



Non-caloric artificial sweeteners: A mini-review of current perspectives on health benefits and potential risks

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ABSTRACT

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Non-caloric artificial sweeteners (NAS) have gained widespread use in food, beverages, and pharmaceuticals due to their intense sweetness and minimal caloric contribution. Initially introduced as sugar substitutes for weight management and glycemic control, their safety profiles have come under renewed scrutiny. This mini-review summarizes current evidence on the health benefits and potential risks associated with NAS. Clinical trials support their short-term benefits, including modest reductions in body weight, improved glycemic indices, and dental health advantages due to their non-cariogenic properties. Additionally, certain NAS exhibit antimicrobial and antioxidant activities, although these may also disrupt beneficial gut microbiota. Notably, some epidemiological studies have paradoxically linked NAS consumption with weight gain, metabolic disturbances, and cardiovascular risk. Alterations in gut microbiota, neuroendocrine signaling, and taste perception are proposed mechanisms for these effects. Emerging data also raise concerns about carcinogenic and genotoxic potential, particularly for aspartame and acesulfame-K, although findings remain inconsistent across studies. Regulatory agencies maintain acceptable daily intake limits based on toxicological assessments; however, individual susceptibility, cumulative exposure, and long-term outcomes warrant further investigation. Overall, NAS offer useful alternatives to sugar but should be consumed with awareness of potential systemic and microbiome-mediated risks. Ongoing research, particularly well-designed longitudinal human studies, is essential to inform future dietary recommendations and regulatory policies.

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1. Introduction

The use of non-caloric artificial sweeteners (NAS) in the food and pharmaceutical industries dates back to the 1800s. With regulatory approval and a general perception of safety, their use has expanded significantly. While NAS are often viewed as beneficial for weight loss and diabetes management, recent research has highlighted potential health concerns [1,2]. This mini-review aims to examine the impact of NAS on human health by summarizing evidence from recent studies, highlighting both their benefits and associated risks.

2. Overview of NAS

NAS are synthetic sugar substitutes that provide little to no caloric energy but deliver high sweetness intensity per gram compared to caloric sweeteners like sucrose and high-fructose corn syrup [3]. They are widely used in beverages, processed foods, and pharmaceuticals, often labeled as "sugar-free" or "diet" products [4]. To date, six NAS (aspartame, sucralose, saccharin, acesulfame-K, neotame, and advantame) have been approved by the U.S. Food and Drug Administration (FDA) for use within specific acceptable daily intake limits. These NAS are significantly sweeter than sucrose and used in very small amounts [3,5].

The pharmacokinetics and metabolic fates of these sweeteners vary widely. Aspartame is hydrolyzed into its constituent amino acids phenylalanine and aspartic acid, and methanol and is therefore absorbed and metabolized similarly to dietary proteins [4,6]. In contrast, sucralose and acesulfame-K are poorly absorbed in the gastrointestinal tract and are primarily excreted unchanged in the urine or feces, contributing to their negligible caloric value [7-9].

Importantly, NAS have been evaluated for their effects beyond sweetening, including their impact on gut microbiota, insulin sensitivity, and taste receptor signaling, which has raised interest in their long-term safety profiles. Additionally, some NAS such as saccharin and sucralose have demonstrated antimicrobial properties, which may influence microbial diversity in the gut and, consequently, host metabolic health [4,10-13]. Despite regulatory approval, ongoing research continues to explore their potential systemic and microbiome-mediated effects, particularly under chronic exposure.

3. Health Benefits of NAS

3.1 Weight management and caloric reduction

NAS are primarily used as a strategy for weight management by reducing caloric intake from added sugars. A meta-analysis of randomized controlled trials (RCTs) by Rogers et al. demonstrated that replacing sugar with NAS led to modest reductions in body weight

and body fat [14]. Similarly, a systematic review by Toews et al. showed that NAS may contribute to small but clinically relevant improvements in body weight and energy intake in adults [15]. These effects are more consistent when NAS are used to replace rather than supplement sugar-sweetened foods.

3.2 Glycemic control and diabetes management

In individuals with diabetes or impaired glucose tolerance, NAS offer a sugar substitute that does not acutely raise blood glucose levels. Studies have shown that short-term use of NAS does not significantly affect glycemic indices [16,17].

However, some evidence suggests that habitual NAS use may impair insulin sensitivity through gut microbiota alterations or neuroendocrine mechanisms [18]. For example, Suez et al. found that saccharin consumption in healthy individuals induced glucose intolerance and altered gut microbiota profiles [13].

3.3 Dental health

Unlike fermentable carbohydrates, NAS are non-cariogenic. Xylitol, while technically a sugar alcohol rather than an artificial sweetener, is well known for its ability to reduce dental plaque and *Streptococcus mutans* levels [19,20].

Artificial sweeteners like sucralose and aspartame are non-cariogenic and commonly included in oral care products and chewing gum, while xylitol-based gums not only share these non-cariogenic properties but also promote enamel remineralization, stimulate saliva, and offer superior anticaries benefits likely due to xylitol's antibacterial effects compared to both sugared and sorbitol-containing gums [21,22].

3.4 Potential antimicrobial and antioxidant properties

Some NAS, particularly saccharin and sucralose, have demonstrated antimicrobial effects *in vitro*. These compounds inhibit the growth of certain Gram-positive and Gram-negative bacteria, although their impact on beneficial gut microbes raises concerns [11,23,24]. Mechanistic investigations further reveal potential pro-oxidant actions: non-caloric sweeteners such as sucralose and aspartame can stimulate reactive oxygen species (ROS) production in bacterial cultures, damaging cell membranes and triggering efflux pump responses [25].

Based on the study by Griebisch et al., aspartame and its metabolites, was shown to significantly elevate oxidative stress in human neuroblastoma cells. Treatment with this NAS increased reactive ROS levels, impaired mitochondrial integrity, and upregulated antioxidant response genes, indicating a cellular stress response to oxidative damage [26].

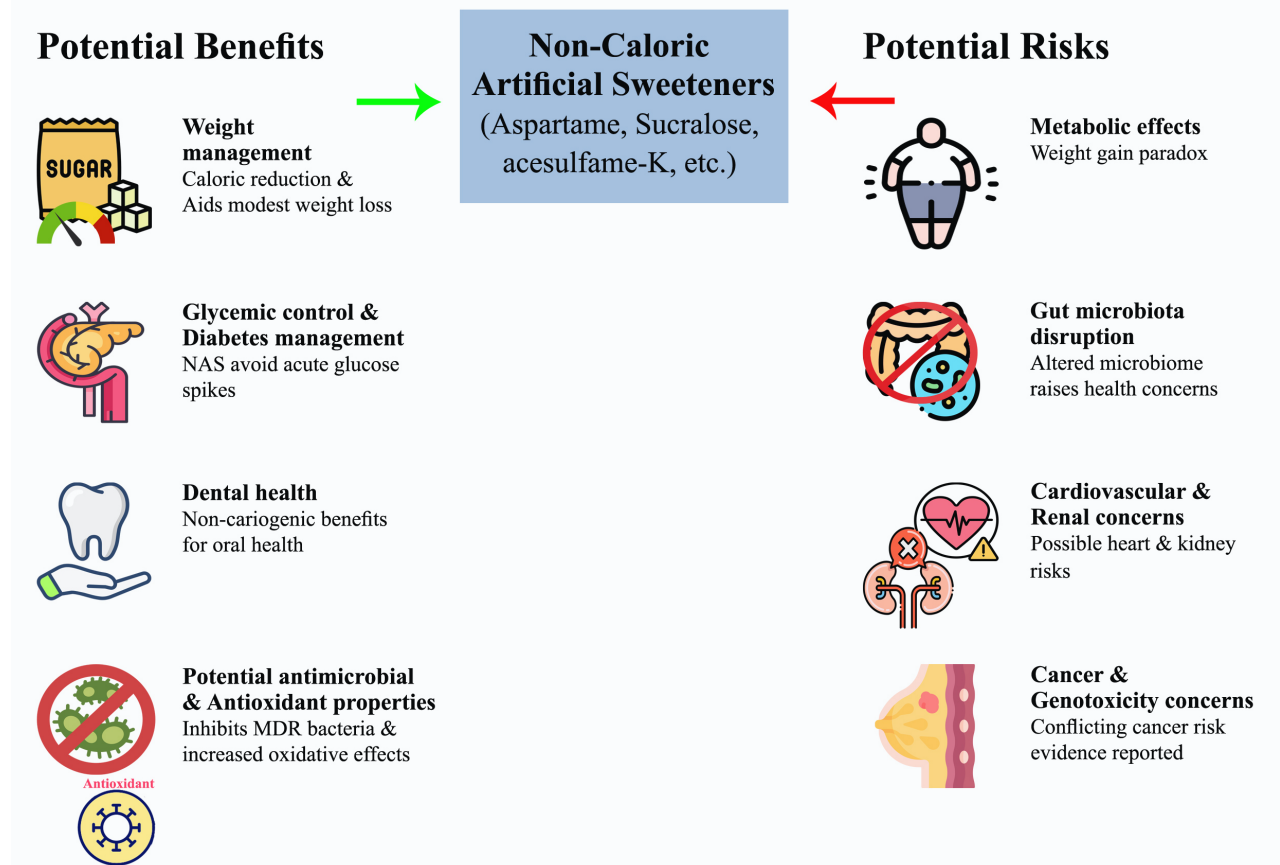


Figure 1. Summary of the potential health benefits and risks associated with non-caloric artificial sweeteners (NAS). NAS offer several potential benefits, including modest weight reduction when replacing sugar, improved short-term glycemic control, dental health advantages due to their non-cariogenic properties, and possible antimicrobial or antioxidant effects. However, emerging evidence has linked NAS consumption to adverse outcomes such as paradoxical weight gain, alterations in gut microbiota, potential cardiovascular and renal effects, and conflicting evidence regarding cancer and genotoxicity risks. The overall health impact of NAS likely depends on sweetener type, dose, duration of use, and individual susceptibility.

4. Health risks and controversies

4.1 Metabolic effects and weight gain paradox

Although NAS are designed to reduce caloric intake, observational studies have paradoxically linked them with weight gain and increased risk of metabolic syndrome. For example, the San Antonio Heart Study and the Multi-Ethnic Study of Atherosclerosis reported associations between diet soda consumption and higher BMI or increased abdominal fat [27,28]. Proposed mechanisms include disruption of energy balance regulation, increased appetite, or neuroendocrine changes associated with sweetness perception without caloric feedback.

4.2 Gut microbiota disruption

Emerging evidence indicates that NAS may alter gut microbial composition. In animal models, saccharin, sucralose, and acesulfame-K have been shown to induce dysbiosis, reducing beneficial taxa such as *Lactobacillus* and *Bacteroides* and increasing pro-inflammatory strains [13,29]. These changes may

underlie observed impairments in glucose tolerance. However, findings in humans remain inconsistent and may depend on dose, duration, and individual microbiome susceptibility [30].

4.3 Cardiovascular and renal concerns

Several epidemiological studies have raised concerns about NAS and cardiovascular health. The Women's Health Initiative reported an association between high intake of diet beverages and increased risk of stroke and coronary heart disease [31]. Other studies have linked chronic sucralose exposure to reduced renal function in animal models [32]. While causality cannot be established from observational data, these findings warrant further mechanistic investigation.

4.4 Cancer and genotoxicity concerns

The potential carcinogenic and genotoxic risks of non-caloric artificial sweeteners remain a topic of active debate. A meta-analysis involving over 116,000 individuals found no statistically significant association between saccharin consumption and bladder cancer,

suggesting that saccharin does not act as a carcinogenic promoter in this context (OR = 0.96; 95% CI 0.79–1.17) [33]. However, contrasting findings have emerged from a large-scale prospective cohort study that reported significantly increased risks of overall cancer, particularly breast and obesity-related cancers among individuals with higher intake of aspartame and acesulfame-K. These results challenge earlier safety conclusions from regulatory authorities and raise concerns about the long-term health implications of these widely used sweeteners. The study calls for a re-evaluation of current dietary guidelines by agencies such as European Food Safety Authority (EFSA) and the World Health Organization (WHO), highlighting the importance of distinguishing between specific sweeteners when assessing carcinogenic potential [34]. A summary of health impacts of NAS illustrated in Figure 1.

5. Dose-response and population considerations

Each NAS has an established Acceptable Daily Intake (ADI) based on toxicological assessments. Typical consumption levels in the general population are below these thresholds; however, heavy consumers, such as individuals with diabetes, may approach or exceed ADIs from multiple dietary sources [35]. Special consideration should be given to children, pregnant women, and individuals with phenylketonuria (in the case of aspartame), who may be more vulnerable to potential adverse effects.

6. Summary of evidence and limitations

Current evidence supports the safety of NAS when consumed within regulatory limits. While short-term benefits in weight and glycemic control are documented, long-term effects remain uncertain. Most adverse findings stem from observational studies or animal models and may not directly translate to human populations. Limitations include heterogeneity in study designs, variability in sweetener types and doses, and potential confounding by dietary and lifestyle factors.

7. Conclusion and future directions

Non-caloric artificial sweeteners provide a useful alternative to sugar for reducing caloric intake and managing blood glucose, particularly in individuals at risk of obesity and diabetes. However, potential adverse effects related to gut microbiota, metabolic health, and cardiovascular outcomes highlight the need for caution and individualized dietary planning. Future research should prioritize well-controlled, long-term human studies and consider microbiome-host interactions and cumulative exposure effects. Regulatory agencies should continue to monitor emerging evidence and revise guidelines as necessary.

Authors' contributions

Conceptualization: KZ; Literature search and Data collection: SK; Analysis and Interpretation of the literature: SK; Writing original draft: SK; Writing review and editing: KZ; Visualization (figure preparation): KZ. All authors read and approved the final version of the manuscript.

Conflict of interest

No potential conflict of interest was reported by the authors.

Ethical declarations

Not applicable.

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