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REVIEW ON: BITTERNESS OF ARTIFICIAL SWEETENERS

Aditya Savaliya[1*], Nirav Rathi[2], Dr. Pragnesh Patani[3]

[1*]Khyati College of Pharmacy, Gujarat Technological University, Ahmedabad, Gujarat, India.
[2]Department of Quality Assurance, Khyati College of Pharmacy, Gujarat Technological University, Ahmedabad, Gujarat, India.
[3]Department of Pharmacology, Khyati College of Pharmacy, Gujarat Technological University, Ahmedabad, Gujarat, India.

***Corresponding Author:** Aditya Savaliya
[*]Khyati College of Pharmacy, Gujarat Technological University, Ahmedabad, Gujarat, India.
Email: aditya.0savaliya@gmail.com

Abstract:
Artificial sweeteners have become ubiquitous in the modern diet, as consumers seek lower-calorie alternatives to sugar-sweetened beverages and foods. This review article delves into the multifaceted aspects of artificial sweeteners, specifically focusing on their bitterness and the potential health implications associated with their consumption. This comprehensive review synthesizes current research findings, offering a holistic understanding of the bitterness and multifaceted health implications of artificial sweeteners. By examining their effects on glucose metabolism, cardiovascular health, toxicity profiles, cancer risks, immune function, and bladder cancer risk, this article aims to inform both the scientific community and the general public about the complex interplay between artificial sweeteners and human health. Ultimately, this knowledge can guide future research, public health policies, and personal dietary choices in an era dominated by these sugar substitutes.

Key words: Artificial sweeteners, Glucose tolerance, Cancer, Negative effect on Immunity

Introduction:

Over a century ago, non-caloric artificial sweeteners (NAS) were developed to give foods a sweet flavour without the high energy content of caloric sugars. Artificial sweeteners are regarded as advantageous for diabetics or obese people where refined sugar can be a concern. Sugar-free foods are now highly well-liked due of their low calorie content. As a result, the food sector substitutes low-calorie artificial sweeteners for high-calorie sugar. Some countries have approved asparmate, acesulfamek, neotame and alitame for their daily use as per ADI (Acceptable Daily Inntake) value. But still now products made with artificial sweetners have controversial health and metabolic effects. [1] Studies revealed that artificial sugars can develop exacerbated gut damage and inflammation in animal models for inflammatory bowel disease (IBD), including those for both ulcerative colitis, and crohn's disease, [2] significantly reduced the hemoglobin level, HCT%, RBC and WBC count [3], Increased Digestive Proteases and Decreased β-Glucuronidase in Feces, [8] Human bladder cancer, [10] development of glucose intolerance through induction of compositional and functional alterations to the intestinal microbiota.[11]

The results of the extensive prospective cohort study point to a probable direct relationship between increased cardiovascular disease risk and higher artificial sweetener usage, particularly aspartame, acesulfame potassium, and sucralose. Like most artificial sweeteners, saccharin was only accidentally discovered. The amount of chronic/carcinogenic studies performed to determine its safety reflects the debate surrounding its usage as a food additive. The research proved that it can lead to cancer in both humans and rats. [9]

❖ **Some Artificial Sweeteners:**

Saccharin: Saccharin is the oldest and first artificial sweetener. The electrochemical oxidation of o-toluenesulfonamide to the equivalent carboxylic acid yields saccharin. This is accomplished with the use of various substances such as potassium permanganate and chromic acid. [37, 38, 39] Experimental studies suggested that saccharin shows both positive and negative outcomes in inducing cancer in rats, dogs and humans.

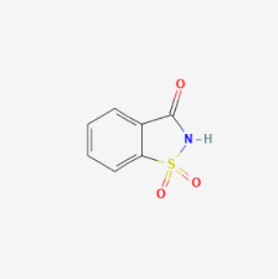

Figure 1: Chemical Structure of Saccharin

Sucralose: Sucralose is made from sucrose by substituting the 3 hydroxyl groups on the sucrose molecule with 3 chloride atoms. In view of the fact that sucralose remains undigested in our body, it is excreted in the faeces without any modifications. [40]

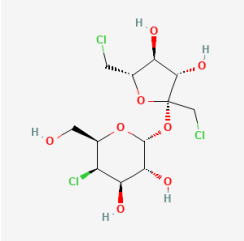

Figure 2: Chemical Structure of Sucralose

Acesulfame-K:

It is potassium salt of 6-methyl-1, 2, 3-axathiazine-4 (3H)-one 2, 2-dioxide with molecular formulaC4H4KNO4S and molecular weight of 201.24. Acetoacetamide, a by-product of ace-K can be toxic if utilized in high amounts [41] Genotoxic and clastogenic studies performed on acesulfame-K showed that it has no toxic effects and hence safe for use. [42, 43]

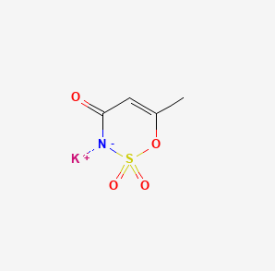

Figure 3: Chemical Structure of Acesulfame K

Aspartame: Aspartame is a dipeptide of the amino acids aspartic acid and phenylalanine joined by a methyl ester (L-aspartyl-L phenylalanine methyl ester). The animal toxicology studies and human trial records confirmed that it is safe to use advantame in food products. [44, 45]

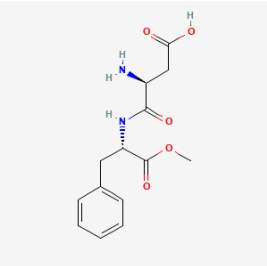

Figure 4: Chemical Structure of Aspartame

Artificial Sweeteners	X Sweeter than sugar	Brand names	ADI (mg/kg body weight per d)
Aspartame	200	Nutrasweet	50
Acesulframe-K	200	Sweet One	15
Saccharin	600	Sweet N' Low	5
Sucralose	300	Splenda	5
Neotame	8000	Newtame	2
Cyclamate	30	-	1
Alitame	2000	-	0-1
Advantame	37000	-	5

Table 1: Example of some artificial sweetener

❖ **Correlation between artificial sweeteners with lymphoma and leukemia in men and women:**

In total, 784,461 person-years were contributed to this analysis by 47,810 males, and 1,493,935 by 77,218 women. The correlation between regular sugarsweetened and diet soda consumption was inverse in subjects with any soda consumption. The mean daily aspartame intake in consumers at the final dietary assessment was 114 mg in the HPFS and 102 mg in the NHS (Nurses Health Study). Men's chance of developing multiple myeloma increased linearly with diet soda usage, and it was considerably higher for those who consumed one or more serving per day. Diet soda was not linked to an increased risk of multiple myeloma in women, and there was a considerable amount of heterogeneity between cohorts for the linear trend and the risk for consumption of more than one drink per day. While in cases of leukaemia both men and women who consumed more diet soda had an increased risk of leukaemia, however these sex-specific findings were not statistically significant. [12]

❖ **Chronic NAS consumption aggravates glucose intolerance:**

While some studies linked NAS consumption to weight gain [49] and an increased risk of type 2 diabetes [46], others linked it to benefits for NAS consumption [47] and little glycaemic response [48]. However, interpretation is made difficult by the fact that NAS are often ingested by people who are already exhibiting symptoms of the metabolic syndrome . The US Food and Drug Administration (FDA) approved six NAS products for use in the US despite these contentious results.

In the healthy/lean condition as well as in obesity [52, 53] and diabetes mellitus [54], food modulates microbiota composition [50] and function [51], and in turn microbiota modifications have been linked to a tendency to metabolic syndrome [55].

Study of three commercial artificial sugars like saccharin, sucralose or aspartame on 10 weeks old C57Bl/6 mice (*Mus musculus*) in division of three groups. Compared to the three mice groups that consumed water, glucose, and sucrose, all three NAS-consuming mouse groups showed pronounced glucose intolerance.

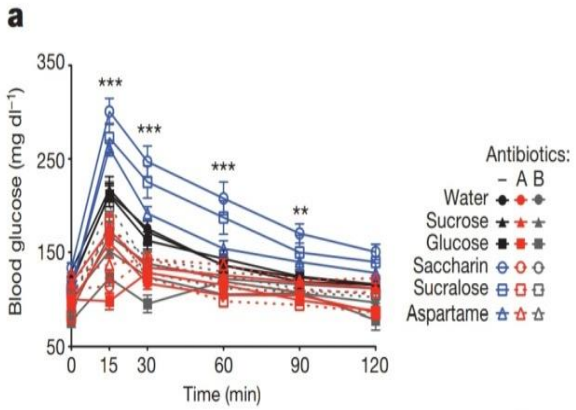

Figure: 5

Figure 5: glucose concentrations in the blood of mice from different intervention groups following OGTT (Oral Glucose Tolerance Test) in intervention groups

In the experiment, the researchers demonstrate how consumption of the sweeteners saccharin, sucralose, or aspartame reduces glucose tolerance, or the capacity to eliminate glucose from the blood stream after ingesting 40 mg of glucose, a procedure known as the oral glucose tolerance test. Compared to glucose or water consumption for the same period of time, they discover that after consuming NAS for 11 weeks, glucose clearance is hindered. The scientists demonstrate this in mice which were fed both a typical chow diet and a high fibre diet (which is also known to impair glucose control in mice). The researchers also made a significant effort to demonstrate that these changes could not be attributed to variation in body weight, physical activity, or energy expenditures.

These findings imply that NAS may cause metabolic disturbance in variety of dosages, mouse strain and diets that mimic human situation, both the lean and obese state. [11]

❖ **Artificial sweeteners and risk of cardiovascular diseases:**

Some experimental in vivo and in vitro studies, observational studies, and human randomised controlled trials examined early markers of cardiovascular health, such as weight status, [14–15] hypertension [16] inflammation [17] vascular dysfunction [18-19], or gut microbiota perturbation [20–23] in relation to consumption of artificial sweeteners or artificially sweetened beverages.

Most of these studies [22–23] revealed negative impacts, whereas only a few suggested neutral or helpful qualities. [14-23] The results of this extensive prospective cohort study point to a probable direct relationship between increased cardiovascular disease risk and higher artificial sweetener usage, particularly aspartame, acesulfame potassium, and sucralose. [13]

- **Toxic potentials of some popular artificial sweetners:**

Toxic Potential of Artificial Sweetners

Common Name	Known Metabolism	ADI (mg/kg/d)	Manifestation of Toxicity	
			Acute	Chronic
Acesulfame-K		15	Headache	Clastogenic, Genotoxic at high dose, Thyroid tumors in rats
Asparmate	Methanol, Aspartic acid, Phenylalanine	50	Headache, Dry Mouth, mood change, nausea, vomiting, reduced seizure threshold, thrombocytopenia	Lymphomas, leukemia in rats
Cyclamate	Cyclohexylamine	1		Bladder cancer in mice, testicular atrophy in mice
Neotame	De-esterified	2	Headache, hepatotoxic at	Lower birthrate, weight loss

	neotame, methanol		high dose	(Due to decreased consumption at higher dose)
Saccharin	O-sulfamoylbenzoic acid	5	Nausea, vomiting, diarrhea	Cancer in offspring of breast fed animals, low birth weight, bladder cancer, hepatotoxicity
Sucralose		5	Diarrhea	Thymus shrinkage and cecal (most proximal part of the large intestine and can be found in the right iliac fossa of the abdomen) enlargement in rats

Table 2: Potential Toxicity of Artificial Sweetners [6]

❖ Colorectal cancer:

The incidence of colorectal cancer (CRC), which ranks third in males after lung and prostate cancer and second in women only after breast cancer, is the third most frequent cancer diagnosed globally. [24-25] Studies have found that CRC may be affected by multiple factors such as race and ethnicity, heredity, smoking, and alcohol. [26] Naturally, diet may have a significant impact on gut microbiota in terms of nutrients as well as dietary chemicals. [27, 28, 29] In fact, it has been long hypothesized that food additives like saccharin and sucralose, which inhibit gut bacteria, may have had a significant causal role in IBD (Inflammatory Bowel Disease) due to the compromised inactivation of digestive proteases by deconjugated bilirubin through the action of bacterial b-glucuronidase. [30, 31] A study on mice which was treatment of mice with sucralose and AOM/DSS

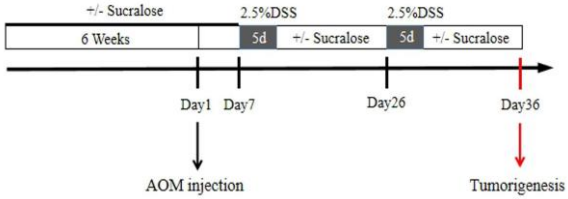

Figure 6: Protocol of sucralose and AOM/DSS treatments used in this study.

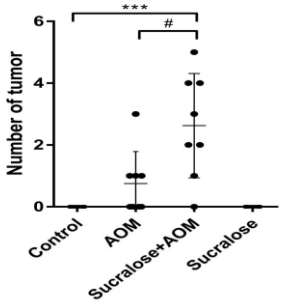

Figure 7: Tumor number in various group of rats

The figure 2 & 3 indicate that Sucralose and combination of sucralose + AOM can produce tumors which are also called tumorigenesis. [4]

❖ Effect on Immunity:

This study examined the effects of these two sweeteners on several blood biochemical parameters, enzyme activities, and immunological parameters in male and female albino mice after 8 and 16 weeks of sweetener administration. Each of the three ingredients—40.5 mg/ml of sucrose, 5.2 mg/ml of sucralose, and 4.2 mg/ml of stevia—was separately dissolved in distilled water. The

sweetened solution was administered to the mice for five hours each day. Both male and female mice preferred drinking water sweetened with stevia or sucralose.
The hemoglobin level, HCT%, RBC and WBC counts were all dramatically decreased by both of the two sweeteners .Both non-caloric sweeteners significantly increased the liver and kidney function enzymes in both male and female mice after 18 weeks.
The biochemical results were verified by histopathological analysis in the sucralose and stevia administered groups, which showed substantial damage to the liver and kidney sections. While giving male mice sugar merely increased their ALT, AST, and cholesterol levels. In groups of male and female mice given sucralose or stevia, there was a marked increase in the levels of various immunoglobulins (IgG, IgE, and IgA) and proinflammatory cytokines (IL-6 and -8), which was accompanied by a marked decrease in the level of the anti-inflammatory cytokine IL-10. In contrast, sugar treatment increased IgA levels and decreased IL-10 levels. [5]

❖ Effect on blood Bladder Cancer:

Various studies on rats and human showed that consumption of artificial sweetners may cause bladder cancer in rats but not associated in humans. [33, 34, 35]
Mechanism of carcinogenicity:
The carcinogenicity in rats and humans both are different due to their different physiology and pharmacodynamics. The artificial sweetener called Sodium Saccharin increase cell proliferation in urinary bladder without interacting with DNA. It results into badder tumor. The physiological changes in bladder are dependent on alteration of urinary composition, especially those of pH and sodium levels which are crucial to tumor development in rat. However there is no evidence that suggest that the above changes are relevant to humans. [32]

Summary:

The evidence presented in this review article suggests that the consumption of artificial sweeteners is associated with several adverse health outcomes. Chronic NAS consumption is linked to aggravating glucose intolerance, which raises concerns about their impact on metabolic health. Furthermore, the potential risk of cardiovascular diseases associated with artificial sweeteners highlights the need for further research in this area to establish causality.
The review also highlights the toxic potential of some commonly used artificial sweeteners, emphasizing the importance of careful consideration when using these substances. The association between artificial sweeteners and colorectal cancer raises concerns about their long-term safety. Moreover, the negative effects of artificial sweeteners on immunity and the potential link to bladder cancer further emphasize the importance of monitoring and regulating their use in food products. While artificial sweeteners have been promoted as sugar substitutes for individuals looking to reduce calorie intake or manage diabetes, this review article underscores the necessity of caution and further investigation regarding their safety.

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