RU Revista Uningá

Revista Uningá, v. 59, eUJ4280, 2022
doi.org/10.46311/2318-0579.59.eUJ4280

ISSN 2318-0579

Health Sciences and Biological I, II, III

Artificial sweeteners: regulation in Brazil, technological implications in food production and health

Edulcorantes artificiais: regulamentação no Brasil, implicações tecnológicas na produção de alimentos e na saúde

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ABSTRACT

Sweeteners provide a sweet taste to foods and are used to replace sucrose and reduce caloric value. Acesulfame potassium, aspartame, sodium cyclamate, saccharin, sucralose and neotame are the artificial sweeteners regulated in Brazil by the Brazilian Health Regulatory Agency (ANVISA). The consumption of these additives has become controversial due to recent scientific evidence questioning their safety and outcomes regarding weight loss, dysbiosis of the intestinal microbiota, insulin resistance, diabetes and cancer. Even today, little is known about the long-term consequences of their consumption. Therefore, this study aimed to carry out a review of artificial sweeteners regulated in Brazil, contextualizing their regulatory framework, the technological implications regarding their use and the effects on health. Considering the now controversial outcomes regarding the consumption of many artificial sweeteners, and the long period in which levels of acceptable daily intake have been in place, it is suggested their consumption should now not be encouraged, being restricted to population groups that have a risk-based physiological or metabolic need to replace sucrose. Also, for these cases, it would be important to differentiate between foods containing different sweeteners (or tabletop sweeteners), to alleviate possible chronic health effects. New studies with more robust and consistent methodologies are required to support the safety assessment reviews of each artificial sweetener.

Keywords: Aspartame. Artificial sweetener. Saccharin. Sugar substitutes.

RESUMO

Os edulcorantes fornecem sabor doce aos alimentos, sendo utilizados para substituir a sacarose e diminuir o valor calórico. O acessulfame de potássio, aspartame, ciclamato de sódio, sacarina, sucralose e neotame são os edulcorantes artificiais regulamentados no Brasil pela Agência Nacional de Vigilância Sanitária (ANVISA). O consumo destes aditivos tem se tornado controverso em função de recentes evidências científicas questionando sua segurança e os desfechos acerca da perda de peso, disbiose da microbiota intestinal, resistência à insulina, diabetes e câncer. Ainda hoje, pouco se sabe sobre as consequências do seu consumo a longo prazo. Portanto o presente estudo teve como objetivo realizar uma revisão sobre os edulcorantes artificiais regulamentados no Brasil, contextualizando seu marco regulamentar, as implicações tecnológicas referente à sua utilização e os efeitos à saúde. Considerando os desfechos controversos acerca do consumo de muitos edulcorantes artificiais e a longa data em que os respectivos níveis de ingestão diária aceitável foram publicados, o seu consumo não deveria ser incentivado, ficando restrito aos grupos populacionais que apresentem necessidade fisiológica ou metabólica para a substituição da sacarose. Ainda para estes casos, seria interessante a diversificação entre alimentos contendo os diferentes edulcorantes (ou de adoçantes de mesa), a fim de se amenizar possíveis efeitos crônicos à saúde. Novos estudos com metodologias mais robustas são necessários para embasar as revisões das avaliações de segurança de cada edulcorante artificial.

Palavras-chave: Aspartame. Adoçante artificial. Sacarina. Substitutos de açúcar.

Received: February, 23rd, 2022. Accepted: May, 17th, 2022.

INTRODUCTION

Obesity is a major and urgent public health challenge worldwide. The increase in its prevalence, as well as its comorbidities, resulted in reduced-calorie food products, mainly related to the reduction of sugars. The association of increased consumption of sugars with cardiovascular diseases, type 2 diabetes mellitus and obesity is already well established in the scientific literature (Sylvetsky & Rother, 2018; SBD, 2019; Brazil, 2020).

Diabetes *mellitus* is one of the main chronic diseases and can be defined as a set of metabolic alterations that lead to sustained high levels of blood glucose, due to a deficiency in the production or efficacy of insulin. The disease can lead to complications if not controlled, such as an increased risk for cardiovascular, renal and neurological diseases (Brazil, 2020).

Non-pharmacological therapy depends on dietary modulation to balance the supply of macronutrients for the adequate maintenance of metabolic control. Therefore, according to the Brazilian Society of Diabetes, the nutritional intervention for control and prevention of diabetes *mellitus* includes the adjustment of body weight for eutrophic classification, fasting and postprandial glycemic control, maintenance of blood pressure outside the risk range, and adequacy of the lipid profile (SBD, 2019). It is also recommended to reduce the consumption of simple sugars, foods rich in carbohydrates, such as refined cereals, prioritizing the consumption of whole foods, and sources of fiber, in addition to avoiding foods rich in saturated and *trans* fats (Brazil, 2020).

The World Health Organization (WHO) recommends sucrose consumption does not exceed 10% of total energy intake. From this, food industries have been making efforts to reformulate their products to reduce sucrose content and provide less calorific products. To this end, one of the strategies used is the replacement of sugars by artificial sweeteners (Sylvetsky & Rother, 2018).

The use of artificial sweeteners has been the subject of numerous debates, putting into question their role in human health (Sylvetsky et al., 2017). On the other hand, researchers suggest positive and discrete effects on weight loss and potential action on longevity (Toews et al., 2019; Nadolsky, 2021; Zhang et al., 2019), while others suggest increased risk of obesity, diabetes, metabolic syndrome, cardiovascular diseases, and dysbiosis of gut microbiota (Swithers, 2013; Pepino, 2015; Chi et al., 2018; Romo-Romo et al., 2018). However, little is known about the long-term consequences of using these substances, particularly for children, or their synergistic effects with other additives (Sylvetsky et al., 2017).

The number of consumers of diet and light foods is increasing, and the profile of consumers has been changing. The demand for these foods is increasingly frequent, not only by individuals diagnosed with high blood pressure, diabetes or obesity, but increasingly by young people. Young people are constantly surrounded by information by the media, where they end up believing in formulas with miraculous results in the search for the “perfect body”. The tireless quest for “the perfect body” has significantly helped to increase the demand and consumption of diet and light foods (Marins, Araújo & Jacob, 2011).

According to the economic bulletin of the Brazilian Association of the Food Industry for Special Purposes and Similar Purposes (ABIAD) published in 2020, imports of diet and low-calorie drinks, between January and September 2020, totaled US$ 60.4 million. In addition, according to the same document, data on the monthly consumption of diet and light foods and beverages were selected through the Family Budget Survey (POF), taking into account monthly income. Findings suggest that the classes with the highest purchasing power (A and B) are the ones that most consume food for special purposes (ABIAD, 2020).

This study aims to review the main artificial sweeteners whose use is regulated in Brazil, the technological implications of their use in food production and their health effects for consumers.

MATERIAL AND METHODS

This research is characterized as a narrative review of published scientific literature and the grey literature in the form of national and international reports, resolutions and guidelines. The descriptors: "artificial sweeteners/*edulcorantes artificiais*", "sweeteners/*edulcorantes*", "sugar substitutes/*substitutos de açúcares*", "technological properties/*propriedades tecnológicas*", "safety/*segurança*", "resolution/*resolução*" and their combinations were searched in different databases (SciElo, PubMed, Web of Science and Google Scholar). Publications found were read and analyzed, in order to enable the construction of a narrative review about the previously proposed objective. References cited in the identified publications were searched, aiming to expand the development and discussion of this narrative literature review.

RESULTS AND DISCUSSION

Regulation of sweeteners

In Brazil, until the mid-1980s, the establishments responsible for the sale of food for special purposes (dietetic) were not grocery stores and supermarkets, as they do today, but pharmacies. This is due to the regulations of the time, which considered them as drugs and not food. They were intended for people with a medical prescription, such as those diagnosed with diabetes mellitus, who needed to control the intake of sucrose and simple sugars. Only after 1988 were the use of products with sweeteners expanded to the general population and this only became possible with the change of its registrations. These products became the responsibility of the National Division of Sanitary Surveillance of Foods (in Portuguese, *Divisão Nacional de Vigilância Sanitária de Alimentos* - DINA), instead of the National Division of Sanitary Surveillance of Medicines (in Portuguese, *Divisão Nacional de Vigilância Sanitária de Medicamentos* - DIMED), fitting, then, into the class of dietetic foods (Ordinance n. 25, 1988; Toledo & Ioshi, 1994; Zanini, 2010).

In 1998, Ordinance Nº. 29, of January 13, was published, which approved the technical regulation of food for special purposes. This ordinance allowed the use of the term "diet" in foods for a diet with controlled intake of sugars, carbohydrates, in addition to those used for weight control. These foods are intended for individuals who have a specific condition of metabolic and/or physiological origin, where modified formulations that adapt to their dietary needs are necessary (Ordinance N.º 29, 1998). For this, the use of food additives is usually required (Nadolsky, 2021).

According to the Codex Alimentarius (1995), additives are defined as:

> any substance which, as such, is not normally consumed as food, nor is it used as a basic ingredient in food, whether or not it has nutritional value, and whose intentional addition to food for technological purposes (including organoleptic) in its manufacturing, processing, preparation, treatment, packaging, transport or storage, is or can reasonably be expected to result (directly or indirectly) by itself or its by-products, in a food component or element that affects its characteristics (Codex Alimentarius, 1995).

In Brazil, sweeteners comprise a category of additives and are defined as organic substances, different from sugars, that impart a sweet taste to foods (Ordinance N.º 29, 1998). These substances are classified as: (I) Intensive sweeteners (or non-nutritive) when they provide high sweetness compared to sugar, without performing any other technological function in the final product and; (II) Body sweeteners (or nutritious) when they provide energy and texture to foods, presenting calorific value and sweetening power "similar" to that of sugar, and therefore, they are used in greater amounts in foods, when compared to intensive sweeteners (II) Codex Alimentarius, 1995; EFSA, 2019).

Jain and Grover (2015) divide the category (I) intensive sweeteners into: (i) synthetic and (ii) natural. The category (II) nutritive sweeteners is subdivided by the authors into (i) carbohydrates,

such as fructose, glucose syrup, corn syrup, and dextrose; (ii) polyols such as sorbitol, maltitol, mannitol, xylitol, lactitol and erythritol. This classification of sweeteners, although didactic, is not officially considered by the Codex Alimentarius.

In Brazil, according to Resolution of the Collegiate Board of Directors (RDC) Nº 18, of March 24, 2008, the artificial sweeteners allowed in foods are: acesulfame potassium, aspartame, cyclamic acid and its salts of calcium, potassium and sodium, saccharin, sucralose and neotame, while the natural ones are steviol glycosides, thaumatin, sorbitol, sorbitol syrup, D-sorbite, mannitol, isomaltitol, maltitol, maltitol syrup, lactitol, xylitol and erythritol. The aforementioned RDC rectifies a portion of the acts in force at the time (Law N.º 6437, of August 20th, 1977 and RDC N.º 3, of January 2nd, 2001), with the following restrictions:

> 1. Sweeteners should only be used in foods in which partial or total replacement of sugar is necessary, in order to comply with the Technical Regulation that provides for the following categories of foods and beverages:- for weight control;- for diets with controlled intake of sugars;- for diets with restricted sugars;- with complementary nutritional information, referring to the attributes "does not contain sugars", "no added sugars", "low in sugars" or "reduced in sugars" or, also, referring to the attributes "low in energy value" or "reduced in energy value", when partial or total replacement of sugar is made.
>
> 2. In compliance with specific Technical Regulations: a) All foods and beverages containing polyols must comply with labeling requirements regarding laxative effects. b) All foods and beverages containing aspartame must comply with labeling requirements regarding the presence of the amino acid phenylalanine, as necessary information for the population group of phenylketonurics...
>
> 3. Steviol glycosides must meet the purity specifications established by the Joint FAO/WHO Expert Committee on Food Additives - JECFA (Resolution N.º 18, 2008, pp. 1-2).

Sweeteners, like any other food additives, must have limitations for use in foods, as well as understanding of the lowest level dose necessary to achieve the desired effect in the product. For this, overall levels of Acceptable Daily Intake (ADI) must be respected. In addition, it is mandatory that toxicological assessments are carried out to analyze long-term effects and interactions between sweeteners before approval (Ordinance N.º 540, 1997). According to the Food Additives Guide, from ANVISA, the ADI is defined as an approximate amount in milligrams per kilogram of body weight (mg/Kg b.w.), which can be consumed daily, throughout life, without harming health, based on the scientific knowledge available at the time (Brazil, 2015).

Based on the JECFA classification (Joint FAO/WHO Expert Committee on Food Additives), ANVISA stipulated the ADI values of artificial sweeteners authorized in Brazil, as shown in Table 1.

In 2011, RDC N.º 46 was published “on food additives and technology adjuvants for infant formulas intended for infants and young children” (Resolution N.º 46, 2011, p. 1). This RDC determined in its article 6 on the non-application of the specific technical regulation of sweeteners in foods, to infant formulas (Resolution N.º 46, 2011). RDC N.º 160, of July 6, 2017, provided for food additives and technology adjuvants authorized for use in formulas for enteral nutrition, revoking RDC N.º 18/2008 for this special category of products (Resolution N.º 160, 2017). With the update of the technical regulation of food supplements in Brazil, RDC N.º 239, of 2018, established the food additives and technology adjuvants authorized for use in food supplements, including sweeteners and their permitted limits (Resolution N.º 239, 2018).

Table 1
Acceptable daily intake (ADI) values in mg/kg of body weight, for artificial sweeteners allowed for consumption in Brazil.

Artificial Sweetener	ADI (mg/kg body weight)
Acesulfame potassium	15
Aspartame	40
Cyclamate	11
Saccharin	3.5
Sucralose	15
Neotame	2

Source: (RDC Nº 18, of March 24th, 2008).

Technological implications

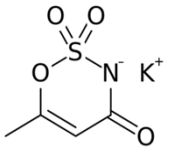
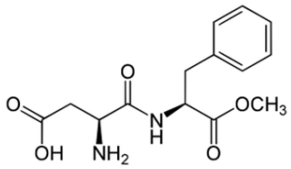
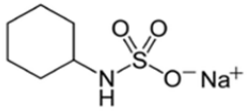
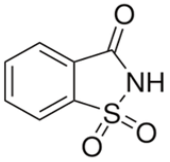
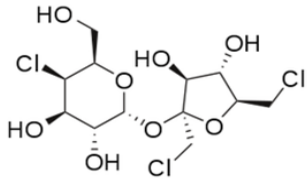
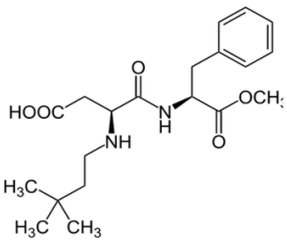
In general, sugars help in the physical, chemical and sensorial characteristics of food products from their ability to crystallize, and have properties which allow for hygroscopicity, and formation of gels and viscous solutions, because they are raw materials for the fermentation of microorganisms, for chemical reactions, non-enzymatic browning and have a sweet taste (Santos, 2009; Cordeiro, Chagas & Dala-Paula, 2021; Dala-Paula & Kringel, 2021).

The practice of selling sweetened product that contains two or more sweeteners is very common, being a strategy for manufacturers that aims to enhance their utility and minimize undesirable effects, especially aftertaste (Torloni et al., 2007). The saccharin/cyclamate association is quite effective in terms of sensory properties, but it is necessary to pay attention to its consumption by hypertensive patients, as they contain sodium in their composition (Andrade et al., 2017). Table 2 presents, in a summarized way, some characteristics of the artificial sweeteners allowed in foods by RDC Nº 18, of March 24th, 2008.

Due to its bitter aftertaste, acesulfame potassium is often paired with another sweetener such as sucralose and aspartame. It is not metabolized by the body and therefore does not provide calories (Chattopadhyay, Raychaudhuri & Chakraborty, 2011). Considering its physical-chemical stability, it is widely used in cooking and can be cooked. However, the ideal is to add it when the preparation is ready. Widely used in soft drinks, canned goods, table top sweeteners, breads, cakes, cookies, carbonated and alcoholic beverages due to its long shelf life (Ul-Ain et al., 2016).

Aspartame is low-calorie and widely used by the food industry (Chattopadhyay et al., 2011), it can withstand the thermal processing commonly used in dairy and juices, such as pasteurization and Ultra High Temperature (UHT). However, intense and sustained thermal processing can hydrolyze its molecule, forming the dipeptide aspartylphenylalanine and methanol, which can be hydrolyzed again into the amino acids aspartate and phenylalanine. Aspartame cyclization can also occur under conditions of extreme temperature elevation with the formation of diketopiperazine, limiting its application in dry products (Abegaz et al., 2012). Regarding its sensory characteristics, a study carried out by Rocha and Bolini (2015) analyzed aspects of various types of sweeteners added to passion fruit juice. Twelve trained tasters were selected, where it was observed that the samples containing aspartame and sucralose obtained the highest score in relation to flavor, general impression and texture. In addition, it was highlighted that these samples resemble sucrose in the sensory aspect.

Table 2
Sensory, chemical and physicochemical characteristics of artificial sweeteners allowed in foods sold in Brazil (2022).

Artificial sweetner (chemical structure)	**Sensory profile**	**Chemical and physicochemical characteristics**	**References**
Acesulfame potassium 	Sweetening potential 200 times higher than sucrose. It has residual bitterness and astringency.	Highly soluble in water and heat stable. Stable over wide pH and temperature range	Chattopadhyay, Raychaudhuri & Chakraborty, (2011)
Aspartame 	Mild sweet taste, 200 times higher than sucrose	Slightly soluble in water. Stable at temperatures below 100 °C and for a few seconds at 120-130 °C	Chattopadhyay et al. (2011); Abegaz et al. (2012)
Sodium cyclamate 	Sweetening potential 30-80 times greater than sucrose. Has residual bitterness	It has water solubility and is stable with respect to pH and temperature.	Chattopadhyay et al. (2011); Carocho, Morales & Ferreira (2017)
Saccharin 	Sweetening potential 300 times higher than sucrose. Residual bitterness when present in high levels	Moderately soluble in water. Stable at low pH and pasteurization, but inferior to aspartame stability	Carocho et al. (2017)
Sucralose 	Sweetening potential up to 650 times higher than sucrose. It has a pleasant taste, with low residual interference	Highly soluble in water, ethanol and methanol. Stable to mild heating (< 119°C), but unstable at higher temperatures	Chattopadhyay et al., 2011; Cadena et al. (2013); Dong et al. (2013)
Neotame 	Sweetening potential up to 13,000 times higher than sucrose	Slightly soluble in water and stable at high temperatures. Dry neotame is extremely stable	Chattopadhyay et al. (2011)

Source of chemical formulas: Wikipedia (2021).

Sodium cyclamate is an artificial sweetener that also provides no calories (Carocho et al, 2017). Considering its sensory profile, it is usually associated with saccharin to alleviate bitterness (Chattopadhyay et al., 2011). Cyclamate is used with other sweeteners to improve its technological aspects and is very common in light-type products and table top sweeteners (Sargaço, Serra, Vasco, 2017).

The use of saccharin in the form of calcium or sodium salt optimizes its solubility in water (Chattopadhyay et al., 2011). Its use is usually associated with aspartame and cyclamate, to optimize its sensory profile. It is present in foods such as beverages, sweets and cookies and has a low cost for the food industry (Neacșu & Madar, 2014). Regarding its sensory aspects, the positive association of saccharin with cyclamate stands out.

A survey gathered 150 untrained tasters to evaluate the sensory characteristics of different isolated and associated sweeteners in a coffee beverage. As a result, the saccharin and cyclamate junction most closely resembled the sucrose sample in terms of sweetness. Thus, the authors highlighted that this association is interesting, since saccharin has great potential for sweetness, but has a bitter/metallic aftertaste, and cyclamate, has less power to sweeten, but has a positive effect in masking the off-flavor of saccharin (Serbai et al., 2014).

Produced through sucrose by replacing the three hydroxyl groups with three chlorine molecules, sucralose is not metabolized by the body (does not provide calories), being eliminated through faeces and urine (Chattopadhyay et al., 2011). Due to its origin, it is one of the most popular artificial sweeteners. Due to its chemical structure, there are changes in sweetness and stability, but without sensory interference, where it is possible to maintain the sweet taste similar to that of sucrose. Widely used in foods, mainly in bakery products, sucralose can undergo thermal degradation (> 250 ºC), in addition to generating toxic components (chloropropanols, dibenzo-p-dioxins and dibenzofurans). Its thermal instability can harm the health of the individual, especially when using utensils made of stainless steel or those that contain levels of oxidation (Al_2O_3, Fe_2O_3 and CuO) when heating sucralose (Dong et al., 2013).

Neotame, in turn, is obtained by the alkylation of aspartame (Chattopadhyay et al., 2011). Its main degradation product (deesterified neotame) is formed at low levels by hydrolysis of the methyl ester group of neotame. Conditions involving higher temperature and humidity result in the formation of increased amounts of deesterified neotame without significant amounts of other degradation components. Therefore, neotame maintains a material balance even under adverse conditions. Products that contain dextrose, maltodextrin and neotame are stable when stored for long periods in storage conditions with controlled room temperature and humidity (Mayhew et al., 2012). One study looked at the stability of neotame and aspartame in pasteurized and sterilized milk. As a result, it was found that during pasteurization (90 °C for 20 min) there was a loss of 8% of neotame and 40% of aspartame. In the storage process, between 4 and 7 ºC, for seven days, neotame showed 4% loss and aspartame 15% in relation to the amount of sugars. Finally, in sterilization at 121°C for 15 minutes, neotame remained intact during the process, while aspartame was completely lost (Kumari et al., 2016).

Artificial sweeteners and health

Cases of chronic diseases such as diabetes, hypertension, heart disease and obesity have been growing exponentially in Brazil and worldwide (ABESO, 2016). The food industry, in turn, meets these challenges and changing demands through the development of food products for special purposes. However, it is necessary to pay attention to the effects on health and human longevity provided by sweeteners, commonly used in foods intended for weight loss or control/restriction of sugars (Sylvetsky et al., 2017).

Cohort studies correlate weight gain with the use of artificial sweeteners. Among them, a study carried out with 3,682 adults over 8 years showed that consumption of more than 21 servings of artificially sweetened beverages per week doubled the risk of obesity and overweight, showing a

positive dose-response relationship between weight gain. and long-term consumption of beverages with artificial sweeteners (Fowler et al., 2012).

Mooradian, Smith and Tokuda (2017) demonstrated in their review that artificial sweeteners can alter eating behavior as demand for food can increase. According to the authors, artificial sweeteners stimulate cravings for sweets and cause dependence on sugar in other foods. Sweeteners such as aspartame, acesulfame potassium and saccharin may be linked to increased motivation to eat (Anton et al., 2010). Saccharin supplementation in rats, for example, significantly increased weight gain and total energy consumption (Feijó et al., 2013).

Kim, Keogh and Clifton (2020) developed a clinical, crossover and randomized study with 39 male and female participants, aged between 18 and 75 years, without a diagnosis of type 2 diabetes, including individuals with adequate weight, overweight and obesity (BMI between 18-45 kg/m^2). Participants consumed 0.6 L/day of a beverage artificially sweetened with 211 mg/L acesulfame potassium and 144 mg/L aspartame (approximately 5-6% of the ADI of sweeteners) or mineral water for 2 weeks, with an interval 4 weeks between treatment changes to reverse possible changes in the intestinal microbiota. The authors did not find a significant difference in the serum levels of glucose, insulin and insulin sensitivity during the two weeks of the research, indicating likely safety of the consumption of sweeteners for a short period.

Bonnet et al. (2018) performed a randomized, double-blind, crossover clinical trial, in which they evaluated the effects of consumption of a carbonated beverage artificially sweetened with aspartame and acesulfame potassium, on insulin sensitivity and secretion and blood glucose in non-diabetic adults. 50 individuals participated in the research, 22 men and 28 women, with a mean age of 31.1 ± 10.3 years, mean BMI of 24.7 ± 3.2 kg/m^2, 28 of them classified as "not overweight" (BMI <25 kg/m^2) and 22 "overweight" (BMI >25 kg/m^2). None of them were in the habit of consuming high-intensity sweeteners. Participants were randomized 1:1 and underwent two treatments over 12 weeks, namely: (i) consumption of two servings (330 mL each) of a carbonated beverage containing 129 mg of aspartame and 13 mg of acesulfame potassium; (ii) consumption of two servings of a carbonated beverage with no calories and no added sugar or other sweeteners. After the end of the 12 weeks, an interval of 4 weeks was performed before the exchange of treatments. Participants showed no difference in body weight, eating habits and physical activity. Furthermore, there was no difference between insulin sensitivity and insulin secretion index between the two interventions. The authors concluded that daily consumption of 2 cans of an artificially sweetened beverage containing aspartame and acesulfame potassium for 12 weeks had no effect on the parameters evaluated in non-diabetic adults. This research, in turn, investigated a period longer than the intervention time studied by Kim, Keogh and Clifton (2020).

Aspartame, because it contains the amino acid phenylalanine in its composition, is contraindicated for patients with phenylketonuria, since it is a disease in which individuals do not convert phenylalanine into tyrosine. Phenylalanine, in turn, accumulates in the brain causing severe neurological symptoms. However, 74% of 206 participants in a survey of individuals diagnosed with phenylketonuria or their parents, responded that they had already consumed foods or drinks, mistakenly or accidentally, containing aspartame. The main justifications pointed out by the study included: (i) the change in the formulation of the products; (ii) the impossibility of checking the list of ingredients in drinks sold in restaurants or vending machines and; (iii) choosing the wrong products on the supermarket shelf. The authors highlight the difficulty of adhering to a diet for patients with phenylketonuria, when not all ingredients of a product are clearly stated on labels or at the point of purchase. In addition, they suggest that manufacturers consider using alternative sweeteners as an option for phenylketonuria patients (Newbould et al., 2021).

For years, the use of aspartame has been questioned, due to the likely carcinogenic potential because of the methanol present in its formulation (Chattopadhyay et al., 2011). In addition, there is evidence in the scientific literature of the potential impairment of the digestive system, through indirect inhibition of the intestinal alkaline phosphatase enzyme, through the by-products of phenylalanine, obtained by aspartame (Gul et al., 2017). A literature review reinforced that in the

long term or at high doses, aspartame can lead to adverse health effects, including kidney damage, especially in individuals who have diabetes mellitus, who practice intense exercise with high production of free radicals or who have advanced age (Ardalan et al., 2017).

An experimental study with Wistar rats, whose test group received 2 mL of aspartame per 100 g by orogastric route daily for 21 days, resulted in an increase in weight and caloric intake compared to the control group (which received water instead of aspartame). However, none of the two groups showed changes in blood glucose levels (Silva et al., 2016).

Recent evidence suggests that exposure to aspartame significantly increases the number of cancer stem cells in a pancreatic adenocarcinoma cell culture (PANC-1), while high glucose does not have this effect. Furthermore, exposure to aspartame was responsible for increased invasion and migration of cancer cells (Gezginci-Oktayoglu et al., 2021). The authors point out that aspartame did not present a tumorigenic effect in cell culture, but it can enhance the evolution of an existing tumor. It is important to consider that the mentioned research was developed with cell cultures, requiring further studies in an in vivo experimental model.

A study with osteoblast culture evaluated the exposure of cells to sodium cyclamate at concentrations of 0.02 μM, 0.04 μM, 0.06 μM, 0.08 μM and 0.10 μM. The study showed that from 0.06 μM of sodium cyclamate, a deleterious effect on bone tissue can already be observed. The authors concluded that the sweetener can affect the microfilament and microtubules of osteoblasts, in addition to decreasing their mineralization and calcium ion levels. This result suggests that sodium cyclamate may act by inhibiting osteoblast differentiation and proliferation in *in vitro* cell cultures. It is important to consider that the experiment was carried out with a cell culture, with the exposure of the sweetener being carried out directly on them. Despite these considerations, the research carried out may drive future studies with animal models for a better understanding of the outcomes found *in vitro* (Chen et al., 2019).

Zhang et al. (2019) evaluated the effects of saccharin, sodium cyclamate, and acesulfame potassium intake on aging-associated parameters such as intestinal lipofuscin deposition, lifespan, locomotion, food intake, and intestinal lipid deposition in an animal study model with *Caenorhabditis elegans*. The use of this nematode is considered an adequate model to evaluate the toxicity of exogenous chemicals, including the gerontogenic effects and the impact of food compounds on the metabolism of diseases. About 100 wild type L1 larvae were split and exposed throughout their life span to 0, 0.03, 0.1, 0.3, 1 and 10 mg/mL of one of the three sweeteners studied. *C. elegans* exposed to 10 mg/mL glucose from day one of adulthood was used as a positive control. Treatments with sodium cyclamate and acesulfame potassium at concentrations below the maximum limit allowed in China, the country in which the research was carried out (650 and 300 mg/kg in beverages and 8,000 and 4,000 mg/kg for food, respectively) did not present adverse effects in the parameters studied. Saccharin, in turn, demonstrated a potential gerontogenic effect, since it shortened the life span of the nematode. However, potassium cyclamate increased its longevity and acesulfame potassium decreased intestinal lipofuscin deposition, indicating potential anti-aging effects. Although the research was carried out with an animal model in nematodes, the results encourage the development of future investigations into the potential protective effect of sodium cyclamate and acesulfame potassium on longevity.

A translational study, involving a double-blind, placebo-controlled clinical trial and an experimental study in mice, aimed to investigate the effect of high-dose saccharin supplementation on gut microbiota and glucose intolerance. The clinical trial involved the participation of 50 volunteers who were randomized into four groups that received the following treatments: placebo, saccharin, lactisol and saccharin with lactisol. Doses were divided into capsules, administered twice daily to achieve the maximum ADI of each artificial sweetener, with 1000 mg/day of placebo, 400 mg/day of sodium saccharin, 670 mg/day of lactisol and 400 mg/day being administered. of sodium saccharin + 670 mg of lactisol for 2 weeks. The experimental research was carried out during 10 weeks, starting from the offer of (i) pure drinking water or (ii) high dose saccharin, equivalent to 4 times the ADI for humans, adjusted for the body surface area of the mouse. in drinking water. The

authors did not observe changes in blood glucose and insulin levels in either humans or mice in any of the tested interventions. Research has reinforced that short-term consumption of saccharin at maximum acceptable levels is not sufficient to alter the gut microbiota or induce glucose intolerance in healthy humans and mice (Serrano et al., 2021).

Leibowitz et al. (2018) also analyzed the relationship between saccharin and health. The authors compared the metabolic effects of saccharin versus fructose in male rats. Thirty rats were used, divided into 3 groups, as follows: (i) fed with regular chow (control group), (ii) regular chow with saccharin (0.1 mg/mL) placed in their drinking water or (iii) high fructose diet. The standard diet consisted of 44.2% carbohydrates, 18.6% protein, 6.2% fat, 18.2% fiber, 5.3% ash and a standard mix of vitamins and minerals. In contrast, the high-fructose diet consisted of 60% fructose, 21% protein, 5% fat, and a standard mix of vitamins and minerals. Regarding metabolic parameters, both groups gained body weight in the same proportion. However, the group of rats fed only with saccharin showed an increase in fasting blood glucose, but without any features of metabolic syndrome. The effects of saccharin on liver fat changes demonstrated that rats fed the high fructose diet exhibited heavier livers and steatosis compared to the other groups. Therefore, the authors concluded that saccharin consumption is safe, since there were no features of metabolic syndrome and liver changes.

Regarding blood glucose control, a randomized, placebo-controlled, paired clinical trial (48 volunteers divided into two groups) performed by Grotz et al. (2017) demonstrated evidence that sucralose may be a safe sweetener for human use, as it did not exert negative effects on glycemic control. In that study, the researchers performed comparative tests over 12 weeks between healthy subjects who consumed approximately 333.3 mg of encapsulated sucralose three times daily and the control group that received the placebo. As a result, no significant differences were observed in resting blood glucose and insulinemia levels, including HbA1c, fasting and postprandial glucose and C-peptide between the two groups.

However, there are controversial reports in the literature about the effects of sucralose. In a randomized, double-blind, placebo-controlled, crossover clinical trial, with 15 participants (11 women and 4 men, mean age 31.9 ± 10 years and mean BMI 23.1 ± 3 kg/m^2) that consumed daily one capsule containing 200 mg sucralose (approximately 19% of the ADI for a 70 kg individual). The authors found reduced insulin sensitivity and reduced acute insulin response, suggesting that this sweetener is not metabolically inactive as it affected insulin response (Lertrit et al., 2018). This research casts doubt on the indication of the safety of consuming sucralose-containing foods, even within the currently established ADI.

It is important to highlight that the research carried out by Grotz et al. (2017) involved a greater number of participants, but did not assess their dietary intake and did not adopt a crossover design, which would minimize possible differences between the two groups of participants. Despite the smaller sample size, Lertrit et al. (2018) monitored the nutritional intake of participants by applying a 24-h food recall and opted for a more robust methodological design, aiming to reduce biases that were not controlled by Grotz et al. (2017). Thus, it is still necessary to carry out research to evaluate the effect of prolonged consumption of sucralose on blood glucose, insulin sensitivity and acute insulin response.

Qian et al. (2020) investigated the role of sucralose in glucose tolerance and sweet-tasting receptor expression through an animal model with rats fed a lipid-rich diet. The authors found that supplementation over 4 weeks with sucralose reduced blood glucose in obese rats. In conclusion, the authors reinforced those different concentrations of sucralose may have different effects on glucose metabolism in rats. From this, they suggest the development of other studies, so that an optimal value of ADI is selected, in order to contribute to glucose metabolism in obese patients. Therefore, further studies are needed to establish an acceptable daily intake that is favorable for obese patients.

Ahmad, Friel, and Mackay (2020) also investigated the effects of sucralose on glucose levels, from a clinical trial. In this study, 17 healthy volunteers were followed for two periods of two weeks, with a washout period of 4 weeks. Participants were instructed to maintain their regular and habitual consumption of water and food. In addition, they were randomly assigned to study groups, where

treatments consisted of daily consumption of one of two drinks containing aspartame or sucralose at 14% and 20% of the ADI, respectively. The doses used in this study were similar to the amounts of aspartame or sucralose present in approximately 3 cans of diet soda (355 ml/can). As a result, the researchers demonstrated that consumption of sucralose or aspartame, with high daily intake doses, but resembling reality for 2 weeks, showed no adverse effects on insulin, glucose and leptin in study volunteers.

Chi et al. (2018) reported the effects of neotame on the intestinal microbiota of mice. The study was carried out with 10 animals that were randomly distributed between the control group and the neotame intervention. The control group received drinking water and the neotame-treated group received water containing neotame by gavage. The administered dose was 0.75 mg/kg body weight per day for 4 weeks. This dose is equivalent to 2.5 times the recommended daily intake for humans, which is 0.3 mg/kg body weight/day established by the FDA in the United States. The consumption of neotame decreased the population of Firmicutes, while increasing that of Bacteroidetes. There were also changes in the metabolic profiles, since fatty acids, lipids and cholesterol were found in higher levels in the faeces and malic acid and glyceric acid were significantly reduced when compared to the control group. Therefore, the authors highlighted that there were negative effects between neotame consumption and intestinal microbiota in mice, since it induced dysbiosis in the intestinal microbiota of this mammal.

Considering the advancement of scientific research, as well as the controversial evidence available in the scientific literature about the safety of sweeteners, it is urgent to carry out new assessments of their ADI. Even today, the WHO recommends the adoption of ADI values determined in 1990 for acesulfame potassium, 1982 for sodium cyclamate, 2006 for saccharin and 1990 for sucralose. Only aspartame had a revision more recently, in 2016, where its ADI defined in 1981 was maintained (40 mg/kg of body weight) (FAO/WHO, 2022).

CONCLUSION

In order to reduce sucrose consumption and promote weight loss, due to the increase in diabetes and obesity, the demand for products with sucrose substitutes has increased. Although artificial sweeteners are a tool for replacing sucrose, their consumption is controversial because of research available in the scientific literature over the last few years. In addition, there is still a lack of information on the long-term effect of artificial sweeteners intake on human health, such as outcomes: intestinal microbiota dysbiosis, weight gain, hypertension, insulin resistance, diabetes and cancer.

This suggests consumption of foods containing artificial sweeteners should not be generally encouraged, being restricted to population groups that have physiological or metabolic risk-based need for sucrose replacement. In addition, there is a need to carry out new studies with more robust and sophisticated methodologies to support the reviews of the safety assessments of each sweetener. Mobilization of the scientific community and health professionals may be necessary in order to coherently argue that inconsistencies suggest competent authorities review the utility and boundaries to the safe use of artificial sweeteners.

ACKNOWLEDGEMENT

To the Dean of Research and Graduate Studies at the Federal University of Alfenas (UNIFAL-MG), the Research Support Foundation of the State of Minas Gerais (FAPEMIG).

The translation of the original article was undertaken by Dr. Susan R. Moore, an independent scholar in the UK, who worked with the Brazilian authors on another project.

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