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Gerontological Implications of Artificial Sweeteners Marketed in India: A Comprehesnsive Review

Muskan Thakur [a*] and Kamal Vatika [a]

[a] Department of Biosciences, University Institute of Biotechnology, Chandigarh University, Mohali, Punjab,140301, India.

Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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Review Article

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ABSTRACT

In our instances, humans frequently use synthetic and non-nutritive sweeteners (AS and NNS) in place of sugar. They do this because these sweeteners taste very sweet but have little energy. Groups like the FDA say it's ok to apply commonplace sweeteners, which include aspartame, saccharin, sucralose, neotame, and acesulfame-K, in foods intended to help with weight and diabetes. Even though many human beings use these sweeteners, some worry about how they could have an effect on health. Studies show that those sweeteners can alter gut microorganism mess with blood sugar manipulation, and make human beings feel less complete. This method could have a link to metabolic syndrome, weight problems, and other fitness troubles. Also, a few assume they may cause autoimmune problems, thyroid troubles, and inflammatory bowel disease. This can be genuine for youngsters' pregnant women and those with long-lasting ailments. Despite being promoted as wholesome options, there is not an awful lot solid proof to back up the use of those sweeteners to cure long-term conditions or useful a resource in weight reduction, partly due to the lack of comprehensive studies on the subject. Emerging substitutes, such as uncommon

**Corresponding author: Email: thakurmuskan3516@gmail.com;*

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sugars, seem promising due to their little consequences on metabolism; nonetheless, manufacturing barriers now hinder their great adoption. In locations like India, where the use of AS and NNS is noticeably limited, mild use is considered safe. It is crucial to elevate public attention and conduct a greater study in order to better recognise their long-term consequences and encourage healthier choices.

Keywords: Artificial sweeteners; gerontology; health implications; India, market analysis; ageing population; non-nutritive sweeteners; metabolic health; chronic diseases; sugar alternatives.

ABBREVIATIONS

AS : Artificial Sweeteners
NNS : Non-Nutritive Sweetener
GI : Gerontological Implications
T2DM : Type 2 Diabetes Mellitus
CVD : Cardiovascular Disease
BMI : Body Mass Index
FDA : Food and Drug Administration
FSSAI : Food Safety and Standards Authority of India
WHO : World Health Organisation
RDA : Recommended Dietary Allowance

1. INTRODUCTION

Due to its extremely sweet property and low, close to negligible calorie content, AS, NNS, commonly referred to has become in demand as a sugar substitute (Liauchonak et al., 2019). Thereby, recognized by international organizations like FDA, FAO, FSSAI, these products have been coming along with our favorite baked sweets, beverages, and diabetic dietary food items, frequently (Lewis (n.d.)) Given the well-known fitness risks related to immoderate sugar intake, which include weight problems, diabetes, and heart ailment, they are usually considered a higher alternative to sugar (Mahmoud et al., 2024). AS are now a part of modern-day diets for the reason that the WHO endorsed that sugar consumption should make up between five and 10% of total calories (Motwani et al., 2024). Despite its apparent advantages, there has been a protection. Long-term users are more vulnerable to the development of type 2 diabetes, obesity, and cardiovascular issues due to changes in gut flora, insulin resistance, and glucose metabolism (Yang et al., 2021). Therefore, further research has shown potential links to various problems, such as metabolic diseases, gastrointestinal disorders, and maybe malignancies, raising doubts about their safety (Aron-Wisnewsky et al., 2021; Sasidharan et al., 2024). Worldwide, the prevalence of type 2 diabetes (T2DM) and diabetes in general is expected to increase dramatically by 2045 (Ikwuka et al., 2023). Patients with type 2 diabetes and other metabolic disorders are often advised to use artificial sweeteners instead of sugar (Schiano et al., 2021). However, research has shown that these substitutes have a range of effects on the human body, sometimes even negative ones, particularly on metabolic pathways and gut flora (Li et al., 2024). A wide range of artificial sweeteners, along with their uses and safety aspects, have been thoughtfully explored in earlier studies (Chattopadhyay et al., 2014).

2. ARTIFICIAL SWEETENERS

2.1 Saccharin

The first artificial sweetener was developed in 1879 from petroleum and is considered to be 200–700 times sweeter than sucrose, or common sugar (Mooradian et al., 2017a). Artificial sweeteners, also referred to as non-nutritive, are often present in beverages and health-oriented food products and are a low-calorie substitute for sugar (Mooradian et al., 2017b). The FDA has carefully evaluated the safety of these sweeteners by evaluating the evidence from animal toxicity studies, daily intake levels, and total exposure (Roberts, 2016). Moreover, the European Food Safety Authority (EFSA) ensures that no health risk, among others, cancer risk, is associated when these sweeteners are used within the Acceptable Daily Intake (ADI) guidelines (Bayram and Ozturkcan, 2022).

The ADI is the maximum quantity of sweetener that a person can safely ingest each day for the rest of their lives, as determined by the FDA (Castle et al., 2024). In animal studies, the ADI is typically 100 times lower than the level of the dangerous chemical. A sweetener is tested by the FDA to make sure its EDI is lower than the ADI, indicating that it is safe to eat (Tran et al., 2021).

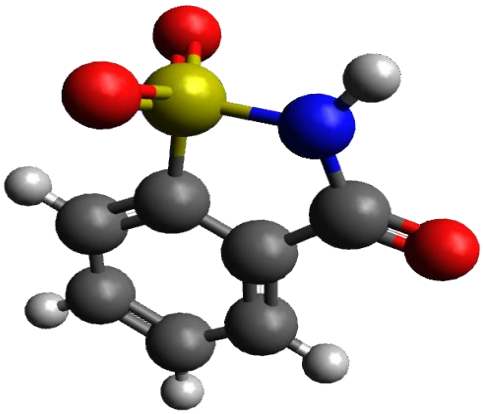

Fig. 1. 3D structure of Saccharin

2.2 Aspartame

Aspartame, which was approved in 1974, has four calories per gram and is around 200 times sweeter than sugar. If aspartame is produced in accordance with established rules and consumed within authorised levels, it is safe for the general public to consume, according to FDA statistics (Czarnecka et al., 2021). Since the approval of aspartame, the scientific community has continuously backed this view. However, people with phenylketonuria, a rare inherited metabolic disease, should either stay away from aspartame entirely or use it sparingly (Burh et al., 2021). The World Health Organisation, which includes the International Agency for Research on Cancer, and the Food and Agriculture Organisation's Joint.

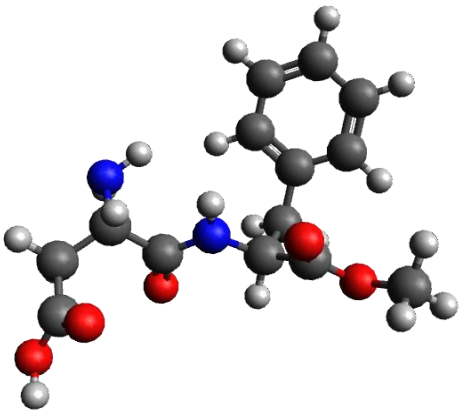

Fig. 2. 3D structure of Aspartame

The Expert Committee on Food Additives are two of the major health organisations that have looked into the purported health risks associated with aspartame (Ali et al., 2019). The IARC has classified aspartame as "possibly carcinogenic to humans" (Group 2B) due to the lack of evidence that it can cause cancer in humans**.** (Zhu et al., 2024a) However, JECFA states that a healthy daily intake of aspartame is 40 milligrams per kilogram of body weight. Despite being separate entities, the totality of these evaluations provides a comprehensive study of the health hazards and benefits of aspartame use (Zhu et al., 2024b).

2.3 Cyclamate

Because of this research, the use of sodium cyclohexyl sulfamate, sometimes known as cyclamate, in diet foods and beverages was banned in the 1950s and 1960s, which was first identified in 1937, was a common low-calorie sweetener in the US. The FDA prohibited the use of cyclamate and its salts, such as sodium, calcium, magnesium, and potassium, after animal research in the 1970s revealed that cyclamate may be carcinogenic (Clemens et al., 2023). Because of this research, the use of sodium cyclohexyl sulfamate, sometimes known as cyclamate, in diet foods and beverages was prohibited in the United States due to its carcinogenic properties (Puttegowda et al., 2024).

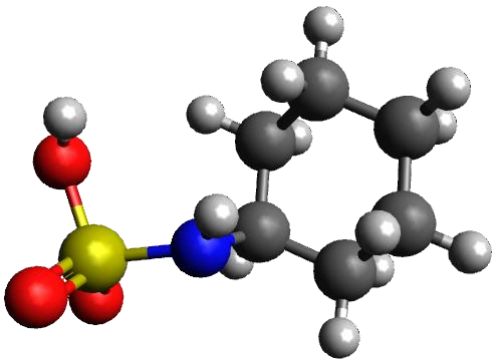

Fig. 3. 3D structure of Cyclamate

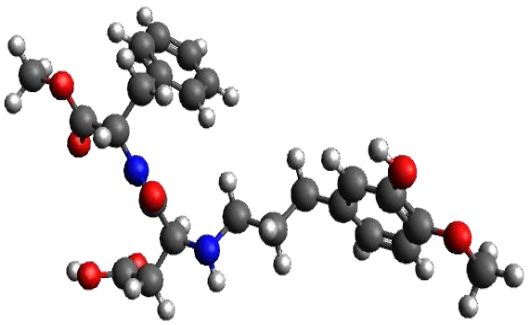

Fig. 4. 3D structure of Advantame

2.4 Advantame

With the exception of meat and poultry, Advantame is a versatile sweetener and flavour enhancer that was most recently approved by the FDA in 2014 (Acunha et al., 2016). Aspartame and vanillin are combined to create Advantame, which is stable in the presence of heat and contributes less phenylalanine than aspartame (Newbould et al., 2021a). Since it is not linked to PKU (phenylketonuria), it will not need to have extra warning labels on its package (Newbould et al., 2021b).

2.5 Rare Sugars

In nature, monosaccharides and their derivatives are uncommon. However, it is now possible to produce these sugars on a commercial scale due to recent advances in large-scale biosynthesis (Bilal et al., 2018a). L-glucose, D-allose, D-psicose, D-tagatose, xylitol, and L-ribose are examples of these uncommon sugars. Of them, D-tagatose (TAG) and D-psicose (PSI) have each been recognised as generally recognised as safe (GRAS). Since these sugars are not metabolised by the body and are not counted toward caloric intake, they offer sweetness without having a high calorie content (Clemens et al., 2016a). Because there is no set Acceptable Daily Intake for these sugars, individuals with diabetes find them more appealing (Evert et al., 2014).

When combined with carbohydrates, PSI and TAG appear to considerably lower postprandial blood glucose increases, according to human studies (Barclay et al., 2021). This is a huge benefit for people with increased blood glucose levels. There may be further health advantages linked to the uncommon sugars, including lowering pro-inflammatory cytokine levels, maintaining gut flora, and enhancing lipid profiles (Bagheri et al., 2022). According to one study that has even ventured into investigating their effects on gut health, PSI can help prevent fructose-induced Non-Alcoholic Fatty Liver Disease by encouraging the growth of beneficial bacteria like Lactobacillus. Because of these advantages, unusual sugars are being considered more and more as a possible substitute for the traditional sweeteners depicted in Fig. 5 (More et al., 2021a).

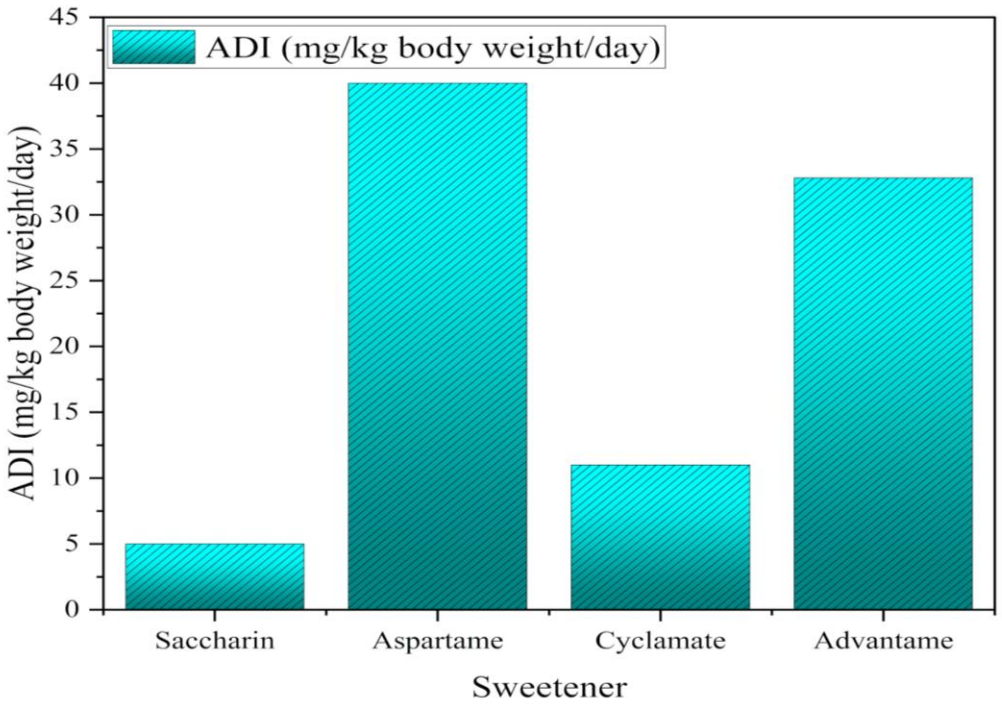

Fig. 5. Safe consumption levels of artificial sweeteners and rare sugars: comparing Acceptable Daily Intake (ADI) values across common sweeteners (More et al., 2021a).

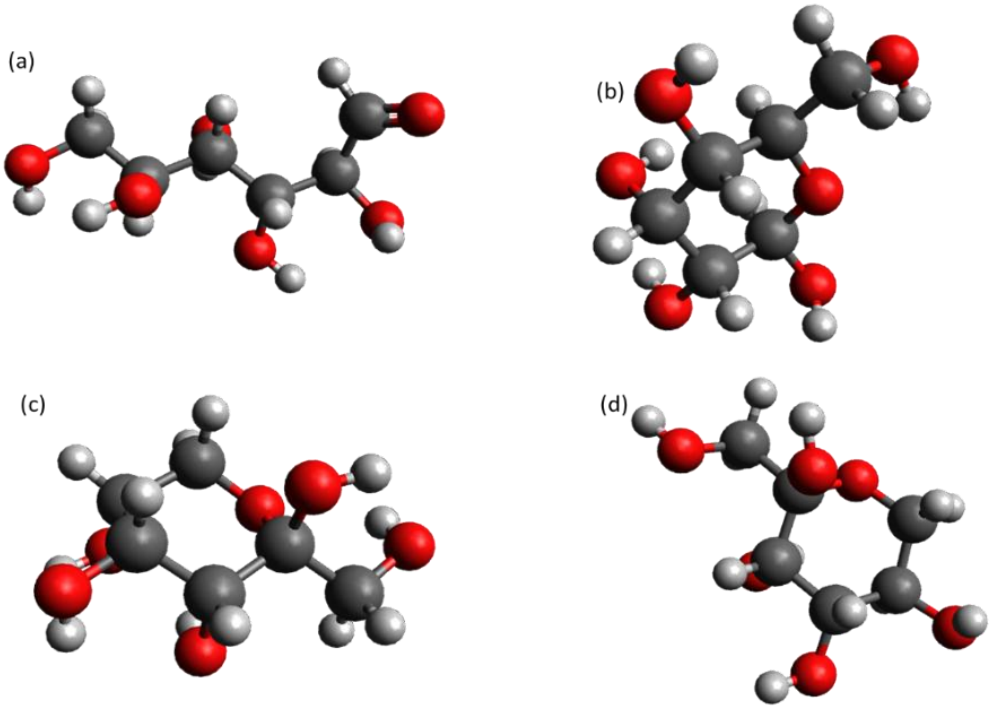

Fig. 6. Some rare sugars 3D conformation (a) L-glucose, (b) D-allose, (c) D-psicose, (d) D-tagatose

Table 1. Summarises the approval and usage of the mentioned artificial sweeteners in the Indian market (Gopalakrishnan et al., 2024)

Sweetener	Approval Status in India (FSSAI)	Common Uses
Saccharin	Approved	Diet soft drinks, sugar-free chewing gums, and tabletop sweeteners
Aspartame	Approved	Diet beverages, sugar-free desserts, chewing gums, and tabletop sweeteners
Cyclamate	Not Approved	Used in diet beverages and low-calorie foods in countries where permitted
Advantame	Not Approved	Beverages, dairy products, confectionery (in countries where permitted)
Rare Sugars	Limited Approval	Baked goods, dairy products, and beverages (used in regions with necessary approval)

3. GERONTOLOGICAL CONSIDERATIONS

3.1 Altered Taste Perception

People's sense of taste tends to deteriorate with age, primarily as a result of diminished smell and taste buds (Sergi et al., 2017). The elderly may find food unattractive due to their inability to taste some flavours, especially sweetness, which could result in low nutrient intake**.** (Lorenz et al., 2022) Traditional sugars have the ability to counteract this, increasing the risk of obesity, type 2 diabetes, and heart disease in older persons (Mozaffarian, 2016). Artificial sweeteners, which are produced from saccharin, aspartame, or advantame, provide sweetness to a food without significantly increasing its calorie content (More et al., 2021b). These are safe, according to regulatory bodies, and the daily allowances are clearly stated. Second, advantame and aspartame cause very little change in blood sugar levels (Iizuka, 2022). Older adults at risk for metabolic disease or with a history of diabetes benefit from them (LeRoith et al., 2019). It is possible to level and improve

the lipid profile and blood sugar content because unusual sugars D-psicose and D-tagatose are metabolised differently than regular sugars. (Bilal et al., 2018b) Although these substitute sugars typically have no negative effects, they can occasionally upset your stomach. The long-term consequences of artificial sweeteners need to be studied, particularly in elderly adults (Malik et al., 2019).

3.2 Increased Risk of Chronic Disease

Obesity, type 2 diabetes, heart disease, and hypertension are a few of these chronic illnesses. Poor diet, inactivity, and the metabolic changes that typically accompany ageing are all linked to these illnesses (Booth et al., 2017). Due to factors including changing taste, diminished appetite, and a slowed metabolism, most elderly people find it difficult to maintain a healthy diet (Yannakoulia et al., 2018). This could eventually cause them to eat more meals that are high in calories but low in nutrients. In order to overcome these challenges, many older adults strive to establish good eating habits, such as choosing whole, unprocessed foods, reducing added sugars and saturated fats, and increasing fibre. If you lose your sense of taste, though, it could be hard to follow. In this case, artificial sweeteners and rare sugars could be good alternatives. Because they provide the body with fewer calories, some sweeteners help people maintain their weight and avoid the associated health problems. Examples of rare sugars that don't significantly increase caloric intake are cellulose and tagatose. They might also provide other advantages, including better blood glucose regulation and intestinal health. By adding these sweeteners to their diet, older individuals can still enjoy the sweetness while eating fewer calories (Bartolotto, 2015). This will lower the chance of long-term health issues, encourage a balanced diet, and enhance blood sugar regulation.

3.3 Medication Interactions

The nutritional status of elderly individuals might be significantly impacted by polypharmacy (Liu et al., 2024). The chemical sensation of taste is interfered with by the majority of medications provided to older patients, such as hypertension, antidepressants, and several chemotherapy therapies (Wang et al., 2017). This leads to hypogeusia, or decreased taste sensitivity, and dysgeusia, or a warped sense of taste. These alterations frequently result in symptoms including xerostomia, metallic aftertaste, and decreased food enjoyment, which can lower appetite and perhaps cause malnutrition (Garutti et al., 2023). Given the high rates of diabetes and heart disease in the community, some older persons may use these diminished taste perceptions as an invitation to consume more sugary meals. Aspartame, saccharin, and Advantame—which have a saccharine flavour—are the best artificial sweeteners (10.4103/0253-7613.182888). These raise blood sugar levels and provide almost no calories. Incorporating caloric content, less frequent sugars have benefits since their concentration somewhat raises blood glucose levels (Clemens et al., 2016b). These carbohydrates have been demonstrated to lower bad fat, enhance blood glucose homeostasis, and lessen inflammation—all of which may have a beneficial impact on how some medications work. Last but not least, adding rare sugars and artificial sweeteners to older people's diet improves their nutrition, reduces the negative effects of medications on taste perception, and boosts the efficacy of their treatment because there is a lower chance of nutritional deficiencies.

4. POTENTIAL BENEFITS

4.1 Metabolic Disturbances

The artificial sweeteners aspartame, ACE K, sucralose, saccharin, neotame, and advantame are among the most often used substitutes for sugar in food preparation (More et al., 2021c). Aspartame is around 200 times sweeter than sugar and is composed of amino acids and methanol (Makar, 2015). Aspartame is typically found in gum, soft drinks, and desserts. However, the amount included in foods does not supply nearly zero calories, even though its body breaks it down into methanol and amino acids after consumption. Aspartame has two derivatives: neotame and advantame (O'donnell, 2012). Advantame is added to various product lines, such as dairy and fruit goods, to add flavour. Neotame is more than 13,000 times sweeter than sugar, but it is calorie-free and non-carcinogenic. Another sweetener that is stable at high temperatures and 200 times sweeter than sugar is ACE K (Mariotti and Lucisano 2014). It is perfect for sauces, desserts, and beverages. To get rid of the bitter aftertaste that occurs with other sweets, it is typically combined with them. The body does not digest these sweeteners after they are consumed. Saccharin, which is 300 times sweeter than sugar and heat stable, was one of the first artificial sweeteners and is

frequently added to baked products and soft drinks (Kaur et al., 2024). Sugar is used to make sucrose, which is 600 times sweeter and more heat-stable. Since sucrose is not absorbed by the body and is therefore eliminated virtually unaltered, it does not provide any calories.

4.2 Cognitive Decline

There has been a scarcity of research on the neurological effects of aspartame (Shaher et al., 2023). Studies in healthy adults indicated no effect of aspartame on reaction time, headaches, hunger, sedation, and brain activity in EEG. (Fowler et al., 2023) Results were mixed for those who tend to experience a migraine, but these studies were not valid because of their weak research design and reliance on subjective, non-validated self-assessments. In children, a study on epilepsy and another on hyperactivity showed no significant effects associated with aspartame (Choudhary and Lee 2018). Current evidence does not indicate that aspartame has significant neurological effects, though there are still restrictions in the quality of the results performed (Gardener and Elkind 2019).

Table 2. Key Indian companies in artificial sweeteners

Company Name	Key Contributions in Artificial Sweeteners
Dabur India Ltd.	Offers sweeteners, honey, and stevia-based substitutes for health-conscious consumers.
Zydus Wellness Ltd.	Produces 'Sugar Free' brand with various sugar alternatives, including artificial sweeteners.
International Prakash Chemicals Pvt. Ltd.	Specialises in sodium cyclamate, a non-caloric sweetener used in food and beverages.
Blue Circle Organics Pvt. Ltd.	Leading producer of saccharin, a widely used artificial sweetener, since 1969.
Vishnu Chemicals Ltd.	Manufacturer of saccharin, supporting the food and beverage industry's demand for artificial sweeteners.

Fig. 7. Images depicting various artificial sweeteners

4.3 Cardiovascular Risks

There is still much disagreement over the research on artificial sweeteners and cardiovascular risk (Lin et al., 2021). The Women's Health Initiative findings indicate that while there was no correlation with hemorrhagic stroke, higher consumption of artificially sweetened beverages was linked to an increased risk of stroke, coronary heart disease, and all-cause mortality. According to research on animals, ACE K may make lipid abnormalities worse, which could lead to atherosclerosis (Debras et al., 2022a). A new study involving 103,388 members of the NutriNet cohort found that consuming artificial sweeteners in general was linked to an elevated risk of cardiovascular disease, whereas ACE K and sucralose were particularly linked to an increased risk of coronary heart disease. Aspartame was not linked to coronary heart disease, but it was linked to an increased risk of cerebrovascular disease (Debras et al., 2022b).

4.3.1 Cancer risk

The results of the 55 studies that were evaluated about the association between the consumption of artificial sweeteners and the risk of cancer varied greatly (del Pozo et al., 2022a). The majority of these have to do with bladder cancer. Saccharin was the sweetener that was examined for this effect more than others, but in order to get a more certain result, very few of them were controlled with any other potentially significant factors, such as environmental toxins (del Pozo et al., 2022b). There was no discernible connection between IS consumption and research on other types of cancer, specifically kidney, intestinal, or brain cancer. But according to a cohort research, men who consume significant amounts of artificially sweetened beverages may be somewhat more susceptible to multiple myeloma and non-Hodgkin lymphoma than women.

4.3.2 Leading Indian companies in artificial sweeteners

Several Indian companies are pioneering the use of artificial sweeteners to meet the growing demand for low-calorie and sugar-free products. From stevia-based substitutes to saccharin and sodium cyclamate, these firms are shaping the future of healthier food and beverage options.

5. CONCLUSION

Artificial sweeteners (AS) and non-nutritive sweeteners (NNS) have been widely accepted due to the reduced calorie count when replacing natural sugars, potentially reducing weight gain and improving blood glucose control. In fact, a number of products have received approval from the FDA, such as saccharin, sucralose, aspartame, neotame, and cyclamate; yet others, alitame, for example, remain under investigation. Yet with growing popularity comes concerns over their safety. These sweeteners are linked to problems such as interruptions in gut health, metabolic challenge, and, potentially, relations with chronic illness, including autoimmunity or cancer. No-calorie ingredients are often used in blends with other ingredients, and excessive and prolonged consumption past the recommended levels can pose quite a health danger. The natural options, such as stevia, are safer, but not as inexpensive and also more difficult to locate. A lot of ongoing research will have to be conducted before much is known about the long-term effects of such sweeteners. For now, moderation or using them in as few natural sweeteners as possible is a much healthier approach to good health.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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