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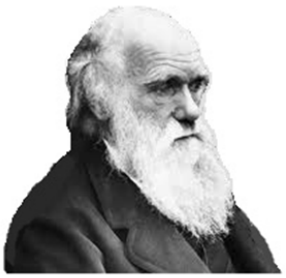

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Sugar Substitutes/Artificial Sweeteners: Benefits Vs Health Issues, and Alternatives

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ABSTRACT

The meals we eat every day contain sugar, which is an essential component. It is a soluble carbohydrate with a sweet flavor that imparts sweetness to food. Sugar consumption has been linked to health problems like cavities, weight gain, inflammation, diabetes, obesity, etc. As a result, using artificial sweeteners in place of sugar is now possible. Food additives known as artificial sweeteners work similarly to sugar but have less nutritional value. Saccharin, sucralose, aspartame, and acesulfame-K are a few examples. Artificial sweeteners can help with weight loss, diabetic management, dental decay prevention, cost savings, and other therapeutic and non-therapeutic benefits. However, research has also revealed that some health issues are associated with even these artificial sweeteners. Obesity, allergic reactions including hives and swellings, metabolic acidosis, and cancer are a few of these disorders. Additionally, it could encourage flatulence, nausea, and diarrhea. The purpose of this study is to examine the advantages and health implications of using artificial sugar substitutes as well as substitutions for them. It also supports the need for additional investigation to determine the precise mechanisms of action of these sugar substitutes employing *in vitro*, animal, and human models.

***Keywords*:** Artificial sweeteners, Natural sweeteners, Sugar, Sugar substitutes

1. INTRODUCTION

A sugar substitute, often known as an artificial sweetener, is a food additive that mimics the taste of sugar but typically has lesser calories. There are both natural and artificial sugar replacements. Artificial sweeteners are generally used to describe those that are not natural.

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Artificial sweeteners are synthetic substances used to replace sugar in the sweetening processes of several products (Mooradian et al., 2017). Glycerol, mannitol, tagatose, and xylitol are examples of natural sweeteners, whereas aspartame, acesulfame potassium, saccharin, and sucralose are examples of artificial sweeteners. Artificial sweeteners are increasingly being used in a variety of goods that previously contained sugar or corn syrup by the food and beverage industry. Despite the extraordinarily large profit margins for artificial sweetener producers, the cost of artificial sweeteners to the food business is much lower than the cost of natural sweeteners. Animal studies have conclusively shown that artificial sweeteners promote weight gain, brain tumors, bladder cancer, and a host of other health risks in addition to their benefits. Humans have also reported several health-related negative effects, such as carcinogenicity. These chemicals have been the subject of numerous investigations, with findings ranging from "safe under all circumstances" to "unsafe at any dose".

This research paper, therefore, aims to explore the health controversy over the perceived benefits of sugar substitutes and possible alternatives to the use of artificial sugar substitutes.

Benefits of Sugar Substitutes

This can be grouped into therapeutic and non-therapeutic uses

Therapeutic

1) **Facilitates weight loss:** By the substitution of high-energy foods with low-energy foods that contain artificial sweeteners.
2) **Dental care:** Sugar replacements are not fermented by the dental plaque bacteria like sugar is. In this fermentation, tooth decay results.
3) **Diabetes mellitus management:** Some sugar replacements do release energy, but because of their slower rate of metabolism, blood sugar levels are stabilized over time.

Non-Therapeutic

1) **As sugar substitute:** Aspartame and sugar taste remarkably similar, according to studies using taste-test panels. As a result, it is substituted for sugar in many meals.
2) **Enhances and extends flavours:** In meals and beverages, aspartame has the power to enhance and prolong fruit flavors like cherry and orange. Aspartame, for instance, prolongs the sweetness and flavor of chewing gum longer than sugar-sweetened gum.
3) **Avoiding processed foods:** People may choose to replace less-processed sweeteners like fruit juice or maple syrup with refined white sugar.
4) **Cost:** Many sugar substitutes are cheaper than sugar

2. HEALTH ISSUES

Aspartame

The low-calorie sweetener aspartame, which was first developed in 1965, tastes similar to sugar but is 200 times sweeter than sucrose. It stands out from other low-calorie sweeteners because the body totally breaks it down into amino acids, aspartic acid, phenylalanine, and a trace quantity of ethanol.

Phenylalanine is a necessary amino acid that must be consumed as part of a balanced diet in order to support healthy growth and maintenance, but prolonged high blood levels can harm the brain.

One child in 20,000 is born with "phenylketonuria" (PKU), an inherited disorder, and they are quite concerned about this. Phenylalanine accumulates in lethal quantities in these kids' brains because they are unable to metabolize it. Therefore, throughout at least the first six years of life, phenylalanine intake must be severely restricted due to the disease. As a result, aspartame must be labeled on items containing it to warn consumers that it may cause PKU because of the phenylalanine level of aspartame (Wurtman and Mahe, 1987).

In animal models that are frequently used to find substances impacting (i.e., typically protecting against) seizure incidence, aspartame has been shown to promote seizures. Similar to this, it's feasible that sweetener levels that sufficiently raise brain phenylalanine could either make susceptible humans more prone to seizures or could allow seizures to happen in people who are vulnerable but have never had one before (Wurtman and Mahe, 1987).

One investigation supported a case of an allergic reaction leading to edema and hives in susceptible people. The development of the allergy, however, was not really explained. Diketopiperazine, a substance that is created when aspartame breaks down, has been proposed as a potential culprit.16 The wood alcohol in aspartame turns to formaldehyde and ultimately to formic acid at temperatures above 86°F, resulting in metabolic acidosis. People may receive a false diagnosis of multiple sclerosis because methanol poisoning mimics the disease. Death from multiple sclerosis does not occur, although it does from methanol intoxication (Markle, 2011).

Aspartame may have a negative impact on those who already have mental problems, according to more recent studies that have been conducted and all of the most recent information that has been published. Some people's immune systems may be impacted by it as well.

The consumption of aspartame has also been associated with different health effects, including oxidative stress in blood cells (even at the recommended dose of 40 mg/kg per day), interference with neuronal cell function, hepatotoxicity, and kidney disfunction (Ardalan et al., 2017; Choudhary and Pretorius, 2017).

Saccharin

Saccharin has been used as a non-caloric sweetener in foods and beverages for more than 100 years since it was first identified. Saccharin, which was initially created in 1879 by Remsen and Fahlberg, was the first artificial sweetener—aside from Sugar of Lead. Approximately 600 times sweeter than sugar, it is chlorinated sugar. It is created from sucrose by swapping out three hydroxyl groups for three chlorine atoms. Sucralose can be used as a sugar substitute in almost all food and beverage items (more than 4,000 food products in total), as well as frozen desserts, chewing gum, baked goods, and other meals because of its exceptional stability and flavor is similar to sugar.

One animal study revealed that ingestion of saccharin-containing food may cause an increase in body weight and obesity by interfering with essential physiological and homeostatic processes (Hampton, 2008). It was later established that saccharin induces cancer in male rats via a mechanism that is not present in humans. It precipitates in rat urine at high doses. This precipitate harms the bladder lining cells, and when the cells renew, a tumor develops (Calorie control council, 2011).

Sucralose

British scientists made the discovery of sucralose in 1976. It is regarded as the most recent international zero-calorie sugar alternative because it is the only non-caloric sweetener manufactured from sugar. About 600 times as sweet as sugar, it is chlorinated sugar. Sucralose's inclusion in the group of substances known as organic chlorides, some of which are toxic or carcinogenic, has led to safety concerns; however, the presence of chlorine in an organic compound does not in any way guarantee harm. Sucralose metabolism may point to a decreased risk of toxicity (Daniel et al., 2000).

Stevia/Rebaudioside A

The South American plant *Stevia rebaudiana* is the source of stevia, which has been used for millennia in the plant's native Paraguay to sweeten drinks and prepare tea. One of the components of the stevia plant that contributes sweetness is rebaudioside A. Infertility or other issues may result from large dosages of substances provided to rats, which decreased sperm production and boosted cell proliferation in their testicles, according to one study. Steviol can be transformed into a mutagenic substance in a lab setting, which may aid in the development of cancer by altering the DNA of cells (Chemcuisine, 2004). The American FDA rejected stevia as a food component in the 1990s. Stevia must be labeled because the FDA approved its use as a dietary supplement in a 1995 statement. The same scientific body in Canada and the European Community rejected it and said that stevia could not be used in food (FAO/WHO, 2004).

Tagatose

Although this novel synthetic addition shares molecular similarities with fructose, it is poorly assimilated by the body. That is why it only produces roughly a third as many calories. Flatulence, nausea, and diarrhea are all symptoms of excessive consumption. Even though it is chemically a sugar, it does not cause tooth decay (Chemcuisine, 2004).

Acesulfame-K

Early Acesulfame-K testing is still debatable, and several safety boards contend that the safety of the drug has not been sufficiently shown by existing research. According to scientists, there is a chance of cancer and hormone disturbance, as well as a chance for pregnant women. Despite this, it has been awarded an ADI level of 9mg/kg by the EU's consumer protection agency.

3. STUDIES ON THE HEALTH EFFECTS OF ARTIFICIAL SWEETENERS

Several studies have been carried out to ascertain the negative health effects of intake of artificial sweeteners using different models. Studies have been carried out *in vitro*, using human samples and animals. Below are some studies that have been carried out.

In a study, Cardici et al. assessed the potential for cytotoxicity, genotoxicity, and oxidative damage of the oral artificial sweetener aspartame on cultured human blood cells. The aim of the study was to evaluate the in vitro cytotoxic effects by using 3-(4,5-dimetylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) and lactate dehydrogenase release tests, genotoxic damage potential by using chromosome aberration (CA) assay, and antioxidant/oxidant activity

by using total antioxidant capacity (TAC) and total oxidative stress (TOS) analysis in primary human whole blood cell cultures. The results of the MTT test demonstrated that APM caused clear concentration-dependent significant reductions in cell viability. Furthermore, it was discovered that the APM-treated cells had a higher frequency of CA. TAC and TOS levels in whole blood cultures did not significantly change as a result of APM therapy. The findings led to the conclusion that aspartame exhibited a concentration-dependent cytotoxic activity in human blood cells and the potential to be genotoxic.

Another investigation by Tsakiris et al. examined the impact of aspartame metabolites on the acetylcholinesterase activity of human erythrocyte membranes. The purpose of this study was to assess the amount of acetylcholinesterase (AChE) activity in human erythrocyte membranes following incubation with phenylalanine (Phe), methanol (met), and aspartic acid (aspt), either collectively or individually. The ASP hydrolysis products were treated with erythrocyte membranes from 12 healthy persons for 1 hour at 37 °C. AChE was determined using spectrophotometry. Higher amounts of the ASP metabolites Met, Phe, and Aspt decreased the activity of the enzyme when incubated with membranes. AChE activity in the membrane was unaffected by doses of aspartate or phenylalanine of 0.82 mM or 0.07 mM, respectively.

It is found that whereas high or hazardous quantities of ASP metabolites significantly or partially lowered the membrane AChE activity, low concentrations of ASP metabolites had no influence on the enzyme activity. Additionally, excessive or dangerous quantities of the sugar metabolites may be associated with neurological problems, including learning and memory impairment.

Using two-bottle preference studies, Yin et al. assessed the impact of several sweeteners on the behavior and neurotransmitter release in mice. The findings revealed that mice displayed highly significant preferential behavior for 8% sucrose solution, 0.3% stevioside solution, 10 mM acesulfame, 10 mM sucralose, and 10 mM aspartame solutions ($p < 0.01$). There was no discernible variation in feed intake, but there was a significant difference in the amount of solution consumed and the amount of neurotransmitters released ($p < 0.05$) compared to the control group (water group). The consumption of solution and feed did not differ significantly between the acesulfame-A and acesulfame-B groups, however there was a substantial difference in the release of neurotransmitters. The findings also indicated that neurotransmitter release was unaffected by differences in sweetness between sweetener solutions, suggesting that mice exhibit the addictive behavior associated with sucrose.

Al-Eisa conducted a study to see how well L-carnitine (LC) affected the cardiac toxicity brought on by aspartame (ASP). Six groups of rats were created: control with saline, LC (10 mg/kg), ASP (75 mg/kg), ASP (150 mg/kg), LC with ASP at 75 mg/kg, and LC with ASP at 150 mg/kg. The activities of myeloperoxidase, xanthine oxidase, superoxide dismutase, catalase, and glutathione peroxidase, as well as the levels of lipid peroxidation, total thiols, and glutathione, were measured in order to identify the antioxidants. LPO was significantly increased, and superoxide dismutase, catalase, glutathione peroxidase, as well as the non-enzymatic antioxidants glutathione and thiols, were significantly decreased. When ASP was administered to animals, as opposed to control rats, the cardiac myofibrils were discovered in a disordered pattern. Multiple apoptotic cells with a large tail and a small head were visible in the ASP-HD-treated mice, and the relaxed loops of the damaged DNA were stretched to form a comet-shaped structure.

These consequences could result from ASP's increased production of reactive oxygen species, which lowers heart performance. All of the aforementioned metrics that were disturbed

by ASP alone were enhanced by the co-administration of LC and ASP. This study has enough uniqueness in demonstrating how LC protects against the cardiac toxicity of ASP. In their study, Kim et al. examined how aspartame and saccharin affected zebrafish. The goal was to ascertain how AS will behave physiologically in the presence of hyperlipidemia. The zebrafish were given a high-cholesterol diet (HCD) along with aspartame or saccharin. After 12 days, 30% of the aspartame- and HCD-fed zebrafish died from having swimming flaws.

The survival rates for the control and saccharin groups were 100% and 65%, respectively, for the aspartame group. The groups that consumed saccharin under HCD experienced the greatest rise in blood cholesterol (599 mg/dL). A notable rise in blood glucose was seen in the aspartame-fed group (up to 125 mg/dL), which was 58% higher than the rise in the HCD-alone group.

Cholesteryl ester transfer protein (CETP) activity was highest in the saccharin plus HCD group (52% CE-transfer), and lowest in the HCD alone group (42% CE-transfer). According to a histologic investigation, the aspartame and HCD groups had more inflammatory cells infiltrating their brain and liver tissues. In conclusion, aspartame-fed zebrafish showed transient swimming abnormalities and an increase in brain inflammation when hyperlipidemia was present. Zebrafish given saccharin demonstrated elevated CETP activity and a more atherogenic blood lipid profile.

Using oxidative stress biomarkers, Vence et al. conducted research to assess potential sucralose-induced toxicological risks in the blood, brain, gill, liver, and muscle of Cyprinus carpio. For varying exposure times (12, 24, 48, 72, and 96 h), carps were exposed to two distinct environmentally relevant concentrations (0.05 and 155 g L-1). Lipid peroxidation (LPX), hydroperoxide content (HPC), protein carbonyl content (PCC), as well as the activity of the antioxidant enzymes superoxide dismutase (SOD) and catalase (CAT), were examined as biomarkers. SUC was calculated using HPLC-MS/MS, a high-pressure liquid chromatography-tandem mass spectrometry method. The gill, brain, and muscle all showed statistically significant increases in LPX, HPC, and PCC (P 0.05), while the gill and muscle all showed statistically significant changes in the activity of antioxidant enzymes. The biomarkers used in this study are also helpful in determining how this agent's effects on aquatic animals may affect the environment.

In the crustacean Daphnia magna exposed to sucralose, Eriksson et al. looked at alterations in acetylcholinesterase (AChE) and oxidative biomarkers (lipid peroxidation, TBARS, and oxygen radical absorption capacity, ORAC). In the daphnids, the sucralose concentration was a highly significant positive predictor of ORAC, TBARS, and AChE. Additionally, the AChE response was correlated with both oxidative biomarkers, with TBARS and ORAC showing positive and negative associations, respectively. This provided evidence that sucralose intake may cause neurological and oxidative pathways, which could have significant effects on animal behaviour and physiology.

3. 1. Alternatives

Use of Natural Sweeteners

The only alternative to the use of artificial sweeteners asides from the use of sugar is to adopt the use of more natural sources. There are various natural sweeteners in use today that eliminate the risks of the health effects of these artificial sweeteners and also provide nutritional benefits. Some of them include:

1) Raw Honey

Fig. 1. Raw Honey

It is a superfood that is rich in enzymes, antioxidants, iron, zinc, calcium, etc. (Muhammad and Sarbon, 2021; Vara et al., 2019) One tablespoon of raw honey has a lesser glycemic load than a single banana. Note that the darker the honey, the richer the flavor and the better the nutritional value.

2) Dates

Fig. 2. Dates fruit

Dates are rich in minerals such as potassium, copper, iron, manganese, magnesium, and vitamin B6. They are easily digested and help to metabolize proteins, fats, and carbohydrates. Research has also shown that dates may help to reduce LDL cholesterol in the blood and may reduce the chances of having a stroke.

3) Coconut Sugar

Fig. 3. Coconut Sugar

Also known as Coconut palm sugar, It is a natural sugar made from coconut palm sap, the sugary circulating fluid of the coconut plant (Muriel et al., 2019). Coconut sap is known to have high antioxidant activity and phenolic content (Asghar et al., 2020) It is now in use as a replacement for table sugar due to its low glycemic load and rich mineral content.

4) Maple Syrup

Fig. 4. Maple Syrup

Maple syrup is one of the best natural sugar substitutes due to its high mineral content. It is also rich in antioxidants protecting the body from oxidative damage. Maple syrup also presents high phytohormone abscisic acid content, responsible for antidiabetic activity (Mellado-Mojica et al., 2016). Additionally, maple syrup consumption can lower glycemic and insulinemic responses as a result of α-glucosidase activity inhibition, which limits glucose absorption in the intestine (Mora and Dando, 2021).

5) Monk Fruit

Fig. 5. Monk Fruit

Monk fruit is a high-intensity natural sweetener that originated in China and Indonesia. Traditionally, monk fruit has been used as a natural sweetener and medicinal product for pharyngitis treatment (Swiader et al., 2019). Monk fruit is used in a few products, such as sugar, syrup, jam, chocolate, and skimmed milk (Pandey & Chauhan, 2019). Monk fruits contain bioactive compounds such as Mogrosides, which exert antidiabetic and anticancer effects (Liu et al., 2018; Zhou et al., 2018). Other bioactive compounds rutin, kaempferol, and quercetin which propel antioxidant and anti-inflammatory effects

Some other natural sugar substitutes include blackstrap molasses, balsamic glazes, brown rice syrup, banana puree, and real fruit jam.

4. CONCLUSION

From the above study, it can be said that the risks and ills of artificial sweeteners outweigh the benefits in human and animal models. As a result, it is strongly recommended that the intake of foods containing sugar substitutes be reduced or totally eliminated from the human diet. Alternatively, more natural sugar substitutes should be encouraged to eliminate the negative effects associated with sugar intake and the use of artificial sweeteners. The only limitation to this option is how these natural substitutes can be used on a large scale or in industrial preparations, hence, creating a gap for research to be carried out on how they can be processed and used on a large scale and industrial levels. Also, more research needs to be carried out to ascertain and validate the negative effects being claimed in these studies by establishing the possible mechanisms of action through *in vitro* and *in vivo* studies.

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