ORIGINAL ARTICLE

Clearing the Myths around non-nutritive/noncaloric Sweeteners: An Efficacy and Safety Evaluation

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Received: 27 November 2021; *Accepted:* 10 March 2022

Abstract

Non-nutritive sweeteners (NNSs) are used to substitute sugar in the diet and are approved by the regulatory bodies in many countries, including the Food and Agriculture Organization (FAO)/the World Health Organization (WHO). Non-nutritive sweeteners are here to stay, as it is an effective strategy to reduce sugar and caloric intake which is a public health priority today. It is a tool to increase dietary compliance in the management of obesity and diabetes and is a partner for fitness seekers. However, the debate on its safety and efficacy continues, including several myths associated with its usage. This review has evaluated the scientific literature in-depth and concludes that NNSs are safe to use within an acceptable daily intake (ADI). Non-nutritive sweeteners are beneficial for their intended use, including weight management and diabetes control when consumed as a part of a dietary management program. The current data do not provide sufficient evidence that NNSs can affect the gut microbiome, and more research, particularly at relevant doses, is required. We also need more randomized control trials (RCTs) among the Indian population on the impact of sugar reduction with NNSs and its health benefits to strengthen the evidence for its use in medical nutrition management and preventive health, helping the individual make an informed choice.

Journal of the Association of Physicians of India (2022): 10.5005/japi-11001-0029

Introduction

Non-nutritive/noncaloric sweeteners are defined as food additives that are used to replace sugar and give food a sweet taste, thus helping in decreasing caloric and sugar intake. The tabletop sweeteners are products that consist of or include permitted NNSs [approved by regulatory bodies like the United States Food and Drug Administration (USFDA) Joint FAO/WHO Expert Committee on Food Additives (JECFA), country-specific regulatory bodies, etc.] and are intended for use as an alternative to sugar, to their ultimate customers. Predominantly there are two kinds of sweeteners—caloric sweeteners and noncaloric/NNSs/low-caloric sweeteners (LCSs). Sucrose, glucose, and fructose are the foremost bulk caloric sweeteners used in food and beverages or packed in small containers for retail sale. Caloric sweeteners add bulk and calories to the food. These sweeteners are generally carbohydrates or sugar alcohols that have a similar sweetness to sugar, for example, sorbitol, sorbitol syrup, mannitol, isomalt, polyglycitol syrup, maltitol, maltitol syrup, lactitol, xylitol, etc. Sugars add 4 kcal/gm to foods, while sugar alcohols add calories ranging from 0.2 to 2.6 kcal/gm. Conversely, high-intensity sweeteners/NNSs have a sweet taste, are noncaloric, do not provide bulk to the food, have multifold sweetness than sugar, and are consequently used in small amounts. These include steviol glycoside, thaumatin, aspartame, sucralose, neotame, acesulfame potassium, saccharin, etc.[1]

Sugar is deemed as the major contributing factor for the increased risk of obesity since it adds caloric value to the food.[1-3] Obesity is a major public health concern worldwide,[2-4] and its prevalence has increased evidently over the past few decades.[3] It is considered as the major cause of comorbidities leading to diabetes mellitus, cardiovascular disorders, hypertension, certain cancers, and other health problems.[3,4] Owing to a high burden of the disease, the WHO has recommended that the total added sugars should be restricted to below 10% (preferably 5%) of the total energy intake.[4–7] Therefore the regulatory bodies around the world have recommended reducing the intake of sugar to combat the issue of obesity and related comorbidities.[2] The use of NNSs is one of the most important strategies that may help in substituting the sugar due to their sweetness, palatability, and addition of none or few calories to food.[2–5]

Several studies have demonstrated that substituting sugars with NNSs has been useful in preventing and managing obesity and associated disorders.[2,3] In 2011, the European Food Safety Authority (EFSA) concluded that there was sufficient scientific evidence to support the claims that NNSs like sucralose reduced postprandial blood sugar levels and maintained tooth mineralization by decreasing tooth demineralization.[8] Despite the consistent reassurances from food safety authorities, there exists some distrust regarding the use of NNSs among healthcare professionals.[2] The present succinct review focuses on busting the myths surrounding the efficacy and safety of NNSs in humans by deliberating their safety and efficacy on health outcomes.

Non-nutritive Sweeteners: the Journey from Discovery to Human Use

Non-nutritive sweeteners have an intensely sweet taste that provides very low or zero calories. These agents are used in minimal quantities as they have greater sweetness than sugar.[1,3] Non-nutritive sweeteners have been used safely in food and drinks all over the world for over a century. Saccharin was the first NNS to be discovered in 1879 by Remsen and Fahlberg. This was followed by the discovery of stevia, cyclamate, aspartame, acesulfame potassium, sucralose, and neotame. Non-nutritive sweeteners differ from each other in terms of their sweetness, unique structure, metabolic fate, and technical characteristics.[9] The properties of the most used NNSs are summarized in Table 1.

Health Outcomes of NNSs

Several studies have established the effectiveness of NNSs in the maintenance of body weight, treatment of obesity, management of diabetes, and prevention/reduction of dental caries.[1] However, there

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How to cite this article: Tiwaskar M, Mohan V. Clearing the Myths around non-nutritive/noncaloric Sweeteners: An Efficacy and Safety Evaluation. J Assoc Physicians India 2022;70(7):18–26.

Table 1: Characteristics of various NNSs

NNS	*Saccharin*	*Stevia*	*Cyclamate*	*Aspartame*	*Acesulfame potassium*	*Sucralose*	*Neotame*
Discovery year	1879[9]	1931[10]	1937[9,10]	1965[9]	1967[9,10]	1976[9,10]	1992[12]
Chemical composition[10]	Often found as a sodium salt of an organic acid	Consists of steviol glycosides	Exists as calcium or sodium salts of cyclamic acid	Consists of a methyl ester of two amino acids, aspartic acid, and phenylalanine	Potassium salt of an organic acid	Disaccharide made from sucrose	Derived from aspartic acid and phenylalanine
Relative sweetness to sucrose	300–600[1]	250–300[1]	30[10]	160–220[1]	150–200[1]	400–800[1]	7000–13,000[1]
Calories (kcal/gm)[10]	0	0	0	4*	0	0	0
Metabolic and biological properties	Not metabolized; excreted unchanged[9]	Steviol glycosides are metabolized to steviol; excreted in the urine as steviol glucuronide[9]	Generally not metabolized; excreted unchanged[9]	Metabolized to its constituent amino acids and methanol‡[9]	Not metabolized; excreted unchanged[9]	Minimally metabolized; excreted unchanged[9]	Extensively metabolized to phenylalanine and methanol‡; excreted *via* feces and urine[13]
ADI (mg/kg bodyweight) as per JECFA[10]	5	4 mg of steviol equivalents or 12 mg of high purity stevia extracts	11	40	15	15	2
Global status (Codex approval for use in food, beverages, and tabletop sweeteners)[10]	Approved in over 100 countries	Approved in nearly 49 countries	Permitted in more than 100 countries	Approved in over 100 countries	Approved in approximately 90 countries	Approved in nearly 80 countries	Approved in more than 40 countries
US FDA approval[14,15]	Before 1958	2008	Not available	1981	1988	1999	2002
Indian regulatory approval[11]	Allowed as non-caloric sweetener in some of the food product categories specified in Food Safety and Standard Regulations	Allowed as non-caloric sweetener in some of the food product categories specified in Food Safety and Standard Regulations	Not permitted	Allowed as non-caloric sweetener in some of the food product categories specified in Food Safety and Standard Regulations	Allowed as non-caloric sweetener in some of the food product categories specified in Food Safety and Standard Regulations	Allowed as non-caloric sweetener in some of the food product categories specified in Food Safety and Standard Regulations	Allowed as non-caloric sweetener in some of the food product categories specified in Food Safety and Standard Regulations

*Though aspartame provides 4 kcal/gm, due to its high sweetness, it is used in very small amounts thus providing practically no calories[1,8]; ‡Methanol is formed in small quantities lesser than that equivalent to commonly found in many foods[8,11]

exist discrepancies where some studies contradict these results and have shown that NNSs may encourage weight gain,[16] and metabolic impairment.[5] The subsequent section discusses the effect of NNS in the abovementioned therapeutic areas.

Effect on Body Weight/Body Mass Index

Subjects with obesity commonly replace caloric sweeteners with NNSs to maintain the pleasure of sweet taste and reduce energy intake. However, the effect of NNSs on weight gain and reduction is debatable with evidence suggesting weight loss or otherwise.[16] Epidemiological studies in rodent models[5] and human observational studies have recognized that NNSs promote weight gain[3,16–20] by altering taste and metabolic signaling, increasing appetite, hunger, sweets cravings, and decreasing satiety.[3,21] On the contrary, RCTs and human interventional or experimental trials have demonstrated that NNSs assist in weight management by promoting weight loss and maintenance[2,3,5,16,22–26] by reducing intake of sugar-containing foods,[24] thereby reducing the net energy intake.[2,16,22,25] Randomized control trials are at the highest level of evidence in evidence-based medicine as these are designed to be unbiased and have less risk of systematic errors.[27] Tables 2 and 3 display the effect of NNSs on body weight.

The variation in the results of different studies may be due to the following reasons:[16,17,22]

- Observational studies are known to have significant limitations, including the possibility of reverse causality in studies

Table 2: Effect of NNSs on body weight/BMI

Author (year)	*Study type*	*Study population*	*Study duration*	*LCS used*	*Comparator*	*Conclusion*
Stamataki et al. (2020)[28]	Randomized, controlled, open-label two-parallel-arm trial	28 healthy individuals	12 weeks	Stevia	Control	Weight maintenance observed with daily stevia consumption
Peters et al. (2016)[22]	Randomized, equivalence trial	303 weight-stable people with overweight and obesity	1 year	Not specified	Water	NNS beverages were superior to water beverages for weight loss and weight maintenance
Sørensen et al. (2014)[29]	Sub-study of a single-blind, parallel design, intervention trial	24 healthy, overweight subjects	10 weeks	Aspartame, acesulfame potassium, cyclamate, saccharin	Sucrose	Bodyweight and fat mass decreased with the use of artificial sweeteners and increased with sucrose
Koyuncu and Balci (2014)[30]	Crossover study	54 prediabetic patients	6 months	Aspartame	–	Aspartame effectively reduced body weight
Maersk et al. (2012)[31]	Randomized parallel intervention trial	60 healthy, nondiabetic subjects	6 months	Aspartame	Sucrose	Increased ectopic fat accumulation, triglycerides, and total cholesterol levels with sucrose-sweetened soft drinks compared with aspartame-sweetened drinks
Reid et al. (2007)[32]	Long-term study	133 normal-weighted women	5 weeks	Aspartame	Sucrose	The weight loss was observed with aspartame, while weight gain observed with sucrose
Raben et al. (2002)[33]	Parallel design, intervention trial	41 healthy, overweight subjects	10 weeks	Aspartame, acesulfame potassium, cyclamate, saccharin	Sucrose	Gain in weight and fat mass was observed with sucrose, while the loss in weight and fat mass observed with artificial sweeteners
Blackburn et al. (1997)[34]	Prospective, randomized, stratified, two-parallel-arm design trial	163 obese women	Intervention: 16 weeks Maintenance: 1 year	Aspartame	Control	Aspartame may facilitate long-term maintenance of reduced body weight
Parker et al. (1997)[35]	Community-based cohort study	465 individuals	4 years	Saccharin	–	Weight gain with use of saccharin
Colditz et al. (1990)[36]	Questionnaires-based cohort study	31,940 healthy women	8 years	Saccharin	–	Continuing weight gain over time with saccharin use
Stellman and Garfinkel (1986)[37]	Prospective mortality study	78,694 women	1 year	Saccharin (n = 17,016)	Control (n = 61,678)	Long-term use of artificial sweeteners does not help in losing weight or prevent weight gain

where overweight individuals may choose to consume NNS beverages to reduce their risk of weight gain.

- Residual confounding may be another issue with observational studies where insufficient factors about subject characteristics and behaviors were adjusted for in the data analysis.
- The questionnaire-based cohort studies lacked specific information about the use of specific NNSs in the target population.

Effect on Metabolic Health: A Focus on Diabetes

In a 2013 position statement and a 2019 consensus report, the American Diabetes Association stated that "*the use of nonnutritive sweeteners has the potential to reduce overall calorie and carbohydrate intake if substituted for caloric sweeteners and without compensation by intake of additional calories from other food sources.*"[39,40] The committee further added that "*substituting sugar-sweetened beverages with low-calorie sweetened beverages might help to reduce the increases in blood glucose levels associated with high intakes of sugar-sweetened beverages in people with diabetes mellitus.*" This statement was also supported by the American Heart Association (AHA) in a 2012 expert review and 2018 Medical Care Standards for Diabetes. The AHA committee stated that "*when used judiciously, NNSs may facilitate reductions in added sugars and energy intake, help people achieve and maintain a healthy body weight, and lower the risk of cardiovascular diseases and type 2 diabetes mellitus.*" The AHA committee further added that "*For adults who are habitually high consumers of sugar-sweetened beverages, low-calorie sweetened beverages may be a useful replacement strategy to reduce intake of sugar-sweetened beverages.*"[39] Furthermore, clinical evidence supports that the use of low-calorie sweeteners is associated with no increase in blood glucose levels, hemoglobin A1C, fasting and postprandial glucose, and insulin levels in subjects with or without diabetes.[2] Furthermore, a Nurses' Health Study showed that the replacement of sugar-sweetened beverages with low-calorie sweetened beverages was associated with a 7% lower risk of type II diabetes mellitus. However, there exist some discrepancies as certain studies report a positive association between intake of LCSs and increased risk of obesity, type II diabetes, hypertension, and cardiovascular events.[39] This association may be due to several limitations, including potential reverse causation bias,[39] substantial heterogeneity among the cohorts, potential publication bias,[41] use of different types of low-calorie sweeteners, different outcome measures, and different lengths of follow-up times that resulted in exorbitant variability to pool the results.[39] Tables 4 and 5 discuss the outcomes of various studies highlighting the effects of NNSs on glycemia and glucose hemostasis.

Effect on Taste Receptor and Incretin Secretion

Taste receptors are involved in the modulation of multiple metabolic processes like satiation, glucose homeostasis, and gut motility.[55] Activation of sweet-taste receptors in the gut plays a role in the regulation of glucose absorption and promoting insulin release.[9] Exposure to food, sugars, or nutrients

Table 3: Meta-analysis demonstrating the effect of NNSs on body weight/BMI

Author (year)	*Study type*	*LCSs/ASs/NNSs/NNCSs included*	*Conclusion*
Lohner et al. (2017)[38]	Meta-analysis of 15 systematic reviews, 155 RCTs, 23 nonrandomized controlled trials, 57 cohort studies, 52 case-control studies, 28 cross-sectional studies, and 42 case series/case reports	ASs (saccharin, sucralose, advantame, aspartame, acesulfame potassium, neotame, cyclamate, alitame, neohesperidin dihydrochalcone) or NNCSs (stevioside, rebaudioside A, thaumatin, brazzein) or NNSs (defined as any combination of ASs and NNCSs)	• Meta-analysis of RCTs showed no association between LCS intake and increase in body weight/BMI • Positive association between LCS intake and slightly increased BMI was observed in a meta-analysis of observational studies, but no association with body weight or fat mass • Results of the epidemiological studies were highly inconsistent • RCTs reported a weight reduction or no change in weight after intake of NNSs or diet beverages • Prospective cohort studies indicated a positive relationship between NNS or diet beverage intake and weight gain/increased BMI • The majority of cross-sectional studies showed a positive relationship between NNSs or diet beverage intake and weight gain/increased BMI, while a few showed either a negative or no association
Miller et al. (2014)[3]	Meta-analysis of 15 RCTs and 9 prospective cohort studies	LCS (NNS or polyol)	• In RCTs, LCSs modestly but significantly reduced fat mass, waist circumference, body weight, and BMI • Prospective cohort studies showed no association between LCS intake and fat mass or body weight, however, a significant association was observed with slightly higher BMI
Laviada-Molina et al. (2020)[23]	Meta-analysis of 20 RCTs	NNSs (aspartame, saccharin, sucralose, stevia, cyclamate, and acesulfame potassium)	• No evidence suggests that NNS consumption promotes weight gain, even in children or adolescents • Replacing sugar with NNS leads to weight reduction in subjects with overweight/obesity, and those under an unrestricted diet
Rogers et al. (2021)[26]	Meta-analyses of 37 parallel groups studies and 14 crossover studies	LCS (NNS or polyol)	• Both parallel groups and crossover studies showed that body weight, BMI, and energy intake were reduced by intake of LCS compared with sugar • There was no effect of LCS on body weight compared with placebo • Parallel group studies reported a higher energy intake with LCS than with water/nothing; however, crossover studies showed an opposite effect

BMI, Body mass index; ASs, Artificial sweeteners; NNCSs: Natural, noncaloric sweeteners

triggers physiological responses that result in the release of insulin or incretin to reduce blood glucose levels.[9,56] Non-nutritive sweeteners interact with the T1R-family of sweet-taste receptors[56] and may adversely affect glycemic control.[9] Additionally, NNSs have been linked to metabolic diseases due to the activation of gastrointestinal taste receptors, altered hormone secretion, and/or perturbations to the intestinal microflora.[55] However, these results are derived from *in vitro* studies that utilized extraordinarily high doses of these sweeteners. Contrary to the findings of *in vitro* studies, *in vivo* studies and human trials have shown to have no effects on circulating incretin levels.[9,56] A recent review stated that NNSs do not directly induce incretin secretion[56] and activation of the sweet-taste receptors by LCSs fails to replicate any of the effects on gut hormones, gastric motility, or appetitive responses evoked by caloric sugars.[9]

Effect on Dental Health

Frequent consumption of free sugars is associated with the development of dental caries. A systematic review that appraised the relationship between the amount of free sugar intake and the development of dental caries across age groups revealed that limiting free sugar intake to <10% of daily energy intake diminishes the risk of dental caries throughout the life course.[9] Evidence has revealed that the use of NNSs influences the microbial composition of the oral mucosa that may be utilized to reduce the risk of the development of dental caries. Furthermore, *in vitro* studies have uncovered that aspartame, saccharin, and sucralose have antimicrobial activity against common periodontal pathogens.[5]

Bursting the Myths Around the Safety of NNSs

The NNSs have undergone a comprehensive safety assessment by the global regulators before their approval in human use. The USFDA, JECFA, and EFSA have confirmed the safety of all approved LCSs as food additives.[2,7] These bodies have suggested that NNSs should be taken in an amount of ADI. Acceptable daily intake is defined as the estimated amount of NNS that a person can safely consume on an average every day over a lifetime without risk. It is usually set at 1/100 of the no-observed-adverse-effect-level/maximum level at which no adverse effects were seen in animal experiments. The levels of NNSs in food ingredients are set to ensure that the actual daily intakes do not exceed the ADI.[57] However, there are some ongoing debates that NNSs pose health risks[58] like the development of cancer,[59] renal toxicity,[60] genotoxicity,[61] and neurotoxicity[58] and adversely affect the gut microbiota.[62] These myths are busted in the subsequent section.

Association of NNSs with Cancer

The risk of developing cancer with the use of NNSs has been widely debated over the last few decades.[59] In 1970, the first reported incident of NNS-induced cancer came into highlight when the USFDA banned cyclamate from the market due to a suspicion of induced cancer in experimental animals. However, cyclamate use was continued in other countries, especially in combination with other sweeteners. Further evaluations of cyclamate toxicity by the WHO, the Cancer Assessment Committee of the Center for Food Safety and Applied Nutrition of the FDA, and the Scientific Committee for Foods of the European Union concluded that cyclamate is not a carcinogen, thereby readmitting it to the food market.[63]

Similarly, several animal studies had discovered that extremely high doses of saccharin were associated with an increased risk of bladder cancer.[59] A review comprising 20 study groups analyzed the long-term effect

Table 4: Effect of NNSs on glycemia and glucose hemostasis

Author (year)	*Study type*	*Study population*	*Study duration*	*LCS used*	*Comparator*	*Conclusion*
Kim et al. (2020)[42]	Randomized, crossover trial	39 healthy individuals	2 weeks intervention 4 weeks washout period	Acesulfame potassium + aspartame	Mineral water	No effect on glucose, insulin, and insulin sensitivity
Higgins et al. (2018)[43]	Parallel-arm design	100 healthy, lean adults	12 weeks	Aspartame	–	No effect on glycemia, appetite, or bodyweight
Engel et al. (2018)[44]	Secondary analysis of a 6-month RCT	60 overweight and obese subjects	6 months	Aspartame	Sucrose	No effect of aspartame on long-term glycemic (fasting glucose and insulin) or on insulin sensitivity
Tey et al. (2017)[45]	Randomized, crossover study	10 healthy males	24 hours	Aspartame, stevia	Sucrose	Minimal effect on 24-hour glucose profiles with LCS
Grotz et al. (2017)[46]	Double-blind, parallel, randomized clinical trial	47 healthy males	12 weeks	Sucralose	Placebo	Sucralose does not affect glycemic control
Sylvetsky et al. (2016)[47]	Four-period, crossover study	61 healthy adults	24 hours	Diet soda with sucralose, acesulfame potassium, aspartame	Water with sucralose Seltzer water with NNS	Diet sodas augmented GLP-1 responses to oral glucose
Temizkan et al. (2015)[48]	Prospective study	8 healthy volunteers and 8 newly diagnosed, drug-naive T2DM patients	Not specified	Sucralose, aspartame	Water	Sucralose lowers blood glucose in healthy subjects by enhancing GLP-1 release; however, this is not observed in newly diagnosed T2DM patients
Hazali et al. (2014)[49]	Prospective study	32 healthy subjects	24 hours	Stevia	Sucrose	Stevia maintained blood glucose even when consumed in a short length of time
Bryant et al. 2014[50]	Prospective study	10 healthy subjects	Not specified	Aspartame, saccharin, acesulfame potassium	–	No additional effect of aspartame or saccharin on blood glucose
Pepino et al. (2013)[51]	Randomized crossover design	17 obese subjects	2 days with 7 days washout period	Sucralose	Water	Sucralose increased peak plasma glucose concentrations, C-peptide, and insulin concentrations, and total insulin AUC after an oral glucose load
Brown et al. (2009)[52]	Prospective study	22 healthy subjects	24 hours	Sucralose and acesulfame potassium	Carbonated water	Increase in GLP-1 secretion

GLP, Glucagon-like peptide; T2DM, Type II diabetes mellitus; AUC, Area under curve

Table 5: Meta-analysis demonstrating the effect of NNSs on glycemia and glucose hemostasis

Author (year)	*Study type*	*LCSs involved*	*Conclusion*
Nichol et al. (2018)[53]	Meta-analysis of 29 RCTs that investigated the glycemic impact of aspartame, saccharin, steviosides, and sucralose	Aspartame, saccharin, stevia, sucralose	• No increase in blood glucose level • Blood glucose levels decreased at different time intervals with increasing age and BMI
Greyling et al. (2020)[54]	Meta-analysis of 34 RCTs that investigated the effect of low-energy sweeteners on acute postprandial glucose or insulin responses	Acesulfame potassium, saccharin, stevia, sucralose, aspartame, stevioside, erythritol	No acute effects on insulinemic responses or the mean change in postprandial glucose levels compared with a control group
Lohner et al. (2017)[38]	Meta-analysis of 15 systematic reviews, 155 RCTs, 23 nonrandomized controlled trials, 57 cohort studies, 52 case-control studies, 28 cross-sectional studies, and 42 case series/case reports	ASs (aspartame, acesulfame potassium, advantame, alitame, cyclamate, neotame, neohesperidin dihydrochalcone, saccharin, sucralose) or NNCSs (stevioside, thaumatin, rebaudioside A, brazzein) or NNSs (defined as any combination of AS and NNCS)	• Systematic reviews reported an increased risk of diabetes with the intake of artificially sweetened soft drinks • Substantial heterogeneity was reported among the cohort studies

BMI, Body mass index; ASs, Artificial sweeteners; NNCSs, Natural, noncaloric sweeteners

Table 6: Association of NNSs with risk of cancer development

Author (year)	*Study type*	*Safety assessment population*	*LCS used*	*Conclusion*
Chappell et al. (2021)[66]	Systematic evaluation and integration of mechanistic data	*In vivo* and *in vitro*, including human cells	Steviol glycosides	• Lack of genotoxic and carcinogenic activity • Anti-inflammatory, antioxidant, and antiproliferative activity observed
Chappell et al. (2020)[67]	Systematic evaluation and integration of mechanistic data	Human and animal studies, *in vitro* assays in either human or nonhuman mammalian cells	Acesulfame potassium	• Exposure of acesulfame potassium unlikely to pose a carcinogenic risk to humans • Rodent bioassays showed absence of treatment-related tumor
Chappell et al. (2020)[68]	Systematic evaluation and integration of mechanistic data	Human and animal studies, *in vitro* assays in either human or nonhuman mammalian cells	Sucralose	Sucralose was considered to be safe for its intended use in humans without concern for mutagenicity and carcinogenicity
Wikoff et al. (2020)[69]	Systematic evaluation and integration of mechanistic data	Human and animal studies, *in vitro* assays in human or nonhuman mammalian cells	Aspartame	Lack of carcinogenicity in humans from aspartame consumption
Haighton et al. (2019)[70]	Epidemiology studies looking at cancer endpoints against quality appraisal criteria (9 case-control studies and 5 prospective cohort studies)	Humans	Aspartame	Certain studies reported the risk of cancer with aspartame use. However, these studies had limitations of inadequate sample size. Overall, the results of this review do not support that aspartame use is associated with an increased risk of cancer in humans
Berry et al. (2016)[71]	Review of human and animal studies	Humans and animal models	Sucralose	Sucralose metabolites have no carcinogenic potential in humans No evidence of carcinogenic potential was observed with sucralose in long-term carcinogenicity studies in animal models
EFSA Panel (2013)[72]	Scientific opinion	Human and animal studies	Aspartame	Safe as a food additive for human use
EFSA Panel (2010)[73]	Scientific opinion	Human and animal studies	Steviol glycosides	Noncarcinogenic, nongenotoxic, or no association with any reproductive/developmental toxicity
Gallus et al. (2007)[59]	A large and integrated network of case-control studies (598 cases)	Humans	Saccharin, aspartame, and other sweeteners	Lack of association between saccharin, aspartame, and other sweeteners and the risk of cancer

of high doses of saccharin in one generation of rats. Only one study reported an increased incidence of bladder cancer, while none of the remaining studies found significantly more neoplasia in the saccharin-fed animals than in controls. In the positive study, August Copenhagen Irish rats were used that are susceptible to saccharin-induced bladder cell proliferation due to frequent bladder infection with *Trichosomoides crassicanda* parasite. Further reports on animal studies have revealed that the high urine osmolarity in rodents enhances the precipitation of cytotoxic calcium phosphate-containing crystals in the bladder leading to regenerative hyperplasia and tumors.[63]

A few earlier human epidemiological studies reported an increased risk of bladder cancer with extremely high doses of saccharin. However, further human epidemiological studies failed to reproduce these findings since it was observed that saccharin metabolism varied in different species. This led to the affirmation that saccharin was not associated with the formation of either urinary tract stones or epithelial lesions in humans. Similarly, a few case-control studies revealed an increased risk of bladder cancer in nonsmokers and men consuming artificial sweeteners; however, the largest case-control study analyzing the issue found no relation between the cancer risk and the use of artificial sweeteners. An ecological study reported that aspartame use was associated with an increased risk of brain cancer; however, such ecological studies are known to be subject to ecological fallacy.[59] Similarly, in 1999, a journal reported an increased risk of breast cancer which might have been a result of increased aspartame use. However, the apparent correlation was based on an error that aspartame was introduced into the market in 1974 rather than 1981.[57] In 2014, the USFDA reported that NNSs are safe for the general population under certain conditions of use.[64] This was supported by the American Cancer Society (ACS) more recently in 2020 when ACS stated that *"all NNSs appear to be safe when consumed in moderation."*[65] Table 6 summarizes the evidence to show the association between NNSs and risk of cancer development.

Effect of NNSs on Gut Microbiota

Evidence from animal models has demonstrated that NNSs alter the gut microbiota. A study conducted on mice proved that the exposure of saccharin and aspartame was associated with alterations in the gut microbiota and glucose intolerance.[5] However, a recent human study reported that daily consumption of pure sucralose or aspartame in doses reflective of typically high consumption has minimal effect on the composition of gut microbiota composition or production of short-chain fatty acids.[62] Furthermore, the panelists of the latest expert consensus on LCSs suggest that human studies are limited to providing adequate evidence that LCSs influence gut health at doses relevant to human use.[2] Table 7 summarizes the studies that appraised the effect of NNSs on human gut microbiota.

Table 7: Effect of NNSs on gut microbiota

Author (year)	*Study type*	*Study population*	*Study duration*	*LCS used*	*Conclusion*
Serrano et al. (2021)[74]	Randomized double-blind, placebo-controlled, parallel-arm study	46 healthy adults	10 weeks	Saccharin	No change in microbial diversity or composition at any taxonomic level in humans. Therefore, intake of saccharin for a short period at maximum acceptable levels does not induce glucose intolerance or alter gut microbiota in healthy individuals
Ahmad et al. (2020)[62]	Randomized double-blinded crossover clinical trial	17 healthy participants	12 weeks in a crossover design	Sucralose and aspartame	Daily repeated intake of pure aspartame or sucralose has minimal effect on the composition of gut microbiota or production of short-chain fatty acid

Association of NNSs with Renal Toxicity

The increasing rates of obesity and diabetes mellitus have contributed to the rise in the prevalence of chronic kidney diseases (CKDs) worldwide. Several studies have reported that sugar-sweetened beverages, as well as artificially sweetened beverages, are associated with CKDs. On the contrary, some other studies have shown no association between CKD with these beverages.[60] However, due to the benefits of artificial sweeteners, the National Kidney Foundation's guide, Planning for Emergencies, A Guide for People with Chronic Kidney Diseases recommends adding an artificial sweetener as a part of an emergency diet plan.[75]

Cheungpasitporn et al. conducted a meta-analysis of RCTs and observational studies to evaluate the association between sugar or artificially sweetened beverages with CKD. The results showed that sugar-sweetened beverages increased the risk of CKD by 1.58-fold. Though the study showed an association between the risk of CKD and the consumption of artificially sweetened beverages, this association was not statistically significant. The discrepancies in the result may be due to the following reasons:

- Misclassification of sugar-sweetened and artificially sweetened beverages in some questionnaire-based studies lacking a structured interview.
- Statistical heterogeneities in the study due to differences in methods of CKD diagnosis, type and amount of beverage consumed, and duration of follow-up.
- The observational studies in the analysis inherent the limitations of observational studies which can demonstrate an association, but not a causal relationship.[56]

Safety of NNSs in Special Population

The safety of NNSs in pregnancy and children has been evaluated and accepted in some countries, but its usage is not permitted in other countries. A full risk assessment report on aspartame published in 2013 by EFSA concluded that aspartame and its by-products are safe for the use in general population (including infants, children, and pregnant women).[76] Similarly, the Academy of Nutrition and Dietetics states that the consumption of NNSs is safe during pregnancy and childhood.[77] Health Canada had approved the use of stevia in the general population including pregnant women and children.[78] de Ruyter et al. evaluated the effects of a sugar-free, artificially sweetened beverage in normal-weight children from 4 to 11 years of age. He reported that the replacement of sugar-containing beverages with noncaloric beverages significantly reduced the occurrence of weight gain and fat accumulation in normal-weight children.[79] Clinical studies on the use of NNS in pregnancy and its effect on long-term outcomes in offspring are the need of the hour, however, its use should be clinically evaluated for the dietary management of gestational diabetes and reducing the sugar intake.[79]

Limitations

The present review might be limited due to the following factors. Some relevant studies might have been missed inadvertently despite the extensive literature search. Furthermore, the efficacy and safety of NNSs could not be evaluated from an Indian perspective due to the lack of sufficient Indian trials. However, the outcomes of various ongoing trials registered at Clinical Trials Registry–India (CTRI/2019/12/022470, CTRI/2021/04/032809, and CTRI/2021/04/032686) on the use of various NNSs as food additives are awaited.

Conclusion

Several regulatory bodies have deemed the safe use of NNSs in adults (including pregnancy) and children when consumed within the ADI. Mere replacement of sugars in daily beverages or as tabletop sweeteners hardly increases the chance to exceed the ADI. Systematic reviews and RCTs, along with interventional and observational trials, have demonstrated the efficacy and safety of various NNSs in human trials bursting the myths around them. These trials have testified that the replacement of sugars with NNSs is an effective strategy for weight loss and maintenance in obese adults. Clinicians and dietitians may explore the arena of replacing caloric sugars with NNSs in their patients due to their safety and efficacy in weight management and reducing postprandial blood sugar levels. The present review attempted to resolve the negative perception with the use of NNSs by evaluating the efficacy and safety profile of various NNSs.

Acknowledgments

We would like to thank Medicca Press Ltd. for providing editing assistance. Dr Mohan received funds from Zydus Cadila for research on artificial sweeteners.

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