



Review Paper

Carcinogens in Aspartame: A Critical Review and Alternatives for Diabetics

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ABSTRACT

Aspartame, which is a widely used artificial sweetener, has always been a topic of controversy due to concerns regarding its potential carcinogenicity. This review article studies the existing scientific literature on the safety of aspartame and if it is associated with cancer risk. We will also explore the alternative sweeteners that are suitable for individuals with diabetes. According to the findings, aspartame does not increase the risk of cancer when consumed within acceptable daily intake limits. However, certain vulnerable populations may need to be cautious. Also, natural, and artificial sweetener alternatives provide safer options for diabetic individuals.

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1. INTRODUCTION

Back in 1965, a chemist named James Sch-latter stumbled upon a substance known as- aspartame. It's this artificial sweetener that acts as a stand-in for sugar. The impressive thing about it is that you only need a tiny bit because it's a whopping two hundred times sweeter than regular old table sugar, sucrose. It can be found in things like soda, chewing gum, desserts, and snacks.¹

The reason it has gained so much popularity is because of its incredible sweetness where you use less and consume fewer calories. Aspartame basically mimics the taste of sugar without piling on those extra calories, which is great for people aiming to control their weight or cut down on sugar. That is why it is used in things labeled as "diet" or "sugar-free," and it's a go-to choice for products designed for people dealing with diabetes.²

Even though regulatory agencies like Food and Drug Administration(FDA) and European Food Safety Authority (EFSA) gave their thumbs up to aspartame after some serious scientific scrutiny, this sweetener just cannot seem to escape the controversy. Some people are

worried it might not be as safe as we thought, with reports about things like headaches and even cancer. The debate is still alive, and researchers are on the case, trying to figure out if there is an actual problem.

With aspartame sneaking into all sorts of foods, it's not just a casual topic. Consumers, healthcare professionals, and researchers all have their eyes on it. So, while we're indulging in our favourite snacks, it's important to stay in the loop about its safety and what other options might be floating around out there. After all, making smart choices about what we put in our bodies is all that is effective.³

A. Controversies Surrounding Aspartame and Carcinogenicity Concerns

Aspartame – The widely used artificial sweetener we often substitute for sugar. It's been under the microscope for a while now, mainly because of worries about whether it's safe to consume. The spotlight has been on its potential to cause cancer.

During the 1970s and 1980s, studies with animals set off alarm bells about aspartame and cancer. The thing is, they gave them more than any

average human would ever eat. In the present times, scientists have looked into this a lot more, using humans and animals, and the initial risks have not shown up again and again.

The FDA and the EFSA – have conducted a large number of tests on aspartame before giving it approval for human use. They reckon it's safe if you're not overdoing it. Even though the science says one thing, there's still a lot of back-and-forth, thanks to what people think and what gets splashed across the news.^{4,5}

The Joint (FAO/WHO) Expert Committee on Food Additives (JECFA) has also thoroughly evaluated the evidence regarding aspartame's potential association with various cancers, including those affecting the liver, breast, and blood. However, the committee has found the results inconclusive, with the ongoing studies often suffering from limitations, such as flawed study designs and reliance on self-reported aspartame intake in dietary records.⁶

Studying the effects of aspartame poses a challenge due to the presence of its breakdown products. Phenylalanine, aspartic acid, and methanol. In food and beverage items. This makes it difficult to pinpoint and identify any issues, with the sweetener during blood tests.

Concerns have been raised regarding methanol, which is a byproduct of metabolism. It is said that methanol can potentially convert into formic acid posing risks such as DNA damage and carcinogenic effects. However, experts argue that the amount of methanol produced from the breakdown of aspartame is extremely small and falls within consumption limits. Consequently, it does not pose any threat of liver cancer.^{1,7}

Despite experts confirming the safety of aspartame there are still lingering concerns and misinformation, among the public. It is therefore essential to launch public awareness campaigns that provide information regarding the safety of aspartame. These campaigns will help address any misunderstandings and enable individuals to make decisions. In order to obtain an understanding of how aspartame affects our metabolic processes and its potential connections to other health conditions further research and studies need to be conducted. The International Agency for Research on Cancer (IARC) also acknowledges the importance of investigation in order to gather evidence and gain a robust global perspective, on the potential health implications of this sweetener.

In conclusion, while controversies regarding aspartame's safety persist, the weight of scientific evidence and regulatory assessments support its safety when consumed within approved limits. Public education, ongoing research, and an evidence-based approach are vital in providing clarity and addressing concerns surrounding aspartame as a sugar substitute.

Objective of the Review Article

The objective of this review article is to conduct a thorough examination of aspartame's safety, mainly about its potential carcinogenicity. The article's main aim is to provide a proper analysis of the animal and human studies, to examine the validity of claims that link aspartame consumption to cancer. By evaluating these methodologies, results, and limitations of relevant research, the review aims to provide a balanced view of the evidence.

This article delves into the history of aspartame, covering its discovery, official approval, and widespread adoption as a sugar substitute. It

explores why aspartame has become so well-liked in various food items and why it's a go-to option for individuals with diabetes and those seeking to cut calories.

Furthermore, the review will address the role of regulatory bodies and scientific organizations in evaluating the safety of aspartame. It will examine the conclusions and recommendations provided by these entities based on comprehensive risk assessments and data reviews.

To offer a holistic perspective, the article will also discuss alternative sweeteners available for individuals with diabetes and those seeking healthier sugar substitutes. By providing information on the benefits and limitations of various alternatives, the review aims to help readers make informed choices about sweeteners that align with their dietary needs and preferences.

Ultimately, this review article aims to help you grasp the debates about aspartame's safety, especially regarding cancer worries. We'll also share science-backed info about using aspartame instead of sugar, particularly for diabetes management and better health.

2. HISTORICAL OVERVIEW AND REGULATORY RESPONSES

Back in the 1970s and later, they did some tests on aspartame using rats, giving them a lot of it. This raised concerns about aspartame possibly causing bladder cancer in rats. But rats are different from humans, and they used way more aspartame than we usually have.

To ease worries and settle public debates, big agencies like the FDA and EFSA did their homework. They looked at all the research available, not just in animals but also in humans. Their main goal was to make sure people are safe and decisions are based on good evidence.

Over time, experts from all around the world kept checking aspartame's safety, considering new studies and info that popped up. They did this to address any concerns people had and give out the right info for public health. And every time they looked; they said aspartame was safe if used as directed.⁸

But in July 2023, a part of the World Health Organization called the International Agency for Research on Cancer IARC said, aspartame might possibly cause cancer, mainly because of some liver cancer hints in studies on humans and rodents. This kind of decision usually sparks more discussions and research.⁹

Aspartame is two hundred times sweeter than regular sugar. You can find it in more than 6,000 things worldwide, from diet drinks to gum, toothpaste, and even chew-able vitamins. The FDA said it's okay to use as a sweetener back in 1974. There's a group called JECFA, and they say you can have about 2,800 milligrams of it per day if you're a typical adult.⁵

Now, IARC group has made calls in the past, like saying stuff like glyphosate, a weedkiller, is "probably carcinogenic" in 2015. That caused some companies, like Bayer in Germany, to deal with lawsuits from individuals who thought it gave them cancer. But sometimes, the IARC gets criticized for making a big fuss about things that are hard to avoid in everyday life.

The IARC has four types of class for substances: carcinogenic, probably carcinogenic, possibly carcinogenic, and not classifiable. Aspartame falls

into the "possibly carcinogenic" category, indicating limited evidence of its potential to cause cancer in humans or sufficient evidence in animals.⁸ In 2019, an advisory group to the IARC recommended a high-priority assessment of various substances, including aspartame, based on emerging scientific evidence. So, the IARC says aspartame might possibly cause cancer, mainly because of three studies that checked out how people drink artificially sweetened stuff. One study in Europe, back in 2014, followed lots of individuals for a long time and found that drinking sweetened drinks, even ones with aspartame, might up the chances of a kind of liver cancer.¹⁰

Another study in the US in 2022 said the same thing, especially for individuals with diabetes who drink artificially sweetened drinks. And a study that ran from 1982 to 2016 in the US said there might be a higher risk of pancreatic cancer for people who sip on these sweetened drinks.¹¹ But there are these industry groups, like the International Sweeteners Association and the International Council of Beverages Associations, who are worried about the IARC's decision. They say it's not complete and could make people worry for no reason. They also say loads of studies show that aspartame is safe, and regulators around the world say it's fine to use.¹²

So, the IARC looked at a whopping 1,300 studies and said they needed more research to really be sure about aspartame and cancer. This might start some big debates about what the IARC should be doing and if sweeteners, in general, are safe.

Now, Pepsi-Co made some changes to their sodas because of all this. They took out aspartame, then put it back in. It shows how tricky it is for the food industry to make things taste good and also be healthy.⁸

There were a couple of studies in France and a study from the Ramazzini Institute in Italy that hinted at a tiny increase in cancer risk from aspartame. But the evidence isn't clear, and some experts have doubts about how the second study was done, according to EFSA.

The WHO, the World Health Organization, said non-sugar sweeteners might not be great for controlling weight. This caused a big stir in the food world because some individuals think these sweeteners help cut down on sugar.

So, because of the IARC's "possibly carcinogenic" label on aspartame, we'll probably see more research happening. But it's also likely to kick up dust about what the IARC should be doing and whether sweeteners are safe. And for regular individuals and companies, it might mean some uncertainty.¹³

3. METHODOLOGY OF CARCINOGENICITY STUDIES

Explores the approach and design of studies investigating the potential carcinogenicity of aspartame in both animal models and human populations.

Animal Research

In studies with animals like rats and mice, scientists give them different amounts of aspartame for a long time to see if it causes tumors or other cancers. There are two main ways they do this:

Chronic Exposure Studies

Animals are exposed to aspartame for a big chunk of their life to evaluate potential long-term effects. Researchers closely monitor the animals for the development of tumors or any signs of carcinogenicity.

Ramazzini Institute Study

Research by the Ramazzini Institute in Italy exposed Sprague-Dawley rats to aspartame for life. The researchers divided the mice into groups and put different doses of aspartame in their diet, from low to high. The study then followed the mice for life and looked at potential cancer changes.

The scientists in the study said they found more lymphomas and leukaemia (types of cancer) in the rats that got a high dose of aspartame. This made people really worried, and the news talked about it a lot. However, the study faced criticism from the scientific community as well due to several experimental design flaws and issues with data interpretation.

But here is the thing to note: Other scientists did not trust this study. They said the rats used in it were already prone to getting tumours even without aspartame. So, it was hard to say if the aspartame really caused those cancers. Plus, the way the study was done didn't follow the usual rules for this kind of testing, and the cancers didn't happen more when they got more aspartame. So, some individuals questioned if the results were really true.¹⁴

National Toxicology Program (NTP) Study (2007)

In the U.S., the National Toxicology Program (NTP). They conducted a study to check if aspartame might cause cancer. They used Sprague-Dawley rats and administered them with different amounts of aspartame in their food for their whole lives. It was made sure to do the study really with precision to fix the problems with previous studies.

They found that the rats that were being administered with aspartame didn't get more tumours or cancer. Their study matched what other big groups like the FDA said before - that aspartame is safe as long as you don't have too much.

In conclusion, while some early studies made the scientists worry about aspartame causing cancer, newer and better studies, like the one from the NTP, say it's safe to use as a sugar substitute.¹⁵

Transgenic Mouse Models

In these studies, scientists use mice that have been specially altered in their genes. These changes help researchers understand how cancer starts and grows. Sometimes, these mice are more likely to get certain kinds of cancer or help scientists look at how cancer works in the body.

Soffritti et al., 2010: In this study, conducted by Soffritti et al. at the Ramazzini Institute in Italy, transgenic mice were used to investigate the carcinogenic potential of aspartame. The mice were genetically modified to carry the Tg.AC (v-Ha-ras) oncogene, which makes them more susceptible to developing skin tumours in response to cancer-promoting agents.

The mice were exposed to aspartame through their diet at various concentrations throughout their lives. The researchers monitored the mice for tumor development and observed their overall health and longevity.

The study reported an increased incidence of lymphomas and leukaemia in the transgenic mice exposed to aspartame, raising concerns about the potential carcinogenic effects of the sweetener. However, like the Ramazzini Institute's rat study mentioned earlier, this mouse study faced criticism from the scientific community due to several experimental design flaws and issues with data interpretation. The findings were not consistent with other studies, and the observed tumours were not dose-dependent, which raised questions about the validity of the results.^{16,17}

Trocho et al., 1998: A while back, a study led by Trocho and team looked at how aspartame gets broken down in mice, both regular ones and ones with some gene tweaks. They were mainly interested in a part of aspartame called methanol, which individuals worried could turn into something bad called formic acid.

They used special mice to see what happened when they had aspartame. They found that these mice had more formic acid and another not-so-good thing called formaldehyde, which can be harmful. But this study didn't directly look at whether the mice got cancer.

Now, when it comes to aspartame and cancer, some studies, like the one led by Soffritti we talked about earlier, have made people worry. But other scientists aren't fully convinced because these studies had some issues, and they don't match what most studies found. The big experts who check this stuff, like the FDA, still say aspartame is safe as long as you don't go overboard.

When it comes to these animal studies, scientists do their best to be careful and fair, but it's important to remember that mice and humans aren't the same. So, what happens in mice might not always be exactly what happens in people, as differences in metabolism and physiology between animals and humans can impact the relevance of the findings to human health.¹⁸

Human Research

Epidemiological investigations stand as pivotal instruments for the examination of plausible associations between the consumption of aspartame and the incidence of cancer within human populations. These studies are conventionally categorized into two primary genres:

a. Cohort Studies

In the domain of cohort studies, researchers undertake the meticulous surveillance of a cohort or group of individuals over an extended temporal expanse. The core objectives encompass the evaluation of these individual's consumption patterns of aspartame and the continuous monitoring of cancer-related outcomes. This methodological approach yields a wealth of protracted data, thereby furnishing invaluable insights into conceivable links between the ingestion of aspartame and the potentiality of cancer risk.

b. Case-Control Studies

Case-control studies, on the other hand, involve the comparative analysis of individuals who have received a cancer diagnosis (termed "cases") with a control group of individuals who have not developed cancer. The principal focus pertains to retrospectively scrutinizing the historical

aspartame consumption of these individuals, thereby striving to discern the existence of an associative nexus between aspartame and the incidence of cancer.

Epidemiological inquiries serve as indispensable instruments for comprehending how the consumption of aspartame might influence the genuine risk of cancer. Nevertheless, these inquiries grapple with a series of challenges, encompassing the accurate quantification of aspartame intake and the requisite adjustment for an array of confounding variables that could potentially exert an influence on cancer risk.

By amalgamating evidentiary support derived from both animal experimentation and human studies, researchers can methodically construct a comprehensive comprehension of the plausible carcinogenicity of aspartame. It is, however, imperative to wield a judicious interpretive lens and systematically assess the cumulative evidence garnered from a myriad of research methodologies, thereby culminating in precise determinations concerning the safety of aspartame for human consumption.¹⁹

4. COMPREHENSIVE REVIEW OF ANIMAL AND HUMAN STUDIES

This involves a meticulous and thorough examination, as well as an in-depth analysis of the entire body of research pertaining to the possible carcinogenic effects of aspartame. This comprehensive assessment encompasses a wide spectrum of studies conducted on both animals and humans.

A. Animal Studies

When it comes to animal studies, a comprehensive review entails a critical evaluation of a variety of experiments conducted predominantly on rodents, notably rats and mice. These studies involved the administration of varying doses of aspartame to observe any potential carcinogenic outcomes. The researchers closely scrutinize the methods employed in these studies, their findings, and any inherent limitations to ascertain whether there exists a consistent pattern indicating that aspartame induces cancer in these animal models.

Key facets of this review encompass an assessment of the doses employed in these experiments, ensuring that they align with levels relevant to human consumption. Additionally, researchers delve into the duration of exposure to aspartame, with a particular focus on chronic or long-term studies, which may offer more profound insights into potential enduring effects.

B. Human Studies

Turning our attention to human studies, a comprehensive review necessitates a comprehensive evaluation of epidemiological investigations. These encompass both cohort studies and case-control studies that explore the potential connection between the consumption of aspartame and the incidence of cancer within human populations.

Researchers meticulously inspect the designs and methodologies adopted in these studies, which include the techniques employed to gauge aspartame consumption and assess cancer-related outcomes. Furthermore, the size and representativeness of the study populations are taken into consideration to determine the robustness and applicability of the findings.

Integration of Evidence

The heart of this review process lies in amalgamating findings from both animal and human studies, culminating in a holistic comprehension of the plausible carcinogenicity of aspartame. Researchers sift through the amassed evidence to pinpoint any recurring trends or potential disparities across diverse research methodologies.

In the pursuit of this review, researchers adopt a discerning approach, rigorously evaluating the strengths and weaknesses inherent in individual studies. Their ultimate goal is to gauge the overall cumulative weight of evidence. The objective here is to draw steadfast and well-substantiated conclusions regarding whether there exists substantial evidence either supporting or negating the hypothesis that aspartame consumption may lead to the development of cancer, spanning both animal models and human populations.

Through this comprehensive review of both animal and human studies, researchers aspire to glean invaluable insights into the potential health ramifications associated with the consumption of aspartame. The integration of evidence originating from various research modalities fosters a balanced and informed evaluation, thereby contributing significantly to a more comprehensive understanding of the safety aspects related to aspartame as a sugar substitute.²⁰

5. PROPOSED CARCINOGENIC MECHANISMS AND BIOCHEMICAL EFFECTS

The researchers are trying to find different ways in which aspartame may interact with cancer development, taking into consideration how our body metabolises it. The breakdown products in the process are aspartic acid, phenylalanine, and methanol. The question here is whether these metabolites have the ability to alter our cell functionalities during biotransformation.

a. Aspartic Acid: This is an amino acid that plays an important role in nerve function and metabolism. Some theories suggest that having too much aspartic acid might overstimulate certain types of receptors, putting stress on those cells.

b. Phenylalanine: This metabolite is also an essential amino acid but there are concerns that having too much phenylalanine in our blood could affect certain enzymes and how our cells function. People who suffer from phenylketonuria, a generic condition must watch their phenylalanine intake.

c. Methanol: Methanol is another important metabolite of aspartame. It gets converted into formaldehyde and eventually into formic acid. Formaldehyde is known to be a cancer-causing substance, but the amount of methanol produced is generally considered safe and within acceptable levels.

Biochemical Effects

Researchers are fixated on finding out how efficiently our bodies can get rid of these metabolites. This is what helps in figuring out if the way aspartame might cause cancer makes any sense. Researchers basically examine how aspartame, and its components break down, get absorbed, and get excreted from body. They also study the tolerance levels of it in human cells to see if their presence can harm our cells or accumulate to become toxic in nature.²¹

It's important to note that while researchers are still getting into finding out the possible links between aspartame and cancer, most experts agree that it is safe when consumed within recommended daily limits. This thorough investigation of any potential connections and their effects on our bodies help us understand aspartame better and supports the idea that it's a safe sugar substitute.

6. REGULATORY AND SCIENTIFIC BODIES' ASSESSMENTS

Let's take a closer look at what the experts and official organizations have to say about the safety of aspartame. These assessments are super important because they guide the rules that keep our food safe and provide us with trustworthy advice on what to eat.

EFSA and Other International Regulatory Agencies:

The European Food Safety Authority (EFSA) holds the onus of appraising the security aspects of dietary supplements in the European Union. Just like its American counterpart FDA, EFSA has painstakingly examined aspartame with continuing conclusions vouching for its safety given predefined ADI norms. A multitude of other governing bodies across nations have also undergone comparable assessments ultimately granting their approval for inclusion of aspartame in consumable items.⁴

FDA Evaluation and Re-Evaluations:

When it comes to food additives, particularly aspartame, it's FDA that we have faith in. They carried out an extensive investigation into its properties back in the early 1980s - poring through the literature like stringent researchers they synthesized substantial knowledge.

This scientific analysis led them to derive a measure called "acceptable daily intake" (ADI) from all of their findings - indicating how much aspartame ingestion per day should be without potential harm. It was a benchmark they endorsed.

Ever since those early days, the FDA has vigilantly continued to scrutinize aspartame - ensuring its ongoing safety for our consumption. Though contemporary studies have risen which could challenge initial conclusions; staying committed firm with their position - openly proclaiming that long as we adhere within their prescribed dosage limits consuming this food additive known is indeed safe.⁵

World Health Organization (WHO) and Joint Expert Committee on Food Additives (JECFA):

The World Health Organization, through the Joint Expert Committee on Food Additives (JECFA), also evaluates the safety of food additives, including aspartame, at the international level. JECFA's expert panel conducts risk assessments based on scientific evidence and recommends ADI levels. The ADI values set by JECFA serve as important references for national regulatory bodies worldwide.

Regulatory and scientific bodies assessments play a crucial role in providing evidence-based information to the public and industry stakeholders. These assessments are grounded in comprehensive evaluations of available research, including animal studies, human studies, and biochemical studies. The consistent conclusion across multiple regulatory agencies and scientific organizations is that aspartame is safe for human consumption within approved limits and does not pose a significant risk of carcinogenicity or other adverse health effects.

By considering the evaluations and conclusions of these reputable entities, consumers can make informed decisions about the use of aspartame as a sugar substitute in their diets, fostering confidence in the safety of approved food additives.²²

7. ALTERNATIVE SWEETENERS FOR DIABETICS

The below are some sugar substitutes that can be helpful for individuals who are managing diabetes. It's important for those with diabetes to carefully monitor their carbohydrate intake to control their blood sugar levels and overall health. Alternative sweeteners provide a low or zero-calorie option to replace traditional sugar, allowing individuals to enjoy sweet-tasting foods and beverages while maintaining their health.

Stevia

Stevia, a natural sweetener that comes from the leaves of the *Stevia rebaudiana* plant. It's pretty accessible, easy to manufacture and convenient to use because it gets its sweetness from compounds called steviol glycosides found in the leaves of the plant. The best part being, stevia would not increase your blood sugar, which is immensely helpful if you're managing diabetes. And the best news is, you can find Stevia in liquid, powder, or granulated forms, so it's a versatile choice for all your cooking and baking needs.

Erythritol

Erythritol is a sugar substitute, and its sweetness comes from the fruits and foods that have gone through fermentation. What's great about Erythritol is that it adds sweetness to the food without causing chaos in our blood sugar levels. Although, when you eat it, it can give your mouth a tingly, refreshing sensation, which can be considered as a flavour addictive and some people may find it less desirable. But it is one of the leading substitutes in the market.

Monk Fruit Extract

Monk fruit extract, also known as *luo han guo*, is derived from the monk fruit, a small green gourd native to Southeast Asia. It contains natural compounds called mogrosides, which provide sweetness without calories or carbohydrates. Monk fruit extract is heat-stable, making it suitable for cooking and baking. It is often used in combination with other sweeteners to enhance sweetness in various products.

Xylitol

Xylitol is an alcoholic sugar substitute with a bit of a natural twist. It is obtained from fruits and vegetables and is even made from birch bark or corn cobs in the lab. Xylitol tastes pretty close to sugar but doesn't increase your blood sugar levels too much. It is widely used to manufacture sugar-free chewing gums and mints. It is found in lots of dental products.

Allulose

Allulose is another important sugar substitute found naturally in small quantities in fruits such as figs and raisins. It has a sweetness like sugar but has a very few calories. It is not completely absorbed by the body, hence there is no significant effect on blood sugar levels. It is widely being used in food products as a sugar substitute, especially in the manufacturing of baked items and ice creams.

Sucralose

Sucralose is a clever sugar substitute. It comes from regular sugar but undergoes chemical modification in the lab, making it impossible for our

bodies to digest. Therefore, you get the sweetness without the guilt of calories or carbohydrates. Plus, it remains stable under high temperature and can be used for cooking, baking, and preparing desserts.

For individuals with diabetes, this sweet transformation opens up a world of flavour without the sugar spikes. Although, it's still crucial to keep an eye on your blood sugar levels and work closely with your healthcare team to keep a safe and effective glycaemic control.^{23,24}

8. DIETARY CONSIDERATIONS FOR DIABETICS AND SUGAR SUBSTITUTES

Importance of Glycaemic Control in Diabetes Management:

Managing diabetes effectively is like maintaining a delicate balance in your body. Imagine your blood sugar levels as a tightrope walker, and glycaemic control is their safety net. This safety net is crucial to prevent the walker, representing your health, from falling into the complications that high blood sugar levels can bring.

Now, let's talk about sugar substitutes. They're like the friendly acrobats in this balancing act. They step in to provide sweetness without tipping the walker off balance. However, not all acrobats are the same; some have unique skills and personalities.

1. Taste Preferences: Just like how people have different tastes in music or movies, they have different preferences for sugar substitutes. Some might enjoy stevia, while others prefer erythritol. It is all about finding your sweet spot.

2. Metabolic Responses: Our bodies are as unique as our fingerprints. Some people's bodies get affected by certain sweeteners, causing minor fluctuations in blood sugar levels.

3. Health Conditions: For those with conditions like Phenylketonuria (PKU), should avoid taking aspartame as the body cannot metabolise the amino acid called phenylalanine from which aspartame is made of. These individuals need to be selective with their choices.

4. Dietary Goals: Some substitutes may help with calorie control, like a weight loss assistant, while others may help you fine-tune your carbohydrate intake which works in different ways to satisfy your needs and give the ultimate result if used in a correct way.

5. Lifestyle Fit: Some sugar substitutes are great for baking; others are perfect for your morning coffee or a quick snack. It is up to the person to decide on their preferred substitute.

So, remember, managing diabetes is a quite challenging task, and sugar substitutes can be your assistants, that can help keep your blood sugar levels in check while satisfying your sweet cravings.

Consideration of Total Carbohydrate Intake

It emphasizes the importance of evaluating the carbohydrate content in foods and beverages when using sugar substitutes, especially for individuals with diabetes. Carbohydrates directly affect blood sugar levels, making balanced carbohydrate intake crucial for glycaemic control and overall well-being. The glycaemic index and glycaemic load are valuable measures to understand how different carbohydrates impact blood glucose levels. While sugar substitutes offer lower-calorie alternatives to sugar, they may not uniformly affect overall carbohydrate content, so considering other carbohydrate sources is essential. Maintaining a balanced carbohydrate intake involves choosing whole, minimally processed foods like fruits, vegetables, whole grains, and lean proteins.

When using sugar substitutes, it's vital to be mindful of the type and amount to avoid excessive consumption and potential digestive issues. In conclusion, understanding the carbohydrate content in foods and beverages, and making informed choices about sugar substitutes, can support dietary goals, glycaemic control, and overall health.²⁵

9. CONCLUSION AND RECOMMENDATIONS

In this section, the review provides a concise summary of the key findings and insights derived from the comprehensive analysis of aspartame's potential carcinogenicity. It reiterates the main points from the historical overview, regulatory assessments, and scientific studies. The conclusion aims to provide a balanced perspective on the controversies surrounding aspartame's safety, emphasizing the current scientific consensus based on rigorous evaluations from regulatory bodies and scientific organizations. The review addresses the concerns raised by early animal studies and clarifies that subsequent human studies have not consistently replicated the observed carcinogenic effects in animal models. It highlights the importance of considering species-specific differences between animals and humans when interpreting study results. Moreover, the conclusion emphasizes the significance of the approved daily intake limits for aspartame, which regulatory agencies consistently confirm as safe for human consumption.¹

Recommendations

To dispel misconceptions and address public concerns, the review may recommend public health authorities and regulatory bodies to prioritize accurate and evidence-based educational campaigns on the safety of aspartame and alternative sweeteners. Public education is vital in promoting well-informed decisions about sugar substitutes.¹

For the General Population

The review may recommend that, based on the existing scientific evidence, aspartame is considered safe for most individuals when consumed within approved limits. It advises the general population to use aspartame as a sugar substitute as part of a balanced diet and to follow national dietary guidelines.⁸

Future Research

The review may suggest that further research is needed to address specific knowledge gaps and uncertainties surrounding aspartame and other alternative sweeteners. This may include additional long-term human studies, research on potential synergistic effects when combining sweeteners, and investigations into the metabolic impact of these sweeteners on various populations.⁹

For Diabetic Individuals

The review highlights various alternative sweeteners, such as stevia, erythritol, monk fruit extract and others, which offer suitable sugar substitutes for individuals with diabetes. The recommendations may include guidance on how to incorporate these sweeteners into their diets safely and effectively while maintaining good glycaemic control.^{23,24}

10. CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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12. REFERENCES

1. Czarnecka K, Pilarz A, Rogut A, Maj P, Szymańska J, Olejnik Ł, et al. Aspartame—true or false? Narrative review of safety analysis of general use in products. *Nutrients*;13(6):1957.
2. Department of Nutrition, Harvard School of Public Health. Low-Calorie Sweeteners [Internet]. The Nutrition Source. 2019. Available from: <https://www.hsph.harvard.edu/nutritionsource/healthy-drinks/artificial-sweeteners/>
3. Cohut M, et al. Has Safety Commission Misled the Public about Aspartame? [Internet]. *www.medicalnewstoday.com*. 2019 [cited 2024 Jan 20]. Available from: <https://www.medicalnewstoday.com/articles/325848>
4. European Food Safety Authority. Aspartame [Internet]. European Food Safety Authority. 2023. Available from: <https://www.efsa.europa.eu/en/topics/topic/aspartame>
5. Center for Food Safety and Applied Nutrition. Aspartame and Other Sweeteners in Food. FDA [Internet]. 2023 Jul 14; Available from: <https://www.fda.gov/food/food-additives-petitions/aspartame-and-other-sweeteners-food>
6. JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES Ninety-sixth meeting. Safety Evaluation of Certain Food Additives

- [Internet]. 2023. Available from: https://cdn.who.int/media/docs/default-source/food-safety/jecfa/summary-and-conclusions/jecfa96-summary-and-conclusions.pdf?sfvrsn=f7b61f6c_4&download=true
7. Aguilar F, Crebelli R, Dusemund B, Galtier P, et al. Scientific Opinion on the re-evaluation of Aspartame (E951) as a Food Additive [Internet]. European Food Safety Authority. 2013. Available from: <https://www.efsa.europa.eu/en/efsajournal/pub/3496>
8. Rigby J, Naidu R, Rigby J, Naidu R. Exclusive: WHO's cancer research agency to say aspartame sweetener a possible carcinogen - sources. *Reuters* [Internet]. 2023 Jun 29; Available from: <https://www.reuters.com/business/healthcare-pharmaceuticals/whos-cancer-research-agency-say-aspartame-sweetener-possible-carcinogen-sources-2023-06-29/>
9. World Health Organization. Aspartame Hazard and Risk Assessment Results Released [Internet]. *www.who.int*. 2023. Available from: <https://www.who.int/news/item/14-07-2023-aspartame-hazard-and-risk-assessment-results-released>
10. Goodman JE, Anneser EG, Khandaker A, Boon DN. The Role of Study Quality in Aspartame and Cancer Epidemiology Study Reviews. *Global Epidemiology* [Internet]. 2023 Dec 1 [cited 2023 Jun 18];

- 5:100110. Available from: <https://www.sciencedirect.com/science/article/pii/S2590113323000135>
11. Davis EW, McCann SE, Joseph JM, Yearly KHK, Fountzilias C, Moysich KB. Sugar sweetened and artificially sweetened beverage consumption and pancreatic cancer: A retrospective study. *Nutrients* 2023;15(2):275.
12. Jolanda van Hal. Sweet relief? Industry Welcomes WHO's Aspartame Safety Reconfirmation but Consumers Left Confused [Internet]. www.foodingredientsfirst.com/. 2023 [cited 2024 Jan 20]. Available from: <https://www.foodingredientsfirst.com/news/sweet-relief-industry-welcomes-whos-aspartame-safety-reconfirmation-but-consumers-left-confused.html>
13. Gregory A. Aspartame Sweetener to Be Declared Possible Cancer Risk by WHO, Say Reports. *The Guardian* [Internet]. 2023 Jun 29; Available from: <https://www.theguardian.com/society/2023/jun/29/aspartame-artificial-sweetener-possible-cancer-risk-carcinogenic>
14. Aguilar F, Charrondiere UR, Dusemund B, Galtier, et al. Updated Opinion on a Request from the European Commission Related to the 2nd ERF Carcinogenicity Study on aspartame, Taking into Consideration Study Data Submitted by the Ramazzini Foundation in February 2009. *EFSA Journal*. 2009 Apr;7(4).
15. Bucher JR, Bristol DW, French JE, Hailey JR, Haseman JK, Herbert RA, et al. NTP Genetically Modified Model Report on the Toxicology Studies of Aspartame (CASRN 22839-47-0) in Genetically Modified (FVB Tg.AC Hemizygous) and B6.129-Cdkn2atm1Rdp (N2) Deficient Mice and Carcinogenicity Studies of Aspartame in Genetically Modified [B6.129-Trp53tm1Brd (N5) Haploinsufficient] Mice (Feed Studies) [Internet]. *PubMed*. National Toxicology Program; 2005 [cited 2024 Jan 20]. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK576265/>
16. BELPOGGI F, SOFFRITTI M, PADOVANI M, ESPOSTI DD, LAURIOLA M, MINARDI F, et al. Results of Long-Term Carcinogenicity Bioassay on Sprague-Dawley Rats Exposed to Aspartame Administered in Feed. *Annals of the New York Academy of Sciences*. 2006 Sep 1;1076(1):559–77.
17. Soffritti M, Belpoggi F, Esposti DD, Lambertini L, Tibaldi E, Rigano A. First Experimental Demonstration of the Multipotential Carcinogenic Effects of Aspartame Administered in the Feed to Sprague-Dawley Rats. *Environmental Health Perspectives*. 2006 Mar;114(3):379–85.
18. The French Food Safety Agency. Opinion on a Possible Link between the Exposition to Aspartame and the Incidence of Brain Tumours in Humans [Internet]. 2002 May. Available from: <https://www.greenfacts.org/en/aspartame/aspartamgb.pdf>
19. Haighton L, Roberts A, Jonaitis T, Lynch B. Evaluation of Aspartame Cancer Epidemiology Studies Based on Quality Appraisal Criteria. *Regulatory Toxicology and Pharmacology* [Internet]. 2019 Apr; 103:352–62. Available from: <https://www.sciencedirect.com/science/article/pii/S0273230019300418>
20. Borghoff SJ, Cohen SS, Jiang X, Lea IA, Klaren WD, Chappell GA, et al. Updated Systematic Assessment of human, Animal and Mechanistic Evidence Demonstrates Lack of Human Carcinogenicity with Consumption of Aspartame. *Food and Chemical Toxicology* [Internet]. 2023 Feb; 172:113549. Available from: <https://www.sciencedirect.com/science/article/pii/S0278691522007475>
21. Chattopadhyay S, Raychaudhuri U, Chakraborty R. Artificial Sweeteners – a Review. *Journal of Food Science and Technology* [Internet]. 2011 Oct 21;51(4):611–21. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3982014/>
22. World Health Organization. Joint FAO/WHO Expert Committee on Food Additives (JECFA) [Internet]. www.who.int. 2023. Available from: [https://www.who.int/groups/joint-fao-who-expert-committee-on-food-additives-\(jecfa\)/about](https://www.who.int/groups/joint-fao-who-expert-committee-on-food-additives-(jecfa)/about)
23. Hugues S. 5 Best Sugar Substitutes for People with Diabetes [Internet]. *Verywell Health*. Verywell Health; 2010. Available from: <https://www.verywellhealth.com/sugar-replacements-for-diabetics-1087191>
24. Sheryl Huggins Salomon. The 9 Best Sugar Substitutes for People with Type 2 Diabetes [Internet]. *EverydayHealth.com*. 2019. Available from: <https://www.everydayhealth.com/type-2-diabetes/diet/sugar-substitutes-for-diabetes/>
25. Gray A, Threlkeld RJ. Nutritional Recommendations for Individuals with Diabetes [Internet]. *Nih.gov*. MDText.com, Inc.; 2019. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK279012/>