

Characteristics of sweeteners used in foods and their effects on human health*

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ABSTRACT

Foodstuffs containing large amounts of sucrose, which is rapidly absorbed by the human body, cause a marked increase in blood glucose levels; for some people, especially those with diabetes, this is undesirable. Therefore, efforts were undertaken to produce food with a reduced calorie content, but maintaining a sweet taste. Additionally, food producers were interested in cutting costs by replacing sugar with a cheaper alternative. Saccharin, one of the first synthetic sweeteners, was discovered in the USA in the 2nd half of the 19th century. Subsequently, other sugar substitutes were developed: synthetic (e.g. aspartame or acesulfame K), semi-synthetic (xylitol, mannitol), or polyols.

The latter were used during the First and Second World War to increase the calorific content of the available food. Nowadays, the advancing obesity epidemic has resulted in the increasing popularity of synthetic and semi-synthetic sweeteners. However, from the beginning of their existence there have been controversies regarding their safety and impact on health. There have been many studies on individual sweeteners, specifying any adverse or side effects. Therefore, the aim of this paper is to summarize the characteristics of the most popular sweeteners and their effects on human health.

Keywords: sweeteners; classification; properties; health.

INTRODUCTION

Sugar plays an important role in the modern human diet. However, sucrose is highly metabolically active and can result in weight gain, type 2 diabetes and promote tooth decay. For this reason, sweeteners have become increasingly popular. Companies have launched a variety of synthetic sweetening agents with very few calories, which are much more sweeter than normal sugar, such as alternative sweeteners, artificial sweeteners, and non-caloric sugars. These low nutrition synthetic compounds can be found in drinks, chocolates, cakes and other baking products. Acesulfame-K, aspartame, saccharin, stevia and sucralose have been approved by the Food and Drug Administration (FDA) for use in foods and/or drinks. People are moving toward artificial sweeteners, even though frequent consumption of sweeteners may dampen their physiological responses and affect metabolism. Therefore, the aim of this work is to summarize the most popular sweeteners and their impact on health.

CLASSIFICATION OF SWEETENING AGENTS

The food industry uses many sweetening agents as sugar substitutes. Their classification is based on physical and chemical properties, as well as their origin. Sweeteners may also be divided into those with a strict limit – with a fixed acceptable

daily intake (ADI) – or a quantum satis principle (without a fixed ADI). In Poland, the status of various sweeteners is regulated by the Ministry of Health. Sweetening agents include classic sugars (sweet carbohydrates, caloric sweeteners), e.g. mono- and disaccharides, semi-synthetic fillers classified as polyols, such as sorbitol, maltitol, and high intensity sweeteners. The latter group can be additionally subdivided according to the origin, into natural sweeteners, e.g. stevia, and synthetic sweeteners, such as the popular aspartame or saccharin. Figure 1 presents a detailed classification of sweetening agents [1].

Aspartame (Aspartyl-phenylalanine methyl ester)

Aspartame was approved by the US FDA for use in dry food products in the early 1980s, and for use in carbonated beverages in 1983. It is an N-(L- α -Aspartyl)-L-phenylalanine,1-methyl ester with the chemical formula $C_{14}H_{18}N_2O_5$ and a molecular mass of 294.31 g/mol. Aspartame is poorly soluble in water or ethanol, and is stable in acidic conditions (pH 3.5–5.0). This snow-white odourless powder is 180–200 times sweeter than saccharose [2, 3, 4].

The chemical structure of aspartame consists of 2 amino acids: L-phenylalanine and L-aspartic acid esterified with methyl alcohol [4]. Phenylalanine is an amino acid that must be supplied with food. It has a side chain that contains alkaline groups. During oxidation it converts into tyrosine; this conversion depends on phenylalanine hydroxylase produced in the liver. The hydroxylation of phenylalanine, tyrosine and

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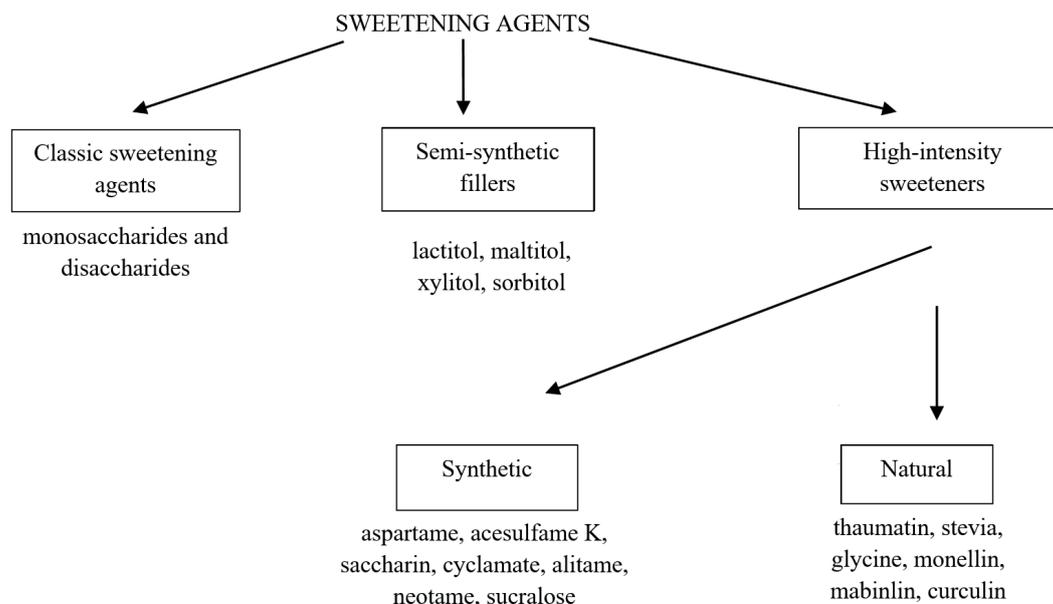


FIGURE 1. Classification of sweetening agents [1]

tryptophan is inhibited in phenylketonuria, i.e. a condition in which this enzyme is low or is not produced. This may result in deficiencies in DOPA neurotransmitters produced from tyrosine and serotonin, a derivative of 5-hydroxytryptophan [5, 6]. Aspartic acid is an endogenous (nonessential) amino acid that has a side chain with sulphur atoms. It strengthens the immune system and eliminates ammonia from the body [5].

Aspartame is hydrolysed in the intestine to methanol, the simplest aliphatic alcohol, which is colourless and highly poisonous. In the human body, methanol is converted in various processes into toxic formaldehyde and formic acid [6, 7]. Aspartame is widely used in the EU and many other countries, e.g. Canada and Japan. Since it is a sweet substance with very low caloric content (4 kcal/g), it is recommended for overweight and obese people, diabetics, and those who want to keep a healthy body weight. Although it is not easy to determine the consumption levels of individual sweeteners, according to data provided by some manufacturers, approx. 10,000–12,000 tonnes of aspartame are consumed every year [8, 9]. The ADI of aspartame was determined at 0–40 mg/kg of body weight a day. According to the Polish Association for the Study of Obesity, the average consumption of aspartame in EU countries is 4 mg/kg of body weight a day, which is 10 times less than the max. ADI.

In the food industry, aspartame is most often added to (usually carbonated) soft drinks, due to the fact that CO₂ reduces the pH, thus ensuring its stability. For diet cola type beverages, pH is close to the value at which aspartame is stable. Its half-life in this type of beverage may be up to 300 days. It is also added to chewing gums, yoghurts, ice cream, various desserts, jams, table-top sweeteners and toothpastes [3, 9, 10, 11]. When storing food rich in aspartame, attention should be paid to appropriate conditions, i.e. max. temperature of 40°C and min. water content of 5%. Failure to comply with these requirements results in the breakdown of aspartame, resulting in the production of

diketopiperazine (DKP) and aspartyl phenylalanine. Diketopiperazine is not sweet, which leads to a loss of sweetness in aspartame, and is estimated to be up to 5 times more toxic than aspartame. The max. acceptable doses in particular foodstuffs are available in the Regulation of the Minister of Health of 22 November 2010 on acceptable food additives – aspartame [12].

Acesulfame K (Acesulfame potassium, potassium salt)

Acesulfame potassium (6-methyl-1,2,3-oxathiazine-4(3H)-one 2,2-dioxide – C₄H₄KNO₄S, molecular mass of 201.24 g/mol), is a potassium salt invented in 1967 but it has been used in foodstuffs only since the 1990s. It is easily soluble in water and only sparingly soluble in ethanol, as well as heat-stable up to 200°C. Its thermal decomposition occurs only at 225°C, so it has found applications in the confectionery industry (due to its stability during cooking, baking and freezing). Acesulfame K is a white odourless crystalline powder that is between 130–200 times sweeter than saccharose. In larger amounts it can have a slightly bitter and metallic aftertaste, so it is combined with other sweetening agents. It is stable in a wide pH range – from 2.0 up to slightly alkaline conditions. Even after storage at temperatures of 30–40°C for several months, its sweetness level does not change [13, 14, 15]. It is used in 50 countries around the world, e.g. Canada, Switzerland, Norway, Japan, the USA and Australia, as well as in some EU countries. Manufacturers of this compound estimate that its consumption at close to 3,000 tonnes per year [16, 17]. The ADI determined by the Scientific Committee for Food (SCF) is 0–15 mg/kg body weight, but some sources give 9 mg/kg body weight. Its applications include non-alcoholic beverages, desserts, dairy products, bakery and confectionery products, snacks, chewing gums, mouthwashes and some medicines, jellies, jams and other fruit and vegetable preserves, as well as diet products and dietary supplements [13, 15]. The max. acceptable doses

in particular foodstuffs are available in the Regulation of the Minister of Health of 22 November 2010 on acceptable food additives – acesulfame K [12].

Saccharin

Saccharin (3-Oxo-2,3-dihydrobenzo(d)isothiazol-1,1-dioxide – $C_7H_5NO_3S$, molecular mass of 183.18 g/mol) is the oldest sweetening agent, developed in the USA in 1879 [18, 19]. Occurring in the form of odourless white crystals or powder, it is 300–500 times sweeter than saccharose and dissolves poorly in aqueous solutions. Saccharin is used as a sodium salt in combination with other sweeteners (most often aspartame and saccharose), which strengthen its activity, as on its own it has an unpleasant, metallic and bitter aftertaste. It is resistant to temperature, and therefore suitable for cooking, baking and freezing. The ADI is 5 mg/kg body weight. It is approved for use in food in 90 countries, e.g. as a table sweetener, in non-alcoholic beverages, fruit and milk drinks, jams, confectionery, ice cream, desserts, etc. While aspartame would be expected to be used most frequently for food production, it is actually saccharin that is produced and used in the largest quantities (20,000–25,000 tonnes per year). It is also used to eliminate unpleasant flavours in foodstuffs and medicines, without increasing their calorific value [1, 16, 17, 19]. The max. acceptable doses in particular foodstuffs are available in the Regulation of the Minister of Health of 22 November 2010 on acceptable food additives – saccharin [12].

Xylitol

Xylitol (D-erythro-pentitol – $C_5H_{12}O_5$, molecular mass 152.15 g/mol) is nowadays the best known and most frequently used polyol in the world. It was developed in 1891, but had not been recognised until Second World War, when Finland suffered a sugar deficit and used xylitol as a substitute. Still, it was only introduced into widespread consumption in the 1960s. Commonly referred to as birch sugar, because of its original source – the birch tree. Its chemical formula is $C_5H_{12}O_5$. It is a white crystalline and odourless hygroscopic powder. There is no need to combine it with other sweeteners. Its sweetness level is comparable to saccharose, but its calorific value is lower (only 2.4 kcal/g), which means it supplies up to 40% less calories. It dissolves well in water and poorly in ethanol. Moreover, it demonstrates stability in high temperatures, i.e. it does not caramelize during heating [7, 20, 21, 22, 23]. Xylitol has been approved for use in the production of food in 35 countries. It is mainly used in chewing gums, pharmaceutical products, chocolate products, but it is also a natural ingredient of some fruit and vegetables, e.g. plums (935 mg/100 g dry mass – DM), strawberries (362 mg/100 g DM), and cauliflower (300 mg/100 g DM), and is also found in the human body. Xylitol is mainly intended for overweight or obese people and diabetics due to its sweet taste and low glycemic index (only 13). In addition, it has been proven to reduce dental caries and bring down blood insulin levels [6, 7, 18, 23]. There are no FDI World Dental Federation recommendations for the consumption of xylitol, but an ADI is 100

g. Xylitol is one of the sweetening agents that is metabolized and absorbed very slowly in the human body, thus stabilizing glycemia and lowering insulin levels. In addition, it is low in calories, releases energy slowly, helps control carbohydrate cravings and reduces appetite [7, 20].

Sorbitol

Sorbitol ((2*S*,3*R*,4*R*,5*R*)-Hexane-1,2,3,4,5,6-hexol – $C_6H_{14}O_6$, molecular mass of 182.17 g/mol) was developed in 1988 during an outbreak of hemolytic uremic syndrome (HUS) in Bavaria. Also known as d-sorbitol, it occurs as a white hygroscopic crystalline powder, flakes or granule, and is not much sweeter than saccharose (0.5–0.6 times), but it is significantly less calorific (only 2.6 kcal/g). It dissolves well in water and poorly in ethanol [24, 25]. Isolated cases of sorbitol overdose (20–30 g/day) have been reported, which manifested as moderate abdominal pain and diarrhea in healthy people. Only these 2 symptoms are known as side effects of an excessive consumption of sorbitol. The FDA approved the use of sorbitol in foodstuffs at no more than 50 g/day, providing that the label includes the warning: “Excess consumption may have a laxative effect”. The World Health Organization has not established a safe daily intake of sorbitol, but taking into account the information above, exceeding 50 g/day is not recommended. It is used in the production of jams, candies, biscuits, ice cream, coloured carbonated drinks, chewing gums for diabetics and toothpastes.

Mannitol

Mannitol (d-mannitol – $C_6H_{16}O_6$, molecular mass of 182.2 g/mol) was invented in the 1940s, but it was not used in food production until 1986. Occurring as a white odourless powder, it is not much sweeter than saccharose (0.5–0.6 times), with a calorific value of 1.6 kcal/g. It dissolves well in water and sparingly in ethanol and is completely insoluble in ethers. Its melting point ranges between 164–169°C. It is produced by crystalline hydrogenolysis of glucose or fructose mixtures, and can also be derived from the discontinuous fermentation of *Zygosaccharomyces rouxii* in aerobic conditions [26, 27, 28, 29]. Mannitol can be found in marine algae, fresh fungi and tree resin. Mannitol is not absorbed by the body, but only works actively in renal tubules and, therefore, a diuretic action is one of its most important clinical properties. For this reason, it is used where appropriate in combination with appropriate chemical compounds, as a diuretic. Mannitol is often used by people who should abstain from consuming too many sweet products (most commonly, type 2 diabetics). The substance is used in the production of “light” food products and chewing gums. The safe daily intake has not been determined. The amount administered in the course of the treatment depends on the nature and intensity of the patient’s symptoms [29, 30]. However, overconsumption of mannitol may produce flatulence, diarrhoea and bloating, and so a daily intake of 20 g should not be exceeded [28]. The max. acceptable doses in particular foodstuffs are provided for in the Regulation of the Minister of Health of 22 November 2010 on acceptable food additives – polyols [12].

Stevia (steviol glycosides)

Stevia is derived from the plant *Stevia rebaudiana* Bertoni (family *Asteraceae*), native to Brazil and Paraguay. The substance is a white crystalline powder derived from stevia leaves. It is estimated that a 1-hectare plantation can yield 1000–1200 kg of dried leaves, which corresponds to approx. 60–70 kg of steviol glycosides, steviol linked by glucosidic bonds with glucose, xylose and rhamnose [31, 32, 33, 34, 35]. Steviol glycosides include stevioside (65%), rebaudioside A (about 25%) and other rebaudiosides (B, C, D, E, F), dulcoside A and C, as well as steviolbioside [28, 35]. Stevia is also rich in B vitamins and minerals (Mg, Cr, Zn, Fe, Se). Dry leaves have a close to 4% fat content (including palmitic and linolenic acid) as well as being a source of proteins, carbohydrates, dietary fibre and antioxidants (phenolic acid, flavonols, flavones). In addition, stevia leaves contain small amounts of anti-nutrients (oxalic acid, tannins) that can reduce the absorption of certain nutrients, e.g. calcium [32, 36].

The steviol glycoside which is the predominant ingredient (5–10%) is between 250–300 times sweeter than saccharose. Rebaudiosides are characterized by a greater variation in the intensity of sweetness compared to saccharose, e.g. rebaudioside A is 350–450 times sweeter, while rebaudioside C is 50–120 times sweeter [32]. The calorific value of dried stevia leaves is 2.7 kcal/g. Apart from different levels of sweetness, steviol glycosides also have different sensory properties. Stevioside is characterized by a slightly bitter and liquorice-like flavour, which is not as pronounced in rebaudioside A. The greater the purity of stevioside or rebaudioside A, the lower the sensation of the bitter taste, which is why it is less perceptible with the combination of these 2 compounds. Rebaudioside A is superior in terms of thermal stability and water solubility compared to glycoside, and is therefore used more frequently [34]. Stevia, due to its low calorie content and sweet taste, is an excellent sugar substitute and is often consumed by overweight and obese people. In addition to the low calorie content, it also has health-promoting properties, including lowering blood pressure and reducing blood glucose. For these 2 reasons, the recommended daily intake is no more than 1000 mg of steviol glycosides [34, 35].

Stevioside was investigated as a sweetener by the SCF in 1984, 1988, 1999. The results pointed to the genotoxicity of steviol and its use in food was prohibited. Subsequently, however, Joint FAO/WHO Expert Committee on Food Additives (JECFA), based on *in vivo* and *in vitro* studies, proved that stevioside and rebaudioside did not demonstrate any genotoxic or carcinogenic effects. The safety of stevia was confirmed in long-term studies carried out in Paraguay (for over 50 years), Japan (for over 25 years), USA (18 years), South Korea (15 years), and Brazil (12 years). In 2008, JECFA determined an ADI for steviol glycosides at 0–4 mg/kg body weight. In the same year it was approved for use in the USA. Two years later, European Food Safety Authority (EFSA) and Australian New Zealand Food Safety Authority (ANZFS) demonstrated the safety of steviol glycosides. In November 2011, stevia was granted authorisation for use in the food industry in the EU [34, 35]. Stevia is used in the production of cookies, jams, chocolates, ice cream, sweets, non-alcoholic beverages, sauces, dairy products, coffee, herbal teas and concentrates. Currently it is cultivated in South Korea, the USA, Paraguay, Brazil, Indonesia, Canada, India, Australia and New Zealand, Israel, Russia, Argentina, Chile, Malaysia, the Philippines, Turkey and Colombia [31, 36].

Table 1 summarises the most important information on the sweetening agents described above [7].

HEALTH EFFECT OF SWEETENING AGENTS

Health effects of aspartame

Despite its common use in the food industry, aspartame has had many enemies since its inception. Just 1 year after it was approved for use in foodstuffs, the FDA became concerned and ordered more stringent tests. It was decided that aspartame will be authorised, on condition that a warning is affixed to the packaging with the information that the product contains sources of phenylalanine, an exogenous amino acid, which some people cannot metabolise due to a deficiency of the enzyme used to metabolise it. Despite the extra precaution, hostility towards aspartame did not decrease. The reason for the opposition is the fact that aspartame is hydrolysed in the intestine

TABLE 1. Information concerning the sweetening agents [7]

Name	E number	Sweetness	Acceptable intake	Molar mass	Classification
Aspartame	951	180–200	40 g/day	294.31 g/mol	high-intensity sweetener, synthetic
Acesulfame K	950	130–200	15 g/day	201.24 g/mol	high-intensity sweetener, synthetic
Saccharine	954	300–500	5 g/day	183.18 g/mol	high-intensity sweetener, synthetic
Xylitol	420	1.0	100 g	152.15 g/mol	semi-synthetic fillers – polyols
Sorbitol	421	0.5–0.6	up to 50 g	182.17 g/mol	semi-synthetic fillers – polyols
Mannitol	967	0.5–0.6	up to 20 g	182.2 g/mol	semi-synthetic fillers – polyols
Stevia	960	250–300	none	–	high-intensity sweetener, natural

to methanol, which is a toxic compound. Aspartame dissolves very well in water, so it is absorbed instantly by the skin and the respiratory tract and from the gastrointestinal tract. The highest serum concentrations are observed approx. 30–60 min after consumption. It does not bind to plasma proteins. In the liver with alcohol dehydrogenase, it is slowly metabolised to formaldehyde and then immediately to formic acid [15, 37, 38]. Formaldehyde is regarded as a neurotoxic substance.

In the Regulation of the Minister of Health and Social Welfare of 1996 on carcinogens in the work environment and monitoring the health condition of workers with occupational exposure to these factors, aspartame was classified in group 3, i.e. as an agent potentially carcinogenic to humans. There are no sufficient analyses or reasons to classify formaldehyde as a substance regarded as carcinogenic to humans. Nevertheless, the above regulation was applicable up to Poland's accession to the EU, i.e. 1 May 2004.

Formic acid inhibits cytochrome oxidase, which in turn upregulates anaerobic metabolism and increases the production of lactates [39, 40, 41, 42]. The toxicity of methanol depends on whether it is consumed on its own or combined with ethanol, which inhibits its metabolism. It is estimated that a dose of 30–150 mL is fatal. Symptoms of methanol poisoning include headache and dizziness, tinnitus, gastrointestinal disorders, numbness, memory loss, chills, behavioural disorders and neuritis. However, methanol intoxication is most commonly associated with visual dysfunction, manifested by blurring, retinal failure and consequent blindness. It is also been implicated in fetal defects and inhibiting DNA replication.

In 2005, the Cancer Research Center in Bologna carried out a study on a group of rats that were given aspartame in amounts safe for humans. It was demonstrated that such a dose increased the incidence of leukaemia and lymphoma [43, 44]. There have also been studies investigating whether aspartame can cause congenital defects. In the early 1980s, a two-year study was conducted to see whether aspartame could cause brain cancer. It was shown to increase the incidence of brain tumors, as they were diagnosed in 12 out of 320 rats receiving meals with aspartame, and there was not a single case of a brain tumour in the control group. This confirmed that approving aspartame for everyday use may increase cancer incidence. The FDA substantiated this information with data on the increase in the number of brain tumours in patients over 65 years of age in the US by as much as 67% in the period between 1973–1990. The most pronounced spike in the number of patients with this type of cancer was noted between 1985–1987 [39, 43, 44].

In 2005, researchers presented the findings from an experiment on rats given 4 mg of aspartame per 100 mg of body weight over 60 days (with the control group receiving no aspartame). The results proved that aspartame increases the accumulation of calcium in the brain, heart, lungs, spleen, adrenal glands and blood, while reducing the levels of this element in the kidneys, stomach and testicles [42]. In another study, mice were given subcutaneous aspartame and were placed in a circular water maze with a platform located in a known

place. The mice swam vigorously, and when they encountered the platform, they climbed on it. With repeated trials, the animals learned the location of the object. Regular administration of aspartame suppressed their memory function and extended the time necessary to locate the platform. In addition, autopsy of post-mortem brain tissue revealed elevated levels of oxidative stress-related enzymes and nitric oxide in brain neurons as well as reduced levels of glutathione and glucose [7]. It was also demonstrated that aspartame exacerbates the clinical symptoms of diabetes, interferes with the control of symptoms in patients on insulin and oral medication, and increases diabetes comorbidities, such as cataracts, neuropathy and retinopathy [39]. Patients suffering from hypoglycemia or diabetes were observed with significant metabolic and neurological complications, and sometimes even developed convulsions. These symptoms subsided abruptly after the administration of aspartame was discontinued, and returned as soon as the substance was ingested again [39]. The FDA also reported that increased levels of phenylalanine in the brain of patients with phenylketonuria were associated with depressed serotonin levels, which could lead to affective disorders. It was observed that daily consumption of 4 half-litre bottles of low-calorie carbonated drinks by children enhances phenylalanine levels in the body. It is also believed that people prone to mood changes are very sensitive to this artificial sweetener and should be advised not to use it in any form [39]. It is also worth mentioning that some works negate the adverse effects of aspartame on human health, for example finding no correlation between the consumption of sweeteners and cancer [40, 41].

Health effects of acesulfame K

Acesulfame K is a synthetic substance that is often mixed with aspartame, although researchers consider it to be less dangerous than aspartame itself. Even though it is a sweetening agent, it leaves a bitter metallic aftertaste, hence the need to mix it with aspartame. The combination of these 2 substances results in a sweetness level up to 300 times higher than that of saccharose (which is why it ranks 2nd among sweeteners) [1, 2, 45]. Acesulfame K does not accumulate in organs nor is it metabolized (in 99%); it is eliminated in an unchanged form from the human body together with urine. However, research has shown that acesulfame K may destroy chromosomes and thereby modify genes. In a study on mice, it was concluded that the genotoxic action of acesulfame is based on its interaction with DNA and the consequent cell damage [42]. Malczyk et al. conducted a study on the consumption of high-intensity sweeteners in selected beverages by children aged 10–12. They found that the max. daily intake of artificial sweeteners per kg of body weight was exceeded only in the case of acesulfame K. Out of 110 examined children, 16% exceeded the daily exposure limit of this substance by drinking beverages. Interestingly, it was discovered that those who exceeded a given dose were underweight [45]. In 1994–1995 an analysis was carried out in Poland regarding the consumption of artificial sweeteners in healthy adults and diabetic patients. Findings showed

a relatively low level of acesulfame consumption that did not exceed the ADI. However, the largest amounts were consumed by people with excess body weight who wanted to reduce the calorie content of their diet [46].

Health effects of saccharin

Saccharin is the best studied and the longest used sweetener in the world. In the early 1880s, shortly after it had been discovered, people started to think it was toxic. Studies were carried out in which participants declared that they would take 5 g of saccharin daily for 6 months. No adverse reactions were reported after that period and so it was then decided in the USA that the consumption of saccharin up to 0.3 g/day is non-toxic. During First and Second World War, when sugar was rationed, millions of people consumed saccharine [16]. Studies carried out in 2010 showed that in certain species of experimental animals, massive doses of saccharin may contribute to the development of bladder, uterine or ovarian cancer. Other epidemiological studies did not confirm an increased risk of cancer in people who did not exceed the ADI of saccharin. It has also been proven that in diabetic patients, saccharin does not lead to significant fluctuations in glucose or insulin levels [44]. In line with US guidelines, this substance is approved for use as a sugar substitute, especially by people who want to limit the calorific value of their diet [10, 44]. There have also been studies on increasing body weight by consuming sweeteners contained in beverages [44].

In the 1970s a positive correlation was demonstrated between saccharin consumption and weight gain. Weight gain as a result of regular consumption of products containing saccharin was related to the amount of drinks containing sweeteners. This may be a consequence of stimulating the appetite centre of the brain. Findings from some studies show that saccharin-sweetened water may increase the sensation of hunger in adults with appropriate body weight, compared to water sweetened with glucose [44]. Studies on rats showed that when taking saccharin, animals consumed increased amounts of calories, which resulted in weight gain, including fat mass, compared to a diet with glucose. Products containing artificial sweeteners may also cause an increased consumption of favourite products or meals, and consequently increase the calorie intake [10, 44]. In the 1960s, the discovery of a new sweetener, i.e. cyclamate, caused another wave of criticism regarding saccharin. Tests were carried out in which rats were fed saccharin throughout their lifespan, in very large quantities (up to 3% of their diet). Some rats were found to develop bladder cancer. However, in order to receive an equivalent dose as that consumed by the rats, one would have to drink 800 cans of beverages sweetened with saccharin. Since then, many studies have been carried out to evaluate the effects of saccharin on the formation of cancer cells, and no such correlation has been observed because saccharin is excreted from the human body unchanged and it does not bind to DNA. It is also believed to be helpful in combating caries as it inhibits the formation of plaque bacteria [16].

Health effects of xylitol

Xylitol is a low calorie substance, which is ideal for people on a diet and diabetics, because it is metabolized without insulin. It contains 75% less carbohydrates compared to saccharose and is absorbed more slowly. One-third of xylitol is absorbed in the liver and the rest passes into the digestive tract, where it is metabolised by stomach bacteria. In addition, it is an excellent probiotic that promotes the growth of beneficial gut flora [23, 47]. Xylitol is an ideal solution for people struggling with dental problems. It has been speculated that the use of xylitol 3–5 times a day between meals, i.e. approx. 15 g/day, contributes to the reduction of caries and prevents bad breath [20, 22]. Xylitol restores the acid/base balance in the oral cavity by not interacting with bacteria inhabiting the mouth. Due to the fact that xylitol is not metabolized in the oral cavity, it cannot be converted into acids by bacteria, whereas an alkaline environment is not suitable for microorganisms, particularly *Streptococcus mutans*. It also inhibits the progression of various conditions. Prolonged and regular use of xylitol was proven to weaken harmful strains of microorganisms living in the oral cavity, even for a long time. Leaving xylitol on the teeth overnight, after brushing and flossing, has a positive effect on gum regeneration and protection. In addition, it promotes enamel mineralization and repairs minor lesions caused by caries. Chewing gum containing xylitol was found to reduce the incidence of dental problems in Finnish children, which was confirmed by studies carried out in Canada, Thailand and Polynesia [47]. In Finland, research was conducted on the colonization of teeth by *Streptococcus mutans* in children at 19–31 months. It showed that these microorganisms get into the child's mouth via the mother as a result of serving meals and using dishes. Mothers chewing gum with xylitol noticed a significant improvement in their dental status and caries reduction up to 70%. Moreover, it was observed that the addition of xylitol in nasal drops prevents the development of *Haemophilus influenzae* and reduces the occurrence of otitis media by about 25–40% in children. Besides, xylitol reduces microbial adhesion to the nasal mucosa and facilitates its clearing, which reduces the risk of sinus infection, allergy and asthma [22, 47]. It also helps maintain an equilibrium between calcium and phosphate levels in saliva, not only in small children, but also in adults. It stimulates the production of saliva, which is a key factor in the elderly population. In a 12-month study, 111 healthy individuals over the age of 60 years were divided into 3 groups. The 1st group did not chew gum at all, the 2nd group used xylitol-sweetened chewing gum, while the 3rd chewed gums with the addition of antibacterial substance and xylitol. In both gum-chewing groups (2 pieces for 15 min, twice a day), the risk of fungal or yeast infections, so-called oral thrush or aphthae, decreased significantly. The risk of angular cheilitis, i.e. irritating lesions at the corners of the mouth, was also reduced. Tests on female rats with ovariectomy showed that regular consumption of xylitol helped maintain adequate bone density. Reduced bone density was observed in animals that were not given this substance, while in rats given xylitol bone

mass increased [47]. It is presumed that the impact of this substance on increasing bone density is due to the mobilization of calcium absorption in the intestine. The use of xylitol in the daily diet may help increase bone mass and improve health. It was established that xylitol is most effective when consumed 3–5 times every day, but total intake should not exceed 10 g [48]. Subsequent studies suggest, however, that the daily xylitol level for human prophylaxis is 40 g/day [47]. Importantly, the consumption of polyols in excess of 50 g/day may cause persistent diarrhea leading to dehydration and deficiencies in minerals and certain vitamins. It has also been demonstrated that xylitol added to green tea increases the rate of absorption of catechins in the body [20, 22, 47].

Health effects of sorbitol

In the 1970s and 1980s, studies were carried out showing the impact of chewing gums with sorbitol on caries prophylaxis. It was found that foods rich in refined sugars reduced the pH of plaque, which may cause caries. On the other hand, chewing gum without saccharose but with the addition of sorbitol stimulated mineralization and inhibited demineralization [49, 50]. In the course of a two-year study, it was proven that chewing gum with sorbitol after every meal, accompanied by basic oral hygiene with a toothbrush and floss, minimized the occurrence of caries and reduced the development of white spots on the teeth, which may have been caused by the increased fluoride content in toothpaste [51]. However, it is important to note that sorbitol is a polyol. Therefore, its consumption should not exceed 30 g/day due to potential adverse gastrointestinal effects, including the most frequent ailments such as abdominal pain and diarrhoea. Among the available studies on sweetening agents in literature, there are not enough publications devoted to sorbitol itself. Frequently, new studies are based on tests from the previous century, but findings tend to be very similar. Sorbitol is often tested together with xylitol, demonstrating similar health-promoting properties as the substance described in the preceding subsection.

Health effects of mannitol

Mannitol, with its low molecular mass, is a substance that passes freely through renal tubules and is therefore used as one of the components in kidney diuresis. It is not metabolised in the kidneys, which is why it is used as an osmotic component of diuretics and as a diuretic agent. Mannitol also stimulates the secretion of kidney prostaglandins which broaden renal tubules and thus increases renal flow. It is also presumed to protect against kidney vessel blocking and failure [30]. In an experiment carried out in 1996, medical teams participating in neurosurgical procedures administered mannitol intravenously for the treatment of intracranial hypertension (ICP) [30]. Mannitol has an immediate effect on reducing blood density, which contributes to increased circulation of oxygen and microcirculation in the brain; this also results in increased heart performance. The substance affects the osmotic gradient between plasma and brain cells, reducing

brain swelling, which is the cause of ICP. It is essential to make sure that the blood–brain barrier is not compromised because the administration of mannitol may worsen the patient's overall condition [28, 30]. Studies have shown that an excessive dose of intravenous mannitol may cause acute and persistent nephrotic syndrome, so the patient's urine needs to be monitored carefully. If urine density is decreasing, the patient should be carefully examined prior to the administration of another dose of intravenous mannitol [26]. Accumulation of this substance may result in increased levels of extracellular fluid, which in turn can cause asymptomatic heart failure. The patient should be monitored during the intravenous administration of 20% mannitol, because it can cause hyponatremia and hypokalemia, as well as disturb the balance of electrolytes in the body. Hypokalemia may cause headache, nausea, vomiting, convulsions and even coma [26]. It is not known whether mannitol affects foetal development during pregnancy and whether it is absorbed by the child together with breast milk. It has not been determined whether the consumption of mannitol is safe for children under 12 years of age. In the elderly and adults, dosage depends on body weight and health status, usually ranging between 20–100 g/day. The majority of respondents reported that the effects started to appear when the dose reached 50–100 g/day. The frequency of application is adjusted to support urine circulation, with a min. of 30–50 mL/h. Such a scheme is widely accepted in the treatment of kidney disease [26].

Health effects of stevia

Stevia is one of the most common sweetening agents of natural origin. Steviol glycosides are only fermented in the large intestine by the microorganisms that live there, as it passes unchanged via the upper digestive tract. Glucose that is secreted there is not absorbed but used by intestinal bacteria. This explains why stevia is the right sweetener for patients with diabetes [36]. Gregersen et al. carried out tests on diabetic rats and proved that the stevioside lowered blood glucose levels but did not change those of glucagon. More importantly, they noted that it delayed the absorption of glucose in the small intestine by approx. 40% [52]. The downregulation of blood sugar is caused by blocking the gene encoding phosphoenolpyruvate carboxykinase enzyme (PEPCK) involved in gluconeogenesis. However, it is effective only while blood glucose levels are elevated [33, 36]. A total of 106 adults with hypertension were tested by being given either a placebo or 750 mg of stevioside a day. It was proven that in the group taking stevioside, systolic and diastolic pressure decreased significantly while BMI and blood biochemistry remained stable. Two mechanisms are involved in reducing blood pressure. The 1st delays the flow of calcium ions into vascular smooth muscle cells, which in turn broadens veins and increases blood flow. The other is characterized by increased diuresis and elimination of sodium in the urine, which results in reduced thickness of extracellular fluid. Importantly, it does not affect healthy blood pressure [33]. The valuable properties of stevia include preventing obesity and tooth decay. In obese people, it reduces the energy content

of food, which stimulates the body to use energy reserves by burning the fatty tissue, resulting in weight loss. Steviol glycosides are not consumed by bacteria that cause dental caries, mainly *Streptococcus mutans*. Stevia has antibacterial properties, so it should be an indispensable ingredient of anti-caries toothpaste [34]. Stevia leaf extract was found to contain antimicrobial compounds inhibiting the growth rate of bacteria such as: *Staphylococcus aureus*, *Salmonella typhi*, *Escherichia coli*, *Aeromonas hydrophila*, *Bacillus cereus*, *Klebsiella pneumoniae* and *Vibrio cholerae*. In addition, an antifungal effect was observed, particularly with regard to *Penicillium chrysogenum* and *Aspergillus niger* [31, 33].

CONCLUSIONS

Saccharin is the oldest artificial sweetening agent, discovered in 1877, followed by xylitol in 1891, while sorbitol is the "most recent" sweetener. Interestingly, stevia was discovered as a plant in 1899, and only drew attention as a sweetening agent at the end of the 20th century. Using saccharose as a reference, the highest level of sweetness is found in saccharine, and the lowest in sorbitol and mannitol, which are polyols with a comparable sweetness to saccharose. Xylitol is a substance with the highest ADI in comparison to other sweetening agents described here; the approved dose is 100 g/day, whereas saccharine has the lowest acceptable intake, at only 5 g/day. All sweeteners are approved by the FDA or JECFA, so they are safe provided the recommended doses are not exceeded.

Xylitol and stevia seem to be the most valuable substances; the former is ideal for people affected by caries because it is not converted into acids by bacteria inhabiting the oral cavity. In addition, it is an ideal sugar substitute for diabetics because it is broken down without insulin. It also delays the onset of osteoporosis, by increasing bone density and calcium absorption. Stevia is appropriate for people suffering from type 2 diabetes, as it is not absorbed in the upper gastrointestinal tract. It reduces glucose and is absorbed in the small intestine. Stevia also has antibacterial and antifungal properties. Also of note are the medicinal properties of mannitol, which passes freely through renal tubules due to its low molecular mass and can be used as an osmotic agent during kidney diuresis. It has also been proven to reduce ICP, by diluting blood, and to contribute to increased microcirculation in the brain. However, it is best not to give mannitol to children because the ADI and safety of use have not been documented for them.

The title of most controversial sweetener has always belonged to aspartame. Studies have shown, among other things, that regular exposure to high doses of aspartame may cause cancer, in particular brain tumours. Patients suffering from phenylketonuria must avoid aspartame due to the presence of phenylalanine. Acesulfame K has a similar effect on health, but is not as toxic. As we reach for sweetening agents, it is important not to exceed the ADI. When trying to eliminate sugar, the best substitutes are xylitol and stevia.

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