, 76: 275–282.

7) Fitch C, Keim KS. Position of the Academy of Nutrition and Dietetics: use of nutritive and nonnutritive sweeteners. Journal of the Academy of Nutrition and Dietetics, 2012, 112: 739–758.

8) American Dietetic Association, Position of the American Dietetic Association: use of nutritive and nonnutritive sweeteners. Journal of the American Dietetic Association, 2004, 104:255–275.

9) Knight I. The development and applications of sucralose, a new high- intensity sweetener, Canadian Journal of Physiology and Pharmacology, 1994,72: 435–439.

10) Neotame: Stability overview (2002) http://www.neotame.com/pdf/ neotame_stability_overview_US. Accessed 27 February 2009.

11) Nofre C. Neotame: discovery, properties, utility, Food Chemistry, 2000, 69(3): 245-257.

12) Abdullateef RA, Osman M, Studies on effects of pruning on vegetative traits in Stevia rebaudiana Bertoni (Compositae). International Journal of Biology, 2012,4: 146- 153.

13) Koyama E, Kitazawa K, Ohori Y et al. In vitro metabolism of the glycosidic sweeteners, stevia mixture and enzymatically modified stevia in human intestinal microflora. Food Chem Toxicol, 2003,41: 359–374.

14) Position of the American dietetic association use of nutritive and nonnutritive sweeteners, Journal of American Dietetic Association, February 2004,104(2) 255-275.

15) Sylvetsky AC, Rother KI. Nonnutritive sweeteners in weight management and chronic disease: a review. Obesity. 2018 Apr;26(4):635-40.

16) Irwin D Mandel, V Lee Grotz; Dental Consideration in Sucralose use, 2002, 13(3):116-118.

17) Makinen KK. Dietary prevention of dental caries by xylitol - clinical effectiveness and safety. J Applied Nutr 1992,44: 16-28.

18) Koyama E, Kitazawa K, Ohori Y et al. In vitro metabolism of the glycosidic sweeteners, stevia mixture and enzymatically modified stevia in human intestinal microflora. Food Chem Toxicol, 2003,41: 359–374.

19) Grotz VL, Henry RR, McGill JB, et al. Lack of effect of sucralose on glucose homeostasis subjects with type 2 diabetes. , Journal of American Dietetic Association. 2003; 103: 1607-1612.

20) Pepino MY. Metabolic effects of non-nutritive sweeteners. Physiology & behavior. 2015 Dec 1;152:450-5.

21) Jennifer A Nettleton, Pamela L Lutsey, youfa Wang, etal, Diet soda intake and risk of incident metabolic

syndrome and type 2 diabetes in the Multi-Ethnic Study of Atherosclerosis (MESA), 2009 Apr;32(4):688-94.

22) Lindseth GN, Coolahan SE, Petros TV, Lindseth PD. Neurobehavioral effects of aspartame consumption. Research in nursing & health. 2014 Jun;37(3):185-93.

23) Walton RG, Hudak R, Green-Waite RJ. Adverse reactions to aspartame: double-blind challenge in patients from a vulnerable population. Biological Psychiatry. 1993 Jul 1;34(1-2):13-7.

24) Jotham Suez, Tal Korem, David Zeevi, etal. Artificial sweeteners induce glucose intolerance by altering the gut microbiota, 2014,181-186.

25) R B Lipton, L C Newman, J S Cohen, etal; Aspartame as a dietary trigger of headache, 1989 Feb;29(2):90-2.

26) Morando Soffritti , Michela Padovani, etal. The carcinogenic effects of aspartame: The urgent need for regulatory re-evaluation, 2014 Apr;57(4):383-97.

27) Morando Soffritti, Fiorella Belpoggi, etal. First Experimental Demonstration of the Multipotential Carcinogenic Effects of Aspartame Administered in the Feed to Sprague-Dawley Rats, 2006 Nov,114(3): 379–385.

28) Eva S Schernhammer, Kimberly A Bertrand, etal. Consumption of artificial sweetener– and sugar-containing soda and risk of lymphoma and leukemia in men and women, The American Journal of Clinical Nutrition, Volume 96, Issue 6, December 2012, Pages 1419–1428.

29) Joao Ricardo Araujo , Fatima Martel etal. Exposure to non-nutritive sweeteners during pregnancy and lactation: Impact in programming of metabolic diseases in the progeny later in life, 2014 Nov;49:196-201.

30) Alyssa J. Archibald, Vernon W. Dolinsky, Early-Life Exposure to Non- Nutritive Sweeteners and the Developmental Origins of Childhood Obesity: Global Evidence from Human and Rodent Studies; 2018 Feb; 10(2): 194.

31) Meghan B. Azad, Atul K. Sharma, etal. Association Between Artificially Sweetened Beverage Consumption During Pregnancy and Infant Body Mass Index. July 2016;170(7):662-670.

32) Thorhallur I Halldorsson, Marin Strom, etal. Intake of artificially sweetened soft drinks and risk of preterm delivery: a prospective cohort study in 59,334 Danish pregnant women, The American Journal of Clinical Nutrition, Volume 92, Issue 3, September 2010, Pages 626–633.

33) Rodriguez-Palacios A, Harding A, Menghini P, Himmelman C, Retuerto M, Nickerson KP, Lam M, Croniger CM, McLean MH, Durum SK, Pizarro TT. The artificial sweetener splenda promotes gut proteobacteria, dysbiosis, and myeloperoxidase reactivity in Crohn's disease–like ileitis. Inflammatory bowel diseases. 2018 Apr 23;24(5):1005-20.

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