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Non-Nutritive Sweeteners: Long-Term Use and Health Effects

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Abstract

Sweeteners without calories have been part of our lives for more than a hundred years. This journey began with the discovery of saccharin and continues today with zero-calorie soft drinks. High-intensity sweeteners (both natural and artificial) are now commonly used in drinks, snacks, and many packaged foods. Government agencies say these sweeteners are safe when used in small, approved amounts. However, new research suggests we should also look more closely at their long-term effects on the body, including how they may influence metabolism, gut bacteria, and even gene activity. This article explains what scientists currently know about the safety, possible risks, and public opinions of popular sweeteners such as stevia, sucralose, and aspartame. It also looks ahead to new ideas like personalized diets and smarter use of sweeteners. The future of sweetness depends not just on what sweeteners are made of, but also how we understand and use them.

1. Introduction

In recent decades, the global rise in metabolic diseases has intensified consumer interest in achieving sweetness without the use of added sugars. As a result, both artificial and natural sweeteners become integral components of modern diets. These high intensity sweeteners (HIS) are used in a wide range of products from protein supplements to infant foods. The World Health Organization (WHO, 2023) reports that more than half of packaged foods worldwide now contain some form of non-nutritive sweetener (NNS). This widespread transition toward "sugar-free" dietary patterns has generated significant scientific and public debate. An important question is whether artificial sweeteners are truly healthier than sugar or whether they introduce hidden risks. Regulatory authorities, including the U.S. Food and Drug Administration (FDA) and the European Food Safety Authority (EFSA), consistently conclude that approved sweeteners are safe when consumed within established acceptable daily intake (ADI) limits. However, emerging evidence suggests that chronic, low-dose exposure to certain sweeteners may influence metabolic pathways and alter gut microbiota composition (Gauthier *et al*., 2024). Thus, the debate on sweeteners arises from the interaction of regulatory assessments, ongoing scientific findings, and public perception. It emphasizes the need for careful interpretation of evidence and moderate use of sweeteners to support long-term health.

2. Emerging Concerns in Modern Food Systems

High-intensity sweeteners are rarely consumed in isolation. Instead, they are incorporated into complex food matrices where they interact with other components such as caffeine, organic acids, and preservatives. Emerging evidence indicates that co-consumption with caffeine, which is common in soft drinks and energy beverages, may modify absorption kinetics and influence neurotransmitter metabolism (Gopalakrishnan *et al*., 2024). Similarly, sodium benzoate (preservative), has been reported to interact with certain sweeteners and may enhance oxidative stress pathways when exposure occurs at high levels (Yewande *et al*., 2024). These findings emphasize the importance of evaluating sweeteners within realistic dietary contexts rather than as isolated compounds. This concern is further amplified by the global increase in consumption of ultra-processed foods (UPFs). Such products often contain multiple sweeteners across different food categories, leading to increased cumulative exposure. As a result, specific population groups, including children, athletes, and weight-conscious adults, may exceed conservative safety thresholds more readily than expected. (Petridi *et al*., 2024). Additionally, the perceived "health halo" of diet or sugar-free products may encourage overconsumption and reduce the intended benefits of calorie control. It may also contribute to disruptions in gut microbiota composition (Bevilacqua *et al*., 2024). In short, while individual sweeteners may be safe, their combined and chronic presence in modern diets requires a systems-level safety reassessment.

3. Nanotoxicology and Food Innovation

Advances in food nanotechnology have enabled the development of nano-encapsulated sweeteners. These systems are designed to improve taste, enhance stability, and allow controlled release (Hao *et al*., 2025). While such innovations can improve product quality, they also raise new toxicological concerns. Nanoparticles may change absorption patterns, interact with gut microbiota, and accumulate in organs depending on their material composition (Bouwmeester *et al*., 2018). A key challenge is regulatory lag, as technological innovation often progresses faster than safety evaluation. In response, regulatory agencies such as the European Food Safety Authority (EFSA) and the U.S. Food and Drug Administration (FDA) recommend a precautionary approach (EFSA, 2010; FDA, 2018). This includes evaluating nanoformulations based on particle size distribution, biodegradability, and interactions with intestinal tissues (Ejazi *et al*., 2023). Overall, nano-enabled sweeteners may represent a new frontier in food innovation. However, their development must be supported by equally advanced and rigorous safety science.

4. Chronic Low-Dose Exposure

Traditionally, research on sweeteners has focused on high-dose toxicity. But some recent studies, now emphasize realistic, long-term exposure levels of sweeteners. These investigations suggest that sweeteners may affect glucose metabolism, lipid regulation, and gut microbiota composition, even at intakes below the acceptable daily intake (ADI) (Steffen *et al*., 2023). For example, sucralose and aspartame have been associated with individual-specific changes in the gut microbiome that influence glucose tolerance (Gauthier *et al*., 2024). Aspartame has also been linked to increased visceral fat accumulation in longitudinal studies, although a direct causal relationship has not yet been established (Steffen *et al*., 2023). In addition, growing evidence indicates that sweeteners may affect the gut–brain axis. They may influence appetite regulation and mood through interactions with neurotransmitter pathways (Liu *et al*., 2025). While these findings do not challenge current safety classifications, they complicate the definition of "safety" by revealing biological effects that occur below traditional toxicity thresholds. Consequently, modern nutrition science must shift its focus from asking "How much is toxic?" to considering "How much alters biological function?"

5. Natural vs. Artificial: A Scientific Comparison

Stevia

Stevia is a natural sweetener extracted from *Stevia rebaudiana Bertoni* with a sweetness intensity approximately 200-400 times than sugar. Its active components, known as steviol glycosides, are not broken down in the upper digestive tract and show good safety and metabolic neutrality (Castle *et al*., 2024). With an acceptable daily intake (ADI) of 4 mg/kg body weight, stevia is considered suitable for people with diabetes and for weight management. However, concerns remain regarding product purity and the limited availability of long-term human data (Kumari *et al*., 2025).

Sucralose

Sucralose is a synthetic sweetener derived from sucrose and is approximately 600 times sweeter than sugar. It is highly heat-stable and only minimally absorbed, with most of it excreted unchanged. Regulatory agencies such as FDA concluded that it is safe for consumption within an acceptable daily intake (ADI) of 15 mg/kg body weight (FDA, 2018). Nonetheless, repeated consumption has been associated with changes in gut microbial diversity (Uebanso *et al*., 2017). There are also concerns about the formation of chlorinated byproducts during high-temperature processing, although current evidence suggests that the risk to humans remains low (McClements, 2024).

Aspartame

Aspartame is metabolized into amino acids and small amounts of methanol and is among the most extensively studied sweeteners. In 2023, the International Agency for Research on Cancer (IARC) classified it as "possibly carcinogenic," yet regulatory agencies continue to affirm its safety when consumed within established ADI limits. The ADI for aspartame is set at 40 mg/kg body weight in Europe and 50 mg/kg in the U.S. (Magnuson *et al*., 2022). Aspartame remains unsuitable for individuals with phenylketonuria (PKU) due to its phenylalanine content.

6. The Psychology of Sweetness: Myths and Misconceptions

Public discussion around sweeteners often mixes scientific evidence with personal beliefs. Many consumers assume that "natural" products are safe and that "artificial" ones are harmful. Media coverage can further strengthen these assumptions (Richardson & Frese, 2022). At the same time, "sugar-free" labels may create a misleading sense of healthfulness. This can encourage overconsumption of sweetened ultra-processed foods (Panidi *et al*., 2025). Behavioral research also suggests that sweeteners can activate reward pathways in the brain without promoting fullness. As a result, they may contribute to higher overall calorie intake (Coccurello, 2025). For this reason, effective health communication should move beyond labeling foods as simply "good" or "bad." Instead, it should emphasize moderation, dietary context, and improved nutrition literacy.

7. The Future of Sweetness: Innovation Meets Responsibility

The sweetener landscape is likely to undergo significant change. Progress in food nanotechnology, microbiome research, and precision nutrition is supporting the development of "smart sweeteners." These are designed to adapt to individual metabolic responses. At the same time, regulatory agencies are broadening safety frameworks. New approaches increasingly consider cumulative exposure, molecular interactions, and personalized risk profiles. Hybrid formulations that combine natural and synthetic sweeteners, such as stevia–sucralose blends, are also emerging. These combinations can provide balanced sweetness, reduced aftertaste, and improved functional performance However, more emphasis is needed on whole foods, clear labeling, and nutrition education to support long-term health.

8. Conclusion

The debate between natural and artificial sweeteners is not about choosing right or wrong, but about context and understanding. Each sweetener has its own scientific narrative shaped by innovation, regulation, and evolving evidence. Ultimately, progress does not require eliminating sweetness from the diet. Instead, it calls for rethinking how sweetness fits into overall eating patterns. Current research shows that safety is more than the absence of toxicity but it should also involve metabolic balance, gut microbial health, and informed consumer choice.

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