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## HEARTBEATS AND SWEETENERS: UNTANGLING A CONTROVERSIAL LINK

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### ABSTRACT

The widespread use of artificial sweeteners has grown significantly as a substitute for sugar in various food and beverage products, driven by concerns over sugar's contribution to obesity and related health issues. However, the potential impact of artificial sweeteners on cardiovascular health, particularly their association with heart attacks, remains a subject of debate and ongoing research. This abstract provides an overview of the current state of knowledge regarding the effects of artificial sweeteners on heart attack risk. Recent studies have shed light on the intricate relationship between artificial sweeteners and cardiovascular health, raising critical questions about their long-term safety. These low-calorie sugar substitutes, such as aspartame, sucralose, and saccharin, are consumed by millions of individuals worldwide, including those with diabetes and those attempting to reduce caloric intake.

**Keywords:** Artificial sweeteners, cardiotoxicity, Jaggery, Date palms, Grapes, Sugar Beet, Lipid metabolism, Gut microbiota, Neurological disorders, Brain function, cardiovascular risks, Sweetener impact, Metabolic effects

### 1. INTRODUCTION

Artificial sweeteners were commonly referred to as non-nutrient sweeteners (NNS) and were prominent during the two

World Wars when sugar output dropped as an outcome of the agricultural crisis. During this time, saccharin was widely accepted as

an alternative to sugar that was less expensive [1] artificial sweeteners, often referred to as non-nutritive sweeteners, included compounds originating from the various chemical families that therefore interact with taste receptors and usually have sweetness ranging between 30 to 13,000 times abundant than sucrose [2] Discovering sugar alternatives, discovering sugar substitutes, like zero-calorie sweeteners, that offer sweetness without adding calories, has been a major endeavour in the struggle over present-day sugar overconsumption [3, 4]. Progress in the realms of food science, chemistry, and production has resulted in the emergence of low-calorie or non-caloric sugar substitutes like sugar alcohols and artificial sweeteners. Concurrently, there has been a shift from conventional refined sugar sources derived from cane and beet to more economical sweeteners extracted from corn, such as high-fructose corn syrup (HFCS). Overconsumption of free sugars [5] is known to have detrimental effects on dental health [6] and a higher risk of obesity, type 2 diabetes, and cardiovascular diseases has been linked to the consumption of beverages with added sugar [7, 8]. Acesulfame K+, cyclamate, saccharin, neotame, aspartame, sucralose, and advantame are the seven main non-caloric sweeteners available today, and the FDA has approved their daily acceptable consumption dosages [3]. The first

generation of ASs, which mostly consists of saccharin, cyclamate, and aspartame, can be separated into two groups. The second generation, which consists of acesulfame, sucralose, neotame, and neo hesperidin dihydrochalcone, can also be divided into two groups [9] Sweeteners like saccharin, sucralose, and aspartame can lead to metabolic irregularities and gut microbial dysbiosis [10].

#### **ARTIFICIAL SWEETENER CONSUMPTION AMONG CHILDREN AND PREGNANT WOMEN**

Children consume the most artificial sweeteners per day per unit of body weight due to their smaller size and high liquid intake [11]. According to a recent systematic analysis, kids consume between 4% and 18% of all carbonated beverages that are artificially sweetened [12] Pregnancy food may influence a child's immune system development and susceptibility to allergy illness, according to certain theories [13]. It might be suggested that certain eating habits, such as consuming sugar and artificial sweeteners, may adversely affect one's ability to conceive since the human fertility rate has fallen over time [14]. Toddlers prefer sweet flavors, and the food industry is aware of this. As a result, lactose has been replaced with sucrose in infant formula, increasing sweetness by six times without reducing the overall carbohydrate amount. At the moment, baby

foods frequently include up to three times as much sugar as what the World Health Organization advises (less than 10% of total calories) [15].

### **MECHANISM OF ACTION OF ARTIFICIAL SWEETENERS ON TONGUE RECEPTORS**

Sweet-taste receptors, such as the T1R family of taste receptors and -gustducin, react to artificial sweeteners like sucralose and acesulfame-K as well as caloric sugars like sucrose and glucose [16-18]. The combined type 1 taste receptor 2 (T1R2)/type 1 taste receptor 3 (T1R3) receptor serves as the detector for all sweetening agents, encompassing both sugars and non-caloric sweeteners, within oral perception [19, 20]. Multiple binding sites on this receptor account for the chemical variety of sweet-tasting chemicals [21] Fortunately eating sugar activates the reward system in our brains, the kind of sweetener we consume affects how happy we feel. Natural sweeteners may trigger this system more strongly than non-nutritive sweeteners (NNS). It's believed that because NNS don't have the same energy as natural sweeteners, the reward pathways aren't fully activated. An increase in appetite and cravings may result from this decreased reward response. Consuming an excessive amount of delicious sweet foods out of control can lead to weight gain [22].

## **2. DIFFERENT TYPES OF ARTIFICIAL SWEETENERS**

### **Aspartame**

Aspartame (ASP, N-I,-a-aspartyl-L-phenylalanine-l-methyl ester) is metabolized in the small intestine, yielding three components: phenylalanine (50%), aspartic acid (40%), and methanol (10% wt./wt. [23]. Sweeteners artificial in nature and amino acids with sweet properties can engage and activate sweet taste receptors (STRs). which function identically to natural sugars since they send information to the regions of the brain that govern taste perception via sensory afferent fibers. In 1878, saccharin was discovered while researching the oxidation of o-toluene sulphonamide. Based on both biology and toxicology, saccharin is well absorbed into the body and stable at standard pH and temperature [24-26].

### **Stevia**

Stevia has been utilized as a sugar substitute previously since it possesses outstanding resilience to high temperatures (up to 80 °C) and various pH levels (from 2 to 10) when incorporated into foods and drinks. Stevia, known by names such as sweet leaf, candy leaf, and honey leaf, derives its intense sweetness from steviol glycosides, which exceed sucrose in sweetness by 100 to 300 times. Apart from its unparalleled sweetness, stevia holds a treasure trove of nutrients like vitamins, minerals, essential

amino acids, and a plethora of health-promoting elements such as non-glycosidic labdane diterpenes, flavonoids, phenolic compounds, fibre, phytosterols, chlorogenic acids, triterpenes, and hydrocarbons—making it an unprecedented source of natural goodness. These elements contribute to its health-promoting properties.

### **Saccharin**

The most common applications of saccharin are low-calorie food additives, dietary supplements, drinks, sweets, and pharmaceuticals [27]. The FDA advises 2.3 mg of saccharin per pound of body weight for adults and children, which is the maximum allowed and considered risk-free. Saccharin, discovered over a century ago, has been a go-to non-caloric sweetener in various foods and drinks. Developed in 1879 by Remsen and Fahlberg, it predates even Sugar or Lead as the initial artificial sweetener. Its creation emerged from experiments involving toluene derivatives [28]. It was the result of a test with toluene derivatives.

### **Sucralose**

Inadvertently discovered in 1976, sucralose (1,6-dichloro-1,6-dideoxy-D-fructofuranosyl-4-chloro-4-deoxy-D-galactopyranoside) is an artificial sweetener and the primary component of the trademarked product Splenda [29]. In 1998, the US Food and Drug Administration (FDA) first authorized its use in only a

handful of foods and beverages, and the following year, it recognized its use as a "general purpose" sweetener in all foods and beverages. A non-nutritive sweetener called sucralose is created by selectively chlorinated sucrose at three of the major hydroxyl groups while reversing the arrangement of carbon-4 from the glucose- to the galactic analog [30]. According to research on absorption, after oral administration, the sucralose hydrolysis products are more easily absorbed than the parent substance. whereas 1,6-DCF undergoes two major metabolic pathways, 4, CG is essentially eliminated intact in the urine whereas 1,6-DCF undergoes either a quick conversion to 1,6-dichloro mannitol or a rapid conjugation with glutathione [31, 32].

### **Neotame**

Neotame (NTM) stands out as a highly potent non-nutritive sweetener, positioned as a promising successor to aspartame (APM)(32)One of five FDA-approved with a sweetness potency of 7000–13,000 times that of sugar, Neotame (N-[N-(3,3-dimethylbutyl)-L-aspartyl]-L-phenylalanine 1-methyl ester) is a potent sweetener [33]. Neotame can replace 20–30% of the sweetness of soft drinks with no discernible taste difference [34]. Neotame was initially developed by French researchers Claude Nofre and Jean-Marie Tinti via modification of the N-terminus of aspartame [35].

Neotame is superior to aspartame in that it is stable at a neutral pH, allowing for use in baked goods, and it is also more affordable. Neotame has a long shelf life in powder

form, especially in cool climates. Neotame's stability in solutions depends on pH and temperature [36].

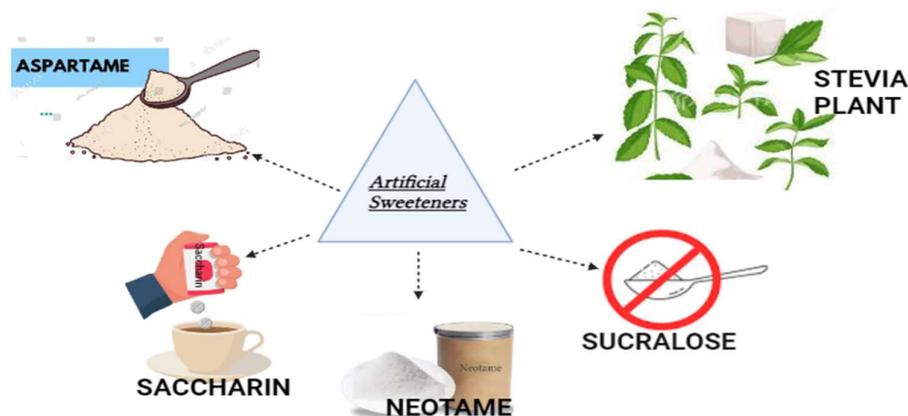


Figure 1: Diagram depicting various artificial sweeteners available in the current market

### 3. CARDIAC PROBLEMS ASSOCIATED WITH ARTIFICIAL SWEETENERS

#### Aspartame

It has been shown that aspartame and monosodium glutamate (MSG) are excitotoxins of cardiac tissue that cause "lone" atrial fibrillation, which implies tachycardia in the absence of heart failure, hypertension, or coronary artery disease. The amino acid products that react with MSG and aspartame are aspartate and glutamate, respectively. The body's tissues, including the heart's electrical conduction system and the heart itself, have glutamate receptors. The ANS plays a major role in the control of cardiac electrophysiology and arrhythmogenesis. It is shown that

aspartame and monosodium glutamate (MSG) are excitotoxins of cardiac tissue that cause "lone" atrial fibrillation, which implies tachycardia in the absence of heart failure, hypertension, or coronary artery disease. These receptors, aspartate, are crucial for the preservation of cardiac electrophysiology. Higher levels of these amino acids can be found in the body when free forms of glutamate and aspartate are ingested as food additives because they can enter the bloodstream quickly and break down protein more slowly after digestion. The autonomic nerve regulates the regulation of cardiac electrophysiology and arrhythmogenesis. The body may experience a variety of consequences from this quick absorption, such as excessive

receptor stimulation and possible excitotoxicity in the cardiovascular system. Subsequent research endeavours may explore diverse varieties of artificial sweeteners, alongside their plausible interplay with additional dietary and lifestyle components. Furthermore, more investigation is required to find novel pathways by which artificial sweeteners might affect cardiovascular health [37]. Aspartate, phenylalanine, methanol, and amino acids are produced when the aspartame dipeptide is hydrolysed in the stomach by peptidases and esterase's. The duodenum and jejunum receive these substances and use their regular metabolic processes to break them down [38]. Aspartame administration in in-vitro studies avoids the digestive process and does not result in biologically plausible scenarios. Aspartame has been declared inert in numerous studies; however, some have indicated a dose-dependent type of hypersensitivity [39]. In vivo, aspartame supplementation, irrespective of body weight, decreased appetite and weight gain, with increased fasting glucose levels and impaired insulin-stimulated glucose elimination [40].

### **Saccharin**

In the small intestine, saccharin is absorbed systemically more than 85%. Saccharin binds to plasma proteins after being absorbed from the (GIT) and is then

transported all over the body. The remaining saccharin is then expelled via defecation and is mainly removed by urination. [41-44]. The volume of saccharin absorbed depends on the pH of the stomach; low pH (as in humans) increases absorption, whereas higher pH (as in mice and rats) decreases absorption. a reduction in absorption [41].

### **Sucralose**

Sucralose mostly flows through the GI tract unabsorbed and is recovered in urine (14.5%) and feces (70–90%) in an unaltered structural state [45, 46]. Certain sucralose molecules are chemically changed as they move through the rodent GIT, indicating metabolism and the synthesis of secondary metabolites, according to mass spectrometry data [47, 48]. Although two glucuronide conjugates of sucralose have been found (making up approximately 2.6 percent of the administered dose%) in healthy volunteers after a one-time oral dose the small amount of absorbed sucralose is mainly eliminated unaltered in the urine [49]. Sucralose may inhibit bacterial growth, according to research on humans, animals, and in vitro cultures [50-52] could specifically prevent or encourage the growth of bacteria(53) .and encourage dysbiosis of the intestines [54] accordance with the finding that bacteria do not use sucralose as a carbon source when growing in a culture [55, 56, 58, 59]. Sucralose functions mechanistically to inhibit sucrose permease

and bacterial invertase, two enzymes that are unable to catalyse the transmembrane transport or hydrolysis of sucralose [57].

#### **Neotame**

Esterase breaks down neotame into de-esterified methanol and neotame, discharged via urination in less than 72 hours [58].

Neotame that has been absorbed is excreted in feces, with the remaining 50% being eliminated in urine as de-esterified neotame that has passed through the gut. Neotame has not demonstrated any toxic effects, even at doses higher than the ADI [59].

#### **4. Artificial sweetener consumption:**

##### **Data**

##### *Case 1*

The absolute CVD incidence rate related to total artificial sweetener intake was 346 /100,000 person-years for Consumers with higher intake (above the sex-specific median) had a higher incidence rate of 314 / 100,000 person-years compared to non-consumers [72]. Artificial sweeteners showed a stronger association with the risk of cerebrovascular disease (1.18, 1.06 to 1.31, P=0.002; incidence rates of 195 and 150). Aspartame consumption correlated with an increased risk of cerebrovascular events (1.17, 1.03 to 1.33; incidence rates of 186 and 151), while acesulfame potassium and sucralose consumption linked to a higher risk of coronary heart disease (1.40, 1.06 to 1.84; incidence rates of 167 and 164; and 1.31, 1.00 to 1.71; P=0.05; incidence

rates of 271 and 161). Categorizing artificial sweetener intake as time-dependent variables yielded similar outcomes. Correlations were identified between sucralose consumption and the risk of angioplasties (based on a study involving 477 participants; showing a correlation of 1.60, with a confidence interval ranging from 1.17 to 2.21, and a significance level of P=0.004). Similarly, connections were observed between the consumption of all artificial sweeteners and instances of transient cerebral ischemia for various cerebrovascular and coronary heart diseases [60].

##### *Case 2*

There is conflicting evidence on artificial sweeteners and CVD. Higher artificial sweetener intake was found to be positively linked with higher a correlation was found that suggested using artificial sweeteners was associated with a higher risk of overall death in women. In the study, however, no such association was found with the men. prospective U.S. Nurses' Health Study (n=80,674) and Health Professionals Follow-up Study (n=37,716) [61]. The use of artificial sweeteners was not linked to an increased risk of coronary heart disease in men, according to a later investigation [32, 62].

##### *Case 3*

According to data from the Northern Manhattan Study, an unprecedented finding

highlights a substantial association between regular consumption of diet sodas and a convergence of vascular events, encompassing stroke, heart attacks, or vascular-related deaths. The daily intake of diet soft drinks revealed an unexpected hazard ratio (HR) of 1.59. (95% CI 0.92-2.74) and for sugar-sweetened beverages were 1.57 (95% CI 1.05-2.35) [63]. These projections were based on 41 combined situations for daily consumers of sugar-sweetened beverages and 15 combined events for daily users of diet soft drinks. The continuous HRs for diet soft drinks were 1.03 (95% CI 1.00-1.07) and for sugar-sweetened beverages were 1.02 (95% CI 0.99-1.04) [64].

#### Case 4

In a city in southern Brazil, a population-based study investigated the use of AS among adults (>20 years) and found that the prevalence was 19%, almost four times greater in the elderly (60 years old) than in people in their 20s and 30s (8.7% versus 32.0%) [65, 66].

#### Case 5

The article by [67]. Analysing Women's Health Initiative data, researchers found that women consuming  $\geq 2$  ASBs daily faced higher risks of stroke, mortality, and heart disease, versus those having  $< 1$  ASB per week. Accounting for various factors, including health history and diet quality, these findings align with some US studies.

They indicate frequent ASB intake linked to increased risks of stroke, diabetes, and dementia, irrespective of vascular disease risk adjustments.

## 5. OTHER ALTERNATIVES OF ARTIFICIAL SWEETENERS

### Date palm

In Asia, palm sugar has been a common sweetener for thousands of years. Because it is natural, little processed, and healthful, it is currently gaining appeal on a global scale. There are numerous significant bioactive components in dates. Dates have been consumed and grown since ancient times in Africa and the Middle East. There are more than 5,000 different date palm kinds worldwide, and they vary from one another in terms of nutrient content, genetics, and morphology [68]. Additionally, it was noted that date palm juice, A highly flavoured beverage for easing thirst, typically found solely during the winter season, comprises sugar levels between 9% - 14%. It also contains minimal organic acid, traces of elements, and a few volatile components. To annually give consumers, the flavour of date palm juice, it can be effectively used to make concentrated juice and ready-to-pour juices [69]. Dates contain nearly all of the following: Isoleucine, Aspartic Acid, Threonine, Serine, Glutamic Acid, Proline, Glycine, Alanine is over 800 times more abundant in dates than it is in apples. About 2000 times as much lysine is found in dates

as in apples, 5000 times more in oranges, and more than 2000 times more in bananas. 3.9%~0.5% of dates are made of pectin. Research demonstrates that foods high in pectin and pectin itself lower metabolic risk factors linked to diabetes and heart disease [70].

### Grapes

Grapes were highly regarded in the ancient Greek and Roman cultures because they were used to make wine. There are currently three primary species of grapes: French hybrids, *Vitis labrusca*, and *Vitis rotundifolia* from North America, and European grapes (*Vitis vinifera*) from Europe [71]. The berry fruit known as a grape is produced by plants in the genus *Vitis*, which includes over 60 different kinds of grapevines. Almost all continents produce and enjoy wine. It has beneficial elements such as tannins, which have antimicrobial properties and an astringent impact, and flavonoids, which help prevent cardiovascular disease. The three basic classes (red, white, and dessert) dictate the vinification process for the various types of wine that are produced across the world [72].

### Sugar beet

In 2004, 51 countries were producing 238 million metric tons of sugar beet. In order of production, the top producers of sugar beet in 2004 were the Russian Federation, France, Germany, the United States, Turkey,

Ukraine, and Poland. Today, over 35% of the world's sugar production comes from sugar beet. Fresh sugar beet pulp (754 kilograms, containing 11% dry matter) was processed in 2000 liters of acidified water that had been purified using reverse osmosis (operated at 70 degrees Celsius with a pH of 1.5). After a 5-hour period, the hydrolysis was halted by introducing a 10% sodium carbonate solution until the pH reached 3.0. The remaining solid pulp was separated using an Alfa Laval NX 409 decanter centrifuge. Further refinement occurred through a disc centrifuge and cloth filter, both pre-coated with Clarcel CBL filter aid, to clarify the pectin-rich juice. This clarified juice underwent an additional purification step using an ion exchange column equipped with Dowex Upcore Mono C600 resin to eliminate multivalent cations. Finally, an ultrafiltration module was employed, combining diafiltration and concentration processes, to refine the pectin juice further [73]. By-products from sugar beets are an intriguing source of bioactive chemicals that may one day be used to help prevent cardiovascular illnesses [74].

### Jaggery

Gur, sometimes known as jaggery, is a staple in Indian cuisine. Jaggery's flavor profile, which combines its sweetness with earthy undertones, creates an incredibly delicious treat. Even though it is consumed all around the world, Gur is most well-known and

adored in India, where the majority of sweet meals wouldn't be complete without it. Both Ayurveda, or traditional Indian medicine, and various old Hindu rites include the use of jaggery. When ingested, sugarcane and palm jaggery both instantly produce heat and energy. Comparatively speaking, jaggery is a lot healthier than cane sugar [75]. Jaggery has a variety of health advantages. Diabetes incidences have been observed to be lower in areas where jaggery is consumed than in areas where other sweeteners are used. Jaggery helps with blood cleansing, aids in the treatment of bile diseases, and has high nutritional qualities. In addition to assisting with digestion, it also helps men increase their energy levels and prevents anaemia in women and children [76].

## 6. REGULATORY AFFAIRS AND SAFETY

Under the Food, Drug & Cosmetic Act and its multiple updates, the (FDA) is responsible for controlling food additives. All novel compounds with a plausible expectation of becoming food components are subject to FDA evaluation. A food additive's use in prepared foods or as tabletop sweeteners may be restricted by the FDA. The petitioner (maker) is obliged to provide evidence of the substance's safety. A few exclusions, nevertheless, might apply to artificial sweeteners. The FDA did not formally identify or regulate chemicals as food additives until 1958, even if they were on the list of substances that were generally regarded as safe (GRAS) at the time. In these situations, the FDA must demonstrate that a drug is Unsafe [77].

**Table 1: Presents data regarding Artificial Sweeteners along with their primary market regions [78]**

ARTIFICIAL SWEETENERS	KEY MARKET AREAS
Aspartame	Asia, North America, Europe
Saccharin	USA, Europe, Asia
Sucralose	North America
Stevia	Asia
Neotame	USA

Artificial Sweeteners Products (ASP) stands as the biggest artificial sweetener worldwide, dominating the market and being the top choice in the U.S. It features over 6000 food products and amounts to around 16,000 tons manufactured annually in the U.S. for global consumption. The U.S. leads the market for SCL (sodium

cyclamate) utilizing over 1500 tons annually. Following closely, Europe consumes around 400 tons yearly, according to a major Chinese company entering the SCL market [79].

## 7. ARTIFICIAL SWEETENERS LEADING TO CARDIOTOXICITY

Artificial sweeteners are linked to a higher likelihood of developing metabolic syndrome, a cluster of risk factors for heart and metabolic health. This syndrome encompasses issues like Elevated blood sugar, high blood pressure, insulin resistance, abdominal fat, and abnormal lipid levels. Three potential mechanisms behind this connection involve changes in gut bacteria, and possible impacts on heart rhythm, brain function, and lipid levels. These associations highlight concerns regarding the use of artificial sweeteners and their potential implications for overall health.

### Mechanism of cardiotoxicity

Recently, scientists have turned to specially created models using human induced pluripotent stem cells (iPSCs) as a superior

option for testing drug effects on the heart. These models closely mimic real heart cells and provide a more consistent and reliable method compared to using cells directly from the heart or cardiac tissue [80]. Randomized trials couldn't directly assess the effects of consuming artificial sweeteners on serious issues like heart disease due to ethical limitations. Similarly, observational studies haven't directly studied the link between daily artificial sweetener intake (in milligrams per day) and the risk of heart problems. Instead, some of these studies have used how many artificially sweetened drinks people have each day as a way to look into this connection. But the results from these studies were inconsistent [81-91].

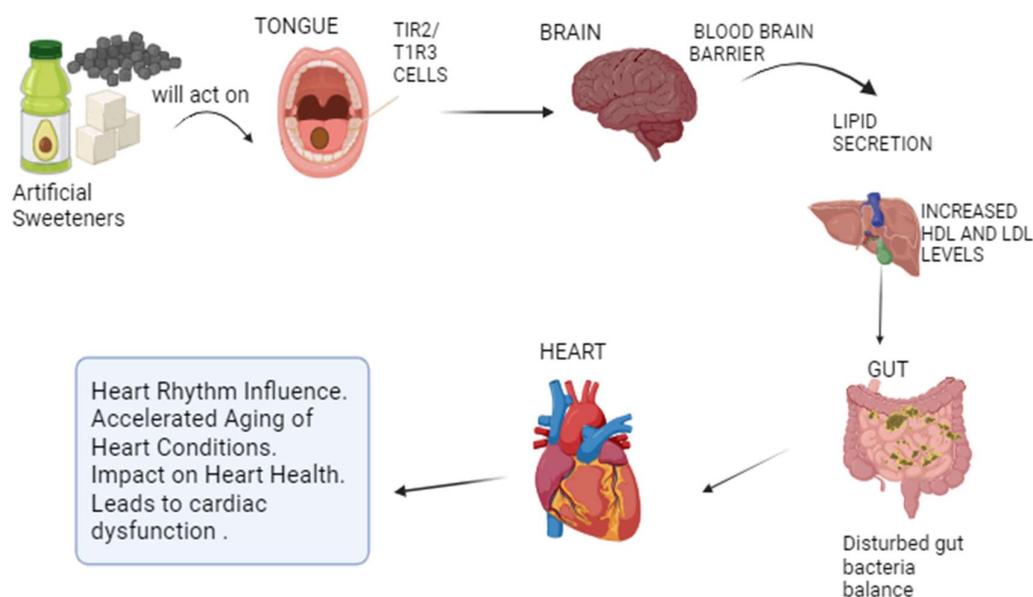


Figure 2: Diagram shows the impact of Artificial Sweeteners effecting the tongue receptors TIR2 /TIR3 Cells sending signals to the brain leading this to increased lipid levels effecting the gut balance which may lead to possible impacts on heart rhythm

## 8. LIPID METABOLISM

On the other hand, aspartame was associated with lower serum levels of HDL cholesterol (0.05 mmol/L; 95% CI, 0.02 -0.09) and higher levels of this lipid when contrasted with controls (-0.03 mmol/L; 95% CI, -0.06-0.01). Furthermore, both HDL and LDL cholesterol were raised in C57BL/6J mice treated with ACE K for up to 40 weeks. Human high-density lipoprotein (HDL) was treated with high doses (final 25, 50, and 100 mM) of AS (aspartame, ACE K, and saccharin), which resulted in both an increase in atherogenic effects and a reduction in antioxidant capacity. These findings imply that while AS treatment may reduce the advantageous effects of HDL, artificial sweeteners may raise plasma HDLc [92]. In the same way, when sweeteners (aspartame, ACE K, and saccharin) were given to apoA-I over an extended period at physiological concentrations (3 mM, 168 h), The antioxidant and phospholipid binding capabilities diminished, leading to alterations in the secondary structure.

## 9. ARTIFICIAL SWEETENER'S EFFECT ON GUT MICROBIOTA

Artificial sweeteners could impact cardiovascular health by disturbing the gut bacteria balance. They might Favor the growth of specific bacteria while suppressing others, upsetting the gut's role in metabolism and immune function. These disruptions have ties to diseases like obesity,

diabetes, and cardiovascular issues. Artificial sweeteners might change how genes handle carbohydrates, affecting gut bacteria, and leading to metabolic shifts and inflammation. These changes could contribute to vascular problems and cardiovascular disease [93].

## 10. ARTIFICIAL SWEETENER CONSUMPTION AND EFFECT ON NEUROLOGICAL DISORDERS

The pervasiveness of Higher regular consumption of sugary beverages was linked to lower incidence of diabetes mellitus and cardiovascular disease, whereas higher consumption of artificially sweetened soft drinks was linked to increased risks of these conditions. Drinking artificially sweetened soft drinks on a daily basis was linked to a higher risk of developing AD dementia as well as all-cause dementia when cumulative beverage consumption was examined. There was no correlation found between the risks of dementia and either type of sugary drink, sweetened with sugar or not. There were no relationships observed between the consumption of any beverage under investigation and the waist-to-hip ratio, the presence of the apolipoprotein E allele, or diabetes mellitus [94].

## 11. ARTIFICIAL SWEETENERS AFFECTING THE BRAIN

The vital area of interest for study into maintaining a good energy balance is the

brain, which plays a regulatory function in both energy homeostasis and eating behaviour [95]. Like wine and tobacco, sugar is also greatly overindulged, according to recent research. Sugar acts on the brain, signalling the body to keep consuming it and stimulating the release of neurotransmitters like Epinephrine (EPI), norepinephrine (NE), dopamine (DA), and 5-hydroxytryptamine (5-HT). It is debatable whether substituting non-nutritive sweeteners for sugar in food may lower calorie intake, Cardio-metabolic risk factors, and body weight [96]. Upon introducing artificial sweeteners, a noticeable spike in food intake occurs, attracting animals due to sweet tastes. These additives disrupt established sweetness effects and the connection between taste perception and typical post-consumption impacts. Signals for energy and sweet taste seem managed by separate neural pathways. Sweet tastes activate gut pathways linked to calories, but recent reviews imply artificial sweeteners might not, potentially disturbing gut-brain connections in humans [97].

Phenylalanine has the potential to penetrate the blood–brain barrier and drastically alter the way that vital neurotransmitters are produced. Formate, the product of the breakdown of methanol, is highly cytotoxic and can even result in blindness. And maybe due to this, there may be a chance of artificial sweeteners affecting the brain [98].

An experiment done by [99]. showed this effect on Wild-type mice, when they are not thirsty, they generally favor sugar over water, showing a clear preference. Yet, when given a choice between an artificial sweetener and sugar, initially, they consume both equally. However, within 24 hours, their preference shifts significantly towards sugar, continuing to escalate over 48 hours. This switch occurs even in mice unable to taste sweetness. Despite lacking the ability to taste, they learn to choose sugar, likely due to powerful positive effects after consumption, as observed in various studies using flavor-conditioning tests.

## CONCLUSION

The review suggests that artificial sweeteners may influence cardiotoxicity via a number of interrelated mechanisms. These sweeteners have the potential to have negative effects on the heart through altering brain function, upsetting gut microbiota, influencing neurological function, and affecting lipid metabolism. Consuming artificial sweeteners may cause alterations in the makeup of the gut microbiota and lipid metabolism, which may increase the risk of cardiovascular disease. Furthermore, heart health may be indirectly impacted by neurological conditions and alterations in brain function associated with these sweeteners. Determining the complete impact of artificial sweeteners on cardiovascular health requires an

understanding of these intricate relationships between gut microbiota, neurological effects, and subsequent cardiotoxicity.

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