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Aspartame: A review of functional properties and physiology impacts of aspartame

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Abstract. Aspartame is a high-intensity, low-calorie, synthetic sweetener which has been approved as a food additive (specifically as a sweetener) in the European Union and several nations worldwide. Primarily, it is employed as a sweetening agent in carbonated beverages, confectionery products, and pharmaceutical preparations. Despite the extensive utilisation of this particular phenomenon, there continues to be ongoing debate over its safety. The Food and Drug Administration (FDA) acknowledges the findings of the International Agency for Research on Cancer (IARC) and the Joint FAO/WHO Expert Committee on Food Additives (JECFA) on aspartame, as stated on July 14, 2023. The classification of aspartame by the International Agency for Research on Cancer (IARC) as "possibly carcinogenic to humans" should not be interpreted as a direct causal relationship between aspartame use and cancer. This review paper presents a theoretical framework for the utilization of aspartame across several industries. It accomplishes this by examining its physical and chemical characteristics, physiological roles, contemporary approaches to chemical synthesis and biological production, as well as its application in the realm of food. The objective of this narrative inquiry is to enhance individuals' comprehension regarding the utilization of aspartame and its potential impact on the human body through an examination of existing research. The present study examined a collection of scholarly papers pertaining to the impact of aspartame on many health aspects, including obesity, diabetes, pediatric and fetal health, phenylketonuria, and the potential carcinogenicity of this artificial sweetener. Further investigation is required in order to provide a comprehensive understanding of the potential impact of aspartame on human health.

Keywords: Aspartame, artificial sweeteners, cancer, metabolism

1. Introduction

1.1. The rise and fall of sugar and the rise of aspartame

Throughout history, individuals have exhibited a distinct inclination for the taste of sweetness. The majority of terms containing the word "sweet" evoke associations of aesthetic appeal and positive emotions. There is a prevailing belief that sweet foods held a significant level of popularity during prehistoric eras. The commodity of sugar has a lengthy historical trajectory and has maintained its status as a luxury good for a considerable duration.

In contemporary society, there has been fluctuation in the perspectives towards sugar. Since the advent of the late 19th century, several nations, including Germany, have employed sugar as a substance with potential medicinal properties, aiming to fortify the human physique. This practise has been rooted in the belief that sugar consumption may lead to weight gain, enhance overall well-being, and facilitate the execution of physically demanding occupations. During the 1920s and 1930s, A study was initiated by the American Medical Association with the objective of investigating the potential association between sugar consumption and the development of diabetes and other related ailments. Nevertheless, throughout that period, several academics provided compelling evidence to support the notion that obesity and excessive fat intake were the primary factors contributing to the development of diabetes. Several sugar business organizations engaged in public relations efforts to downplay the negative effects of sugar, leading individuals to adopt a cautious stance about its potential impact [1]. The recognition of the adverse effects of sugar consumption on diet quality, obesity, and the susceptibility to non-communicable illnesses was not widely acknowledged until 2015, when the World Health Organisation officially proclaimed the association between excessive intake of free sugars and these health concerns [2]. This declaration dispelled the notion that the concerns surrounding sugar were either exaggerated or unfounded. The overconsumption of added sugars has been linked to an elevated risk of several health conditions, including obesity, dental caries, diabetes, and other related disorders. There has been a noticeable change in perspectives towards sugar, with a decrease in discourse surrounding the topic.

The utilization of the artificial sweetener aspartame in the United States can be traced back to the 1980s. Due to its significantly higher sweetness compared to sugar, this substance finds extensive application in several food and beverage products, allowing for less quantities to be employed while achieving equivalent levels of sweetness.

Aspartame is frequently employed as a sweetening agent for tabletop consumption, as well as an additive in processed food and beverage products. Additionally, it is utilised in culinary preparations that do not necessitate excessive exposure to heat, as the thermal degradation of aspartame occurs under such conditions. Additionally, it is present as a flavouring agent in certain pharmaceuticals, chewing gums, and toothpastes.

1.2. The Overview of aspartame

The discovery of aspartame occurred in 1965, credited to James M. Schlatter, a chemist employed by G.D. Searle & Company. Schlatter synthesised aspartame as an intermediary compound in the process of producing a tetrapeptide of the hormone gastrin. This was done with the purpose of evaluating the efficacy of an anti-ulcer medication candidate. The individual had the perception of sweetness upon licking their finger, which had inadvertently come into contact with aspartame, while using it to elevate a sheet of paper [3]. Torunn Atteraas Garin was actively involved in the research and development of aspartame, a synthetic sweetening agent.

Aspartame, a low-calorie sweetener, has been employed for an extended duration to facilitate individuals in reducing their consumption of excessive sugars, while still allowing for the enjoyment of sweet foods. Aspartame possesses a sweetness intensity approximately 200 times more than that of sugar, necessitating a comparatively minute quantity of the sweetening agent to achieve an equivalent level of sweetness. In order to mitigate its inherent bitterness and enhance the overall sensory experience, aspartame is occasionally combined with alternative sweeteners or food constituents within tabletop sachets, prepared meals, and beverages.

Aspartame is composed of two distinct amino acids, namely phenylalanine and aspartic acid. Upon consumption of a substance containing aspartame, enzymatic processes facilitate the breakdown of aspartame into its constituent amino acids. Subsequently, the aforementioned amino acids are utilized in the synthesis of proteins, hence facilitating the maintenance of bodily functions. In addition to the amino acids aspartic acid and phenylalanine, the process of digesting aspartame also results in the production of a small amount of methanol, a naturally occurring molecule present in various food sources such as fruits, vegetables, and their juices. The consumption of a beverage containing aspartame results in a significantly lower production of methanol by the human body, approximately five to six times less, compared to the equivalent intake of tomato juice.

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Aspartame possesses the potential to serve as a constituent in a diverse array of comestibles and beverages, including but not limited to diet carbonated beverages, reduced-sugar fruit juices, and flavored aqueous solutions. Additionally, it has potential applications in the dairy industry, particularly in the production of light yoghurt and low-fat flavored milk. Furthermore, it can be utilized in the creation of nutrition bars, desserts such as sugar-free puddings and gelatins, as well as light ice cream and popsicles. Moreover, it can be incorporated into chewing gum, sauces, syrups, and condiments. Certain tabletop treats with reduced calorie content also contain aspartame as an ingredient. In the United States, the majority of individuals utilize Equal®, a tabletop sweetener that is formulated with aspartame. Canderel® is a brand mostly available in Europe, whereas Pal Sweet® is predominantly found in Asia. Additionally, it is crucial to acknowledge that aspartame is commonly incorporated into numerous prescription and over-the-counter medications, along with chewable pills, with the intention of enhancing their flavor and increasing customer appeal. The suitability of aspartame for use in meals that need lengthy baking is limited because to its susceptibility to diminished sweetness when exposed to elevated temperatures over an extended duration.

1.3. Aspartame hazard and risk assessment

Several papers have been published by reputable organizations such as the International Agency for Research on Cancer (IARC), the World Health Organization (WHO), and the Food and Agriculture Organisation (FAO) Joint Expert Committee on Food Additives (JECFA) about the impact of aspartame on human health. According to the classification of the International Agency for Research on Cancer (IARC), aspartame has been categorized under Group 2B, indicating its potential carcinogenicity to humans. This is due to the limited availability of information supporting its non-cancerous nature. Furthermore, the recommended daily intake of aspartame, as determined by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), is set at 40 mg per kilogram of body weight.

The utilization of the artificial sweetener aspartame has become prevalent in many food and beverage items since the 1980s. Several examples of products include diet sodas, gum, gelatin, ice cream, yogurt, milk, cereal, toothpaste, cough syrup, and chewable pharmaceuticals.

Cancer is well recognised as a significant contributor to mortality on a worldwide scale. Annually, the mortality rate due to cancer is seen to be 1 in 6 individuals. According to Dr. Francesco Branca who is the individual responsible for overseeing the Division of Nutrition and Food Safety at the World Health Organization (WHO), the field of science is constantly increasing its efforts to examine the potential causative or enabling aspects of cancer. This pursuit is driven by the objective of diminishing the incidence of cancer and its associated human consequences. The evaluations of aspartame have found that although safety is not a significant problem at regularly administered levels, there have been descriptions of possible consequences that require more investigation via more rigorous and comprehensive investigations.

Both organisations performed separate yet complementary evaluations to analyse the possible carcinogenicity and other health hazards linked to the intake of aspartame. The evaluation of aspartame by the International Agency for Research on Cancer (IARC) is a novel occurrence, marking its initial assessment of this substance. Conversely, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) had already reviewed aspartame on two separate occasions.

After conducting a comprehensive examination of the pertinent scholarly literature, it was seen that both assessments identified some constraints in the available information pertaining to cancer and other health implications.

The International Agency for Research on Cancer (IARC) has categorised aspartame as potentially carcinogenic to humans (Group 2B) due to the presence of limited data indicating a potential link to cancer in humans, notably hepatocellular carcinoma, a kind of liver cancer. Additionally, the available knowledge about cancer in experimental animals is restricted, as is the evidence pertaining to potential pathways behind carcinogenesis.

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) did not modify the acceptable daily intake (ADI) range of aspartame, which remains at 0-40 mg/kg body weight, following thorough deliberation. The committee has just reconfirmed that a daily consumption of this amount is deemed to be safe. In the case of an individual with a body weight of 70 kilograms, surpassing the recommended daily threshold of 600 milligrams of aspartame would need the use of more than 9 to 14 cans of diet soft drink on a daily basis.

The hazard identifications conducted by the International Agency for Research on Cancer (IARC) serve as a first and essential process in comprehending the carcinogenic nature of a substance. These identifications involve the assessment of the substance’s distinct characteristics and its capacity to induce detrimental effects, including cancer. The categories assigned by the International Agency for Research on Cancer (IARC) are indicative of the degree of scientific evidence supporting the potential of an agent to induce cancer in humans. However, these classifications do not directly convey the amount of risk associated with acquiring cancer at a certain level of exposure. The hazard evaluation conducted by the International Agency for Research on Cancer (IARC) takes into account several forms of exposure, including but not limited to dietary and occupational exposures. The strength-of-evidence category within Group 2B is positioned as the penultimate category among the four. This approach is commonly employed in situations when the evidence supporting the presence of cancer in humans is inconclusive, yet falls short of being definitive, or where the evidence supporting cancer in experimental animals is robust, but lacks corroboration in human subjects.

Dr. Mary Schubauer-Berigan, a prominent researcher affiliated with the International Agency for Research on Cancer (IARC) Monographs program, emphasized the need of doing further investigations to enhance our understanding of the potential carcinogenicity associated with the use of aspartame. The aforementioned requirement arises due to the limited availability of empirical evidence about the potential carcinogenic effects of aspartame on both human and animal subjects. Furthermore, the current understanding of the etiology of cancer remains incomplete.

The risk assessments conducted by JECFA ascertain the likelihood of a particular form of harm, such as cancer, to manifest given certain circumstances and degrees of exposure. Incorporating IARC classifications into its discussions is a common practise for JECFA.

According to Dr. Moez Sanaa, the Head of the Standards and Scientific Advice on Food and Nutrition Unit at the World Health Organisation (WHO), the Joint FAO/WHO Expert Committee on Food Additives (JECFA) evaluated the available data from animal and human research on the potential cancer risk associated with aspartame use. The committee has reached a conclusion that the available evidence is insufficient to establish a causal relationship between the use of aspartame and the development of cancer in individuals. There is a need for improved research endeavours that encompass extended periods of observation and employ recurrent assessments of food habits within established cohorts. There is a requirement for randomised controlled trials, which should encompass investigations into molecular pathways that are pertinent to the regulation of insulin, metabolic syndrome, and diabetes. This is particularly significant given its potential carcinogenic implications.

The reviews undertaken by the International Agency for Research on Cancer (IARC) and the Joint FAO/WHO Expert Committee on Food Additives (JECFA) about the effects of aspartame were founded upon a comprehensive analysis of scientific evidence obtained from many reputable sources. The materials included in this collection encompass peer-reviewed research, government reports, and studies conducted only for regulatory purposes. The studies have undergone scrutiny by impartial specialists, and both groups have implemented measures to safeguard their autonomy and the reliability of their assessments.

The International Agency for Research on Cancer (IARC) and the World Health Organisation (WHO) will persist in their efforts to oversee emerging evidence and promote the involvement of independent research organisations in conducting more investigations on the potential correlation between exposure to aspartame and its impact on consumer health.

2. Physicochemical Properties

Aspartame is widely acknowledged to possess a sweetness intensity that is approximately 180-200 times more than that of sucrose, often known as “table sugar.” Aspartame, similar to sucrose, yields 4 kcal (17

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kJ) of energy per gram during metabolic processes. Nevertheless, the amount of aspartame required to provide a sweet taste is so minimal that its caloric effect is considered insignificant [3]. The duration of sweetness exhibited by aspartame surpasses that of sucrose, hence prompting its frequent combination with other artificial sweeteners such as acesulfame potassium to enhance its resemblance to sugar in terms of flavor.

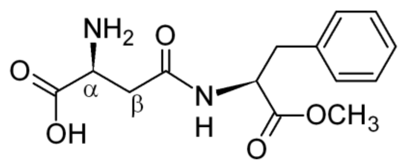
Similar to several other peptides, aspartame has the potential to undergo hydrolysis, resulting in the breakdown of its constituent amino acids when exposed to situations characterised by extreme temperature or high pH levels. Aspartame's suitability as a baking sweetener is compromised, rendering it less appealing, due to its propensity for deterioration in goods with a high pH, which is necessary for achieving an extended shelf life. The thermal stability of aspartame can be enhanced by the utilization of lipids or maltodextrin as a safeguarding agent. The solubility of a substance in water is significantly influenced by the pH level. Under conditions of ambient temperature and humidity, the substance exhibits optimal stability when subjected to a pH level of 4.3, resulting in a half-life of around 300 days. However, when the chemical is exposed to a pH level of 7, its half-life is significantly reduced to a duration of only a few days. The majority of carbonated beverages have a pH range of 3 to 5, within which aspartame demonstrates a satisfactory level of stability. In certain goods that may need an extended duration of preservation, such as syrups intended for use in fountain drinks, it is occasionally seen that aspartame is combined with a more resilient sweetening agent, such as saccharin.

Research investigations examining the sensory attributes of aspartame solutions have consistently shown the presence of a sweet aftertaste, accompanied by bitter and off-flavor aftertastes [4].

3. Chemistry

Aspartame is a methyl ester derived from the dipeptide resulting from the combination of natural amino acids L-aspartic acid and L-phenylalanine. Under conditions of high acidity or alkalinity, the hydrolysis of aspartame can result in the production of methanol. Under more stringent circumstances, the peptide bonds undergo hydrolysis, leading to the liberation of amino acids [5].

Commercially, two distinct ways to synthesis are employed. In the chemical synthesis procedure, the carboxyl functional groups of aspartic acid undergo a condensation reaction to form an anhydride compound. Simultaneously, a formamide compound containing a formyl group is introduced to provide protection for the amino group. The defensive properties of aspartic acid are conferred by its combination with formic acid and acetic anhydride. During this procedure, the conversion of phenylalanine into its methyl ester takes place, followed by its subsequent combination with N-formyl aspartic anhydride. Subsequently, the protective group on the aspartic nitrogen is eliminated during acid digestion. One limitation associated with this particular methodology is the generation of a secondary compound, known as the β-form, which possesses a bitter taste. The occurrence arises when an incorrect carboxyl group originating from aspartic acid anhydride becomes attached to phenylalanine, resulting in the formation of desired and undesired isomers at a ratio of 4:1. The utilization of an enzyme derived from Bacillus thermoproteolyticus for the acceleration of the condensation process involving chemically modified amino acids has demonstrated the capacity to generate substantial quantities of the intended product, while concurrently diminishing the production of the undesirable -form byproduct. An alternative approach to this methodology, which has yet to be used in commercial applications, involves the utilisation of unaltered aspartic acid. However, this particular process delivers rather low quantities. Various enzymatic methods have been explored for the direct synthesis of aspartyl-phenylalanine, followed by subsequent chemical methylation. However, these approaches have not yet been successfully implemented on an industrial scale [6].



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The carboxyl group of aspartate, which forms a bond with the nitrogen of phenylalanine in beta-aspartame, has distinct characteristics compared to the carboxyl group that connects to the nitrogen in aspartame.

4. Physiological Impact

Foods that are very tasty have been found to stimulate brain areas associated with reward and pleasure. The presence of this positive correlation has the potential to stimulate one's hunger, and if not well regulated, the subsequent rise in consumption of food can contribute to the development of excessive weight and obesity [7]. The replacement of meals that include full-calories and added sugars with alternatives manufactured with low-calorie sweeteners has demonstrated a comparable impact on reward pathways, while avoiding the intake of extra calories.

There is a growing worry among certain individuals over the potential unintended consequences of stimulating reward pathways in the absence of caloric intake. Presently, scholars are investigating the impact of low-calorie sweeteners on hunger sensations and the propensity to engage in snacking behaviors. As shown in recent literature reviews [8,9], several studies conducted on animal models have revealed alterations in food consumption and the levels of hormones associated with hunger subsequent to the ingestion of low-calorie sweeteners. However, comparable outcomes have not been observed in human subjects. Currently, there exists a dearth of empirical data to substantiate the aforementioned notion that low-calorie sweeteners, such as aspartame, have the ability to increase appetite or desires in humans. Several randomized examinations have proven that those who consumed water experienced a contrasting effect, characterized by a decrease in hunger and a reduction in treat consumption, in comparison to those who did not. These discrepancies serve to underscore a fundamental disparity between animal research and human study. The careful consideration of extrapolating findings from animal studies to human populations is necessary, primarily owing to the intricate interplay of physiological, psychological, experiential, and dietary factors in humans.

Despite being a very nascent field of study, the gut microbiome has garnered recognition for its possible role in influencing human health. The precise mechanism and site of digestion of aspartame are inadequately elucidated, potentially contributing to the scarcity of research examining its impact on gut microbiota. Within the confines of the small intestine, the metabolic breakdown of aspartame occurs, resulting in the production of its constituent amino acids and a minute quantity of methanol. Given the prominent localization of the gut microbiota in the distal regions of the intestine, it is improbable that aspartame will reach these areas in its intact state. A study conducted in 2014 employed an animal model to investigate the impact of various dietary patterns on aspartame consumption. The research revealed that rats consuming a combination of aspartame-sweetened water and a high-fat diet exhibited an increased abundance of bacteria within their bodies. Furthermore, distinct alterations in the prevalence of several bacterial species were observed. The observed outcomes diverged from those observed in rats consuming a high-fat diet with regular water, a regular diet with water sweetened with aspartame, or a regular diet with regular water [10]. A limited-scale human investigation conducted in 2015 examined and contrasted the microbial profiles of individuals who consumed aspartame and those who did not [11]. No significant changes were seen in the number of gut bacteria, while there were variations in bacterial diversity across the different groups. There exist notable variations in the microbiome profiles among individuals, and scientific investigations have demonstrated that alterations in dietary preferences can induce modifications in the gut microbiota [12]. Further investigation is required in order to ascertain the specific attributes of a robust microbiome and determine the ideal level of diversity among people and groups. A comprehensive literature study conducted in 2019 yielded inconclusive findings on the potential adverse impact of low-calorie sweeteners on the composition of gut microbiota [13]. I In the year 2020, scholars specializing in the domain of low-calorie sweeteners arrived reached a consensus, asserting that the available data is insufficient to establish definitive findings about the influence of low-calorie sweeteners on the human gut microbiota, particularly at levels of consumption that are pertinent to the human population [14].

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Despite the safety certifications granted to aspartame by several worldwide regulatory bodies, there is a persistent emergence of anecdotal reports that associate the use of aspartame with various symptoms, predominantly headaches. Only a limited number of research have examined the potential correlation between these attributes, and even those are hindered by limited sample numbers and methodological challenges. According to a narrative review conducted in 2016, it was observed that out of the four research examined, two studies reported a positive correlation between aspartame exposure and heightened frequency of headaches. However, the other two studies did not identify any significant disparity between the groups exposed to aspartame and the control groups [15]. All of the aforementioned experiments employed aspartame dosages that much beyond the thresholds deemed safe or efficacious for human consumption. In a research conducted by the United Kingdom Food Standards Agency in 2015, it was observed that there were no statistically significant variations in physical, biochemical, or psychological symptoms among participants who self-reported sensitivity to aspartame [16]. It is crucial to bear in mind that aspartame undergoes degradation within the digestive system, resulting in the formation of aspartic acid, phenylalanine, and methanol. These chemicals are naturally present in a diverse range of food and beverage sources, often occurring in significantly greater concentrations. Formulating a hypothesis about the molecular process behind symptoms and/or sensitivities particular to aspartame becomes challenging.

4.1. Weight control

The substitution of meals and drinks that include aspartame as a sweetener in place of their full-sugar counterparts has the potential to contribute to weight reduction or weight control. A majority of participants in a survey conducted by the National Weight Control Registry, which is widely recognized as the largest longitudinal study investigating individuals who have effectively sustained a weight loss of at least 30 pounds for a period exceeding one year, reported consistent consumption of low-calorie beverages. Additionally, a significant majority of 78 percent among this group expressed the belief that such consumption effectively aids in regulating their overall calorie intake [17].

Several observational studies have indicated a correlation between the consumption of low-calorie sweeteners and an elevation in body weight and waist circumference among adult individuals [18]. According to a systematic review and meta-analysis conducted in 2017, the intake of low-calorie sweeteners was found to be linked with elevated body mass index (BMI) and a greater prevalence of obesity, as well as an increased risk of several diet-related diseases in adults [19]. Observational studies have established a correlation between the intake of low-calorie sweetened beverages and heightened weight gain in the pediatric and teenage population. Nevertheless, the correlation between these factors remains unsupported by empirical data derived from randomized controlled trials [20]. According to existing systematic reviews and meta-analyses, it is widely accepted that there is no correlation between the intake of low-calorie sweeteners and weight. However, findings from observational studies do suggest a potential positive link between low-calorie sweetener consumption and increasing body mass index (BMI) [21,22].

It is essential to acknowledge the constraints inherent in observational studies, which investigate the correlation between a specific exposure (e.g., aspartame intake) and a particular outcome (e.g., body weight or a health condition) without making any attempts to establish causation. Observational studies are susceptible to the manifestation of reverse causality, when the causal relationship between variables is contrary to initial expectations. A prevalent illustration of this phenomenon occurs when an individual modifies their food patterns subsequent to receiving a medical diagnosis: The health condition precipitated alterations in their dietary preferences; conversely, the dietary choices did not precipitate the development of the health problem. Furthermore, it should be noted that observational studies lack randomization, which limits their ability to account for all potential confounding variables or exposures that might potentially impact or bias the outcomes.

One hypothesis posits that individuals may engage in compensatory behaviour, wherein they consume additional calories in response to selecting “calorie-free” options, either through increased consumption of other food choices or in subsequent meals [23]. Consider an individual who would rationalise their decision to indulge in a dessert at a dining establishment on the grounds that they had a diet soda alongside their meal. In this scenario, it is posited that the additional caloric intake resulting from the dessert would surpass the caloric reduction achieved by opting for the diet beverage. The inclusion of these supplementary calories has the potential to lead to an increase in body weight or impede future progress in weight reduction efforts. This phenomenon is sometimes referred to as the "licencing effect" or "self-licensing," when individuals rationalise their engagement in indulgent behaviours by identifying justifications that render such behaviours more acceptable despite their inconsistency with their overarching aims [24]. While there may be isolated cases, scientific research provides limited evidence to support the notion that individuals habitually and knowingly consume excessive calories due to the consumption of low-calorie sweeteners or products containing such sweeteners [25].

Additionally, there has been a suggestion that those who are already classified as overweight or obese may opt for food and beverage options that are both sweeter in taste and lower in caloric content as a means of achieving weight loss [26-29]. The presence of reverse causation introduces challenges in attributing weight gain only to the consumption of low-calorie sweeteners.

The utilisation of randomised controlled trials, often regarded as the most reliable method for evaluating causal relationships, provides evidence that replacing regular-calorie alternatives with low-calorie sweetener choices results in a slight reduction in body weight [9,21,22,30,31]. In a randomised clinical study conducted in 2016, a total of 300 individuals were randomly assigned to two distinct groups: one group consumed water while the other group consumed low-calorie-sweetened drinks. This intervention was implemented as part of a comprehensive programme that consisted of 12 weeks of weight reduction therapies followed by 40 weeks of weight maintenance interventions. Participants allocated to the low-calorie-sweetened beverage group exhibited an average weight loss of 6.21 kg, whereas those in the water group witnessed a weight loss of 2.45 kg [32]. However, it is worth noting that alternative research has reached contrasting findings regarding the impact of consuming low-calorie sweeteners on weight changes. For instance, a comprehensive analysis conducted in 2017, which involved systematically reviewing and meta-analyzing randomised controlled trials, determined that there is no significant association between the consumption of low- and no-calorie sweeteners and changes in body mass index (BMI) or other indicators of body composition. One notable distinction among these apparently contradictory research findings is in the kind of comparison employed. According to Mela et al. (year), certain study designs provide researchers the opportunity to assess the outcomes of caloric and non-caloric alternatives, while others do not provide this comparative advantage.

The Scientific Report of the 2020 Dietary Guidelines Advisory Committee (DGAC) encompassed a comprehensive analysis of 37 research, of which six were randomised controlled trials. These studies were published between January 2000 and June 2019, and focused on investigating the impact of low- and no-calorie-sweetened drinks on obesity. According to the DGAC research, the use of low- and no-calorie sweeteners could be regarded as a potential strategy for the management of body weight.

It is important to acknowledge that achieving and sustaining body weight loss necessitates the implementation of numerous concurrent strategies. Implementing a singular modification, such as replacing high-calorie sweeteners with low-calorie alternatives in lieu of sugar-containing items, is only a single facet. In order to achieve weight reduction and weight maintenance objectives, it is crucial to adopt lifestyle and behavioural practises that encompass healthy eating habits, regular physical activity, sufficient sleep, and the cultivation of social support networks.

4.2. Diabetes

Aspartame-containing foods and beverages are commonly suggested to individuals with diabetes as a viable substitute for sugar-sweetened counterparts, enabling them to fulfil their need for sweetness. Numerous studies have demonstrated that aspartame does not elicit an increase in blood glucose levels or exert any discernible impact on blood glucose regulation in the human population [33,34]. The findings of a randomized, controlled investigation conducted in 2018 indicate that the consumption of aspartame did not significantly alter blood sugar or insulin levels when compared to the administration of a placebo over a 12-week period [35]. The present remarks provided by specialists in the fields of nutrition, medicine, physical activity, and public health indicate that low-calorie sweeteners have no impact on haemoglobin A1C, insulin levels, and glucose levels both pre and post-meal. Based on the aforementioned remarks, it can be inferred that the incorporation of low-calorie sweeteners into a diabetes management regimen may contribute to the regulation of blood glucose levels.

Various international organizations of healthcare experts have independently disseminated their own findings about the safety and significance of low-calorie confections for those diagnosed with diabetes. According to the 2022 American Diabetes Association Standards of Medical Care in Diabetes, individuals with diabetes who have a preference for sugar-sweetened products may consider nonnutritive sweeteners as a viable alternative to nutritive sweeteners, provided they are consumed in moderation. Nonnutritive sweeteners are characterised by their low or zero calorie content, whereas nutritive sweeteners, such as sugar, honey, and agave syrup, contain calories. The use of nonnutritive sweeteners does not seem to have a substantial impact on glycemic control; nonetheless, they can contribute to a decrease in total calorie and carbohydrate consumption. Diabetes UK and Diabetes Canada both endorse comparable assertions pertaining to the safety and prospective use of low-calorie sweeteners, such as aspartame, for those afflicted with diabetes.

Despite the aforementioned conclusions, certain studies have periodically raised inquiries regarding the relationship between aspartame and blood glucose regulation. The utilization of low-calorie sweeteners has been associated with an elevated susceptibility to developing type 2 diabetes, as indicated by many observational studies. Nevertheless, it is important to note that these analyses do not establish a conclusive cause-and-effect relationship. Moreover, it is important to acknowledge that these findings are susceptible to the influence of confounding variables and the possibility of reverse causality, similar to studies examining the relationship between body weight and obesity. It is worth noting that obesity is frequently disregarded in academic studies, despite its significant role as a prominent risk factor in the development of prediabetes and type 2 diabetes. The exclusion of low-calorie sweetened beverage consumption among individuals who are overweight or obese is particularly significant, as they tend to consume a greater quantity of such beverages compared to individuals with a normal weight.

5. Food safety

Aspartame has been extensively investigated as one of the most thoroughly examined constituents within the human food inventory, with over 200 research providing evidence in favour of its safety. The approval for the use of aspartame in dry foods was granted by the U.S. Food and Drug Administration (FDA) in 1981. Subsequently, in 1983, the Food and Drug Administration (FDA) extended its approval to encompass carbonated beverages. The approval of aspartame for use in food and drinks was granted by the FDA in 1996. Food additives are subject to comprehensive scientific risk assessments and safety analyses conducted by reputable organizations such as the European Food Safety Authority (EFSA) and the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Numerous reputable institutions have reached a consensus about the safety of aspartame for its intended use. Various governmental regulatory bodies worldwide, such as the Japanese Ministry of Health, Labour, and Welfare, Food Standards Australia New Zealand, Health Canada, and the U.S. Food and Drug Administration, have granted authorization for the utilization of aspartame. This approval is based on the aforementioned research findings and further assessments carried out by diverse independent entities.

5.1. AID

The Acceptable Daily Intake (ADI) refers to the mean daily consumption level across an individual's lifespan that is anticipated to be safe for human consumption, as determined by extensive study. The calculation involves the identification of the no-observed-adverse-effect-level (NOAEL), which is the maximum intake amount that does not result in any detrimental effects in animal models across their lifespan. This NOAEL value is then divided by a factor of 100. By establishing the acceptable daily intake (ADI) at a level 100 times lower than the maximum threshold demonstrated to have no detrimental impacts in scientific investigations, it is ensured that human consumption remains below safe limits.

The acceptable daily intake (ADI) for aspartame, as determined by the Food and Drug Administration (FDA), is set at 50 milligrammes per kilogramme of body weight (mg/kg) every day. The European Food Safety Authority (EFSA) has determined a marginally reduced acceptable daily intake (ADI) of 40 mg/kg per day. The Acceptable Daily Intake (ADI) is equivalent to one hundredth of the quantity of aspartame that has been determined to produce no observable deleterious effects in toxicological trials. The ADI, or Acceptable Daily Intake, is a conservative threshold that is unlikely to be exceeded by the great majority of individuals. Based on the Acceptable Daily Intake (ADI) recommendations established by the Food and Drug Administration (FDA), an individual weighing 150 pounds (68 kg) would surpass the suggested ADI threshold of 3,400 mg of aspartame if their daily consumption exceeded an average of 19 cans of diet Coke or 85 individual packets of aspartame. Individuals who claim to use aspartame self-report an average intake of 4.9 mg/kg per day, a quantity that is less than 10% of the Acceptable Daily Intake (ADI) established by the Food and Drug Administration (FDA). Individuals who fall within the 95th percentile of aspartame intake are anticipated to ingest around 13.3 mg/kg per day, a quantity significantly lower than the recommended daily dosage (ADI) established by the Food and Drug Administration (FDA). On a global level, the consumption of aspartame by individuals remains far lower than the recommended daily intake (ADI) standards set by regulatory bodies such as the Food and Drug Administration (FDA) and the European Food Safety Authority (EFSA). According to a study conducted in 2018, it was observed that people seldom exceeded 20 percent of the Acceptable Daily Intake (ADI), even among the groups with the highest consumption levels.

The use of aspartame within the Acceptable Daily Intake (ADI) is considered to be safe; however, those diagnosed with phenylketonuria (PKU) should exercise caution and restrict their intake of this substance. Phenylketonuria (PKU) is an uncommon hereditary disorder characterised by impaired phenylalanine metabolism, resulting in the affected individual's inability to adequately process this particular amino acid. Phenylalanine is present in several dietary sources, including aspartame, milk, cheese, nuts, and meat. Individuals diagnosed with phenylketonuria (PKU) must adhere to a dietary regimen that involves the avoidance or limitation of phenylalanine consumption from any and all sources. According to regulations set out by the Food and Drug Administration (FDA), it is mandated that all packaged food and beverage products containing aspartame must have a declaration on the label regarding the inclusion of phenylalanine.

5.2. *For children*

The metabolic process of aspartame is comparable between healthy children and healthy adults. The European Food Safety Authority (EFSA), the Food and Drug Administration (FDA), and the Joint FAO/WHO Expert Committee on Food Additives (JECFA) have together determined that aspartame is deemed safe for use by both adults and children, provided it is under the Acceptable Daily Intake (ADI) limits. Similar to adults, the sole exemption pertains to children diagnosed with phenylketonuria (PKU), who must refrain from or limit their consumption of phenylalanine.

Foods and drinks that are sweetened with aspartame have the ability to provide a sweet taste without the associated increase in calorie consumption, intake of added sugars, or susceptibility to dental caries. In recent years, there has been a growing emphasis on the reduction of added sugar intake. Consequently, there has been an observed rise in the frequency of daily use of low-calorie sweeteners among both children and adults, starting from the year 2000. Similar to the consumption patterns observed in adults, the absolute quantities of low-calorie sweeteners ingested by youngsters are generally regarded as falling below safe thresholds.

According to the guidelines provided by the American Heart Association (AHA), it is not recommended for children to routinely consume liquids that include low-calorie sweeteners. Instead, the AHA suggests that children choose for unsweetened beverages like water and plain milk. An important exception in the 2018 American Heart Association (AHA) research advice pertains to children diagnosed with diabetes. These individuals may experience improved blood glucose control by substituting sugar-sweetened drinks with low-calorie-sweetened alternatives. The 2019 policy statement from the American Academy of Paediatrics refrains from offering guidance on the use of foods or beverages containing low-calorie sweeteners by children under the age of two, citing a lack of available data.

5.3. For pregnant and breastfeeding women

Based on the guidelines provided by the Food and Drug Administration (FDA) and the European Food Safety Authority (EFSA), it is deemed OK for women who are pregnant or nursing to consume low-calorie sweeteners such as aspartame within the limits of the OK Daily Intake (ADI). According to scientific research, it has been demonstrated that aspartame does not have any detrimental effects on pregnant or lactating women, nor does it pose any risks to the developing foetus. Aspartame undergoes rapid metabolism within the human body subsequent to ingestion. The process results in the synthesis of the amino acids phenylalanine and aspartic acid, alongside a minor quantity of methanol. Consequently, breast milk does not contain aspartame. It is imperative for pregnant or lactating women to consume the essential nutrients and calories required for the best growth and development of their offspring, while being cautious not to surpass their individual dietary requirements.

6. Aspartame and Cancer Risk

There have been longstanding concerns over the potential health implications of aspartame, with claims suggesting its association with various health issues, including cancer.

Certain worries regarding cancer have arisen due to the findings of study conducted on laboratory rats by a cohort of Italian scientists during the latter half of the 2000s. These investigations indicated a potential correlation between the consumption of aspartame and an elevated susceptibility to certain blood-related malignancies, such as leukaemias and lymphomas, as well as other forms of cancer. Nevertheless, the aforementioned research were subject to several constraints, hence rendering the interpretation of their findings challenging.

The findings from epidemiological investigations examining the potential association between aspartame consumption and cancer, particularly haematological malignancies, have displayed inconclusive results across a majority of cancer types. Several studies have posited a potential association, whereas alternative research findings have failed to establish such a connection.

Typically, the American Cancer Society does not ascertain the carcinogenicity of substances, but rather relies on the expertise of esteemed institutions to assist in this determination.

6.1. Regulations of aspartame

The regulation of artificial sweeteners, such as aspartame, is within the purview of the Food and Drug Administration (FDA) in the United States. Prior to usage, it is imperative that these goods undergo safety testing and receive approval from the Food and Drug Administration (FDA). The Food and Drug Administration (FDA) establishes an Acceptable Daily Intake (ADI) for every sweetener, representing the highest quantity deemed safe for daily consumption during an individual's lifespan.

The Food and Drug Administration (FDA) has established the Acceptable Daily Intake (ADI) for aspartame at a level of 50 milligrammes per kilogramme of body weight per day (50 mg/kg/day), with the conversion of 1 kilogramme being equivalent to 2.2 pounds.

Both the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and the European Food Safety Authority (EFSA) advocate for a marginally reduced Acceptable Daily Intake (ADI) for aspartame, set at 40 mg/kg/day.

In order to provide a contextual understanding of these levels, it is worth noting that the Food and Drug Administration (FDA) has approximated that an individual weighing 60 kg (132 lb) would need to ingest about 75 packets of aspartame within a single day to approach the maximum limit of the Acceptable Daily Intake (ADI) of 50 mg/kg/day.

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In a same manner, an individual with a body weight of 70 kg (154 lb) would need to ingest a minimum of 9-14 cans of diet soda daily (varying based on the concentration of aspartame in each can) in order to surpass the acceptable daily intake (ADI) of 40 mg/kg/day established by JECFA/EFSA.

6.2. World Health Organization (WHO)

6.2.1. International Agency for Research on Cancer (IARC). The International Agency for Research on Cancer (IARC), which operates under the auspices of the World Health Organisation (WHO), plays a significant role in the identification of cancer causes. As part of its mandate, IARC has classified aspartame as "possibly carcinogenic to humans" (Group 2B). The categorization presented below is predicated upon the limited body of research that tentatively indicates a potential association between the consumption of aspartame and the incidence of hepatic malignancy in human subjects. IARC also says that there isn't a lot of proof about cancer in lab animals and how aspartame might cause cancer. It is essential to acknowledge that the classifications established by the International Agency for Research on Cancer (IARC) are predicated upon the strength of evidence indicating the potential carcinogenicity of a chemical in humans, rather than the likelihood of such an occurrence. Aspartame is classified within Group 2B, representing the third tier among a total of four levels. This phenomenon typically occurs in situations when the available data about cancer in humans is inadequate, rendering certainty elusive. Alternatively, it may arise when compelling evidence of cancer is shown in laboratory animals, although no corresponding evidence is found in human subjects.

6.2.2. Joint FAO/WHO Expert Committee on Food Additives (JECFA). The Joint Expert group on Food Additives (JECFA) is an esteemed international group that operates in collaboration with the Food and Agriculture Organisation (FAO) and the World Health Organisation (WHO). One of the primary functions of the organisation is to assess the safety of food additives. The analysis takes into account all potential health consequences, encompassing the development of cancer as well.

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) conducts evaluations to determine the potential risk of certain adverse effects, such as cancer, in various scenarios. These assessments take into account the nature, frequency, and magnitude of human exposure to a particular food additive.

Based on the findings of a dietary exposure assessment, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) has reached the conclusion that the available research does not provide substantial support for a causal relationship between aspartame use and the development of cancer in people.

Based on the present estimations of dietary exposure, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) has reached the conclusion that the consumption of aspartame through diet does not give rise to any significant health concerns.

6.2.3. Overall conclusions. The Director of the Department of Nutrition and Food Safety for the World Health Organisation (WHO) has provided an evaluation of the assessments conducted by both the International Agency for Research on Cancer (IARC) and the Joint FAO/WHO Expert Committee on Food Additives (JECFA). The conclusion drawn from these assessments is that although safety concerns regarding aspartame are not significant at commonly used doses, there are potential effects that have been identified. These effects necessitate further investigation through more comprehensive and improved studies.

Although the field of knowledge around this topic is always advancing, the American Cancer Society aligns with the recommendation put forward by the International Agency for Research on Cancer (IARC) and other reputable organisations, advocating for further investigation into aspartame and other artificial sweeteners. Furthermore, we persist in conducting independent research endeavours aimed at enhancing our comprehension of the potential association between these factors and cancer. Additionally, our

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investigations aim to contribute to the reduction of cancer risk and the enhancement of preventive measures and healthcare in several domains.

6.3. Food regulatory authorities

Although the primary responsibility of food regulatory bodies does not involve establishing the carcinogenicity of substances, they do consider the available data pertaining to this aspect when assessing the safety of food products and additives.

6.3.1. US Food and Drug Administration (FDA). Government Regulations on Food Additives, such as artificial sweeteners like aspartame, is within the purview of the United States Food and Drug Administration (FDA), which is entrusted with ensuring the safety of these substances within the context of the American food supply.

According to the Food and Drug Administration (FDA), there exists scientific evidence that consistently upholds the FDA's determination that aspartame is deemed safe for the overall population, provided it is manufactured in adherence to acceptable manufacturing practises and utilised within the authorised conditions of use.

6.3.2. European Food Safety Authority (EFSA). The regulation of food additives within the European Union is overseen by the European Food Safety Authority (EFSA). In 2013, the European Food Safety Authority (EFSA) declared, subsequent to conducting a risk assessment, that the intake of aspartame and its resultant byproducts is deemed safe for human consumption within the existing levels of exposure.

7. Conclusion and Expectation

There is currently no solid evidence linking aspartame to any particular health issues, save for those diagnosed with phenylketonuria (PKU). Phenylketonuria (PKU) is an uncommon congenital genetic condition characterised by the inability of the body to metabolise phenylalanine, an essential amino acid abundantly available in several dietary sources, including aspartame. Hence, it is imperative for all items, including medications, that contain aspartame to prominently display the cautionary statement "PHENYLKETONURICS: CONTAINS PHENYLALANINE."

To circumvent the use of aspartame, individuals can conveniently adopt the practise of scrutinising product warnings or perusing ingredient labels prior to purchasing or consuming food and beverages. The presence of aspartame in the product will be indicated in the listing.

A wide range of food and beverage options, including those containing aspartame, can be incorporated into a balanced and nutritious dietary regimen. In 1981, the Food and Drug Administration (FDA) granted approval for the use of aspartame, and subsequently, several health authorities in other nations have recognized the safety of this sweetener. Individuals diagnosed with phenylketonuria (PKU), a hereditary metabolic condition, are advised to refrain from or significantly limit their use of aspartame and other dietary sources containing the amino acid phenylalanine.

Extensive research has been conducted to investigate the impact of aspartame on chronic metabolic disorders such as diabetes and obesity, as well as to explore potential associations between this artificial sweetener and these ailments. Observational studies examining the association between low-calorie sweeteners and weight gain exhibit limitations in establishing causality. The studies in question exhibit certain methodological limitations, including confounding variables and issues of reverse causation. Numerous randomized controlled trials consistently demonstrate that the use of low-calorie sweeteners, such as aspartame, into dietary interventions can effectively facilitate weight loss and weight maintenance. Randomised experiments have consistently demonstrated that aspartame does not exert any discernible influence on glucose or insulin levels. Furthermore, it has been observed that aspartame does not elicit any noticeable effect on hunger. The available evidence about sensitivity to aspartame is limited, and there is a lack of established molecular mechanisms to explain symptoms specifically attributed to aspartame. Numerous investigations have been conducted to ascertain the impact of aspartame on gut microbiota. However, because to its limited consumption and subsequent absorption in the small intestine, the intact form of aspartame is unlikely to reach gut microorganisms.

The importance of maintaining a nutritious and active lifestyle, customised to individual objectives and priorities, cannot be overstated in promoting overall well-being. Opting for food and drink options that are sweetened with low-calorie sweeteners, like aspartame, is a viable strategy for diminishing the intake of added sugars and effectively managing calorie consumption. These practises are crucial in upholding overall well-being and mitigating the likelihood of developing illnesses associated with dietary choices, weight management, and lifestyle factors.

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