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Long-term consumption of aspartame & cancer risk

By Hansini Muppaty

Abstract

Artificial sweeteners, specifically aspartame, are present in everyday modern diets due to their low-calorie content and high level of sweetness. They are often used as sugar substitutes to promote weight loss and manage diabetes. Despite their widespread use and approval by regulatory bodies such as the U.S. Food and Drug Administration (FDA), concerns about the safety and potential carcinogenicity of artificial sweeteners persist. This research paper delves into the controversy surrounding aspartame, which was classified as possibly carcinogenic to humans by the International Agency for Research on Cancer (IARC) in 2023. By reviewing literature and analyzing studies published between 2000 and 2024, this paper explores aspartame's metabolism in the human body, its by-products, and its biological effects. The article also delves into a notable experimental study involving male Wistar albino rats that demonstrated significant biochemical changes, histological liver damage, and gene expression alterations at high doses of aspartame, indicating potential cancer risks. The findings underscore the need for further research to clarify the biochemical and molecular mechanisms linking artificial sweeteners to cancer while emphasizing cautious consumption and reevaluation of safety guidelines.

Introduction

Artificial sweeteners, also known as non-nutritive sweeteners (NSS), are of common use in our daily lives. From a wide range of foods and beverages, these sweeteners are used as an alternative to sugar due to their low-calorie content. They claim to promote weight loss as the body cannot break them down, resulting in zero calories (Sharma et al., 2016). Some of the most common artificial sweeteners used include aspartame (a 200x sweeter than usual sugar), acesulfame potassium (also known as acesulfame-K; 200x sweeter than usual sugar), advantame (20,000x sweeter than usual sugar), and sucralose (600x sweeter than usual sugar) are used in a variety of beverages, dietary products, drugs, and even mouthwashes (Care Health Insurance, 2023). A huge number of diabetic patients also opt for these sweeteners as a substitute for sugar in their diet. However, the safety of these food additives is debated, clashing with the findings regarding their contribution to the etiology of various diseases including the risk of cancer. Although the U.S Food and Drug Administration has approved saccharin, aspartame, acesulfame potassium (acesulfame-K, or Ace-K), sucralose, neotame, and advantame ("Artificial Sweeteners and Cancer," 2023), the breakdown products of these sweeteners have had controversial health and metabolic effects to date.

Aspartame, one of the most common artificial sweeteners, is used in various products since the 1980s including diet drinks, chewing gum, gelatin ice cream, dairy products, breakfast cereal, toothpaste, and medications such as cough drops and chewable vitamins (World Health Organization [WHO], 2023). In 2019, high priority was given for review by the International Agency of Research on Cancer. During a meeting in June 2023, an international expert working group classified aspartame as Group 2B, or "possibly carcinogenic to humans". This category is used when there is either limited, but not convincing, evidence for cancer in humans or convincing evidence for cancer in experimental animals ("Artificial Sweeteners and Cancer," 2023). This paper aims to explore aspartame (L-α-aspartyl-L-phenylalanine, 1-methyl ester) and its potential risk of cancer cell growth.

Methodology

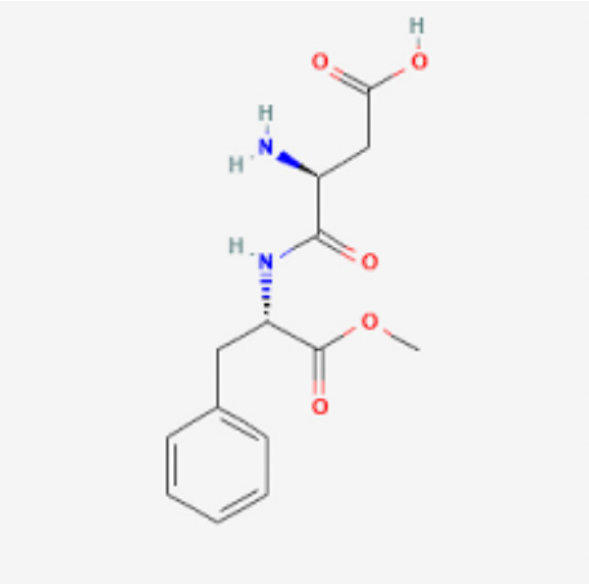
This project included a literature review and analysis, using search engines like Google Scholar, Pubmed, National Cancer Institute, and the National Library of Medicine. These platforms were chosen for their broad coverage of biomedical and scientific literature. When searching for sources, keywords that were used to locate possible sources include *aspartame cancer risk, aspartame carcinogenicity, aspartame animal studies, aspartame and cancer, aspartame mechanism of action, and aspartame epidemiology*. Studies published between January 2000 and August 2024 were included to ensure the review covers recent research and findings. The titles and abstracts of all search results were screened to exclude irrelevant studies. Data was organized into themes that guided the conclusions.

What is aspartame?

James M. Schlatter invented aspartame in 1965 and obtained this compound as a part of research into anti-ulcer drugs. It is approximately 200 times sweeter than regular sugar, while its caloric value, at the concentrations giving the impression of sweetness, is almost zero. According to the FDA, the acceptable daily intake of aspartame for humans is 40 mg/kg body weight in Europe and 50mg/kg body weight in the United States for both adults and children. As many products contain aspartame, both children and adults can unintentionally consume larger amounts

than those recommended by the FDA, which can lead to fatal health complications. Although many studies have been performed to determine the health effects of aspartame, the results of its long-term use remain difficult to predict and its use in pharmaceutical and food products remains controversial (Czarnecka et al., 2021).

Figure 1
Chemical formula of aspartame
(C14H18N2O5)



Note. Source: (PubChem, n.d.-b)

Metabolism of aspartame and its by-products

Aspartame consists of two amino acids, namely L-phenyl ala-nine and L-aspartic acid, and is hydrolyzed and absorbed in the gastrointestinal tract through the action of esterase and peptidases. This process releases 10% of methanol, 40% aspartic acid, and 50% phenylalanine. Prolonged aspartame consumption may be a risk factor as these metabolites can be harmful at high doses. In fact, the metabolism products of aspartame are believed to be more toxic than the original substance itself (Czarnecka et al., 2021). Although many short-term studies have suggested aspartame is safe, an large study assessed the aspartame intake throughout the life span in rats suggested an increased risk of lymphomas, leukemias, and transitional cell carcinomas in a dose-dependent manner within the ranges that are considered safe for human consumption (Aune, 2012).

Methanol is first oxidized in the liver to produce formaldehyde and oxidized again to produce formic acid which is responsible for the destruction of liver cells. In addition, superoxide anions and hydrogen peroxide are formed, which result in protein denaturation and subsequent enzymatic change, all of which are involved in cancer development (Czarnecka et al., 2021). Although they are not direct causes of cancer, they can contribute to cancer through various indirect mechanisms. The role of aspartame in several disorders affecting the human body remains to be investigated.

Influence of aspartame on oxidative stress and antioxidant defence

Excessive intake of aspartame has been linked to oxidative stress, which is an imbalance between free radicals and antioxidants in the body. Excessive intake of aspartame is also linked to cell membrane damage and systemic inflammation in various animal models, specifically, neuronal cell damage, liver injury, and altered kidney function. Deterioration of cell membranes can disrupt normal cell function and contribute to carcinogenesis where cells grow uncontrollably. In the case of liver damage, the liver plays an essential role in detoxifying substances, and its damage can potentially affect how the body processes diverse compounds including possible carcinogens. Even at recommended safe dosages, some studies have reported

oxidative stress and alterations in neurobehavior as well as changes in blood and liver function markers. This suggests that even at safe dosages, aspartame may have biological effects including cancer risk (Griebsch et al., 2023).

While there is evidence that un-suggestible amounts of aspartame can cause oxidative stress and damage to various organs, the direct link to cancer is still unclear and more research is needed to determine whether these effects translate to an increased risk of cancer at standard consumption levels.

Experimental evidence

Alkafafy et al. (2015) investigated the effects of aspartame and saccharin on various biological parameters in male Wistar albino rats. This study occupies an important space in literature as it provides valuable insights into the potential long-term effects of widely used sweeteners. It holds public health relevance and is a controlled experiment conducted by multiple parameters. The depth of analysis, especially regarding gene expression and histopathology, ensures that it remains a crucial reference point for toxicology and public health discussions around artificial sweeteners. Moreover, while many studies focus solely on the biochemical impacts of sweeteners, the inclusion of gene expression data and liver histology makes this study stand out as it explores deeper mechanisms of potential harm that have not been extensively covered in other literature. Other studies on artificial sweeteners or additives may reflect other aspects, such as short-term metabolic responses, alteration of gut microbiota composition, or even psychological consequences like addiction. Such effects are important but may not lead directly to chronic risks such as the induction of cancers or damage to organs. However, this current research draws special interest to the specifics of its relation to cancer pathways and liver damage, a high concern for human health and thus becomes the more compelling case to explore in detail.

The experiment involved aspartame (Cat. No. AL5181-ASPA) and sodium saccharin (Cat. No. AL3367) which were purchased from Alpha Chemika (Mumbai, India) as well as 25 male Wistar albino rats that were 7 weeks old and had an average body weight of 101± 4.8g. The rats were bought from the animal house of the College of Pharmacy, King Saud University, Riyadh, Saudi Arabia, and were acclimatized for 7 days before the experiment. They were maintained at 22°C with good ventilation and a 12 h light/dark cycle.

Having their experimental protocols approved by the Animal Care and Use Committee of Tarif University (Grant No. 434/2514), they began their experiment by feeding a standard pellet diet to the rats along with water ad libitum. The rats were then divided into a control group and four experimental groups with 5 rats per group housed in polycarbonate cages. According to their investigation, “The first and second experimental groups received daily doses equivalent to the ADI of aspartame (250 mg/Kg BW) and four-fold ADI of aspartame (1000 mg/Kg BW).he third and fourth experimental groups received daily doses equivalent to ADI of saccharin (25 mg/Kg BW) and four-fold ADI of saccharin (100 mg/Kg BW).”

Table 1
The different experimental groups along with their doses

Control group	No treatment
Aspartame Low Dose (Asp. L)	250 mg/Kg BW
Aspartame High Dose (Asp. H)	1000 mg/Kg BW
Saccharin Low Dose (Sacch. L)	25 mg/Kg BW
Saccharin High Dose (Sacch. H)	100 mg/Kg BW

Note. Source: (Alkafafy et al., 2015)

The corresponding sweetener was dissolved in water and given to the rats orally daily for 8 weeks. The ADI (acceptable daily intake) was calculated according to human ADI and corrected for rats according to Fernstorm (Alkafafy et al., 2015).

Findings

- Body Weight: Reduced in high-dose sweetener groups compared to controls.
- Biochemical Results: Increased liver enzymes (ALT, ALP) and decreased antioxidant levels (catalase, TAC) in treated groups.
- Gene Expression: Increased h-Ras and decreased P27 expression in sweetener-treated rats.
- Histology: Liver damage including disorganized hepatic parenchyma, congestion, fibrosis, and bile duct hyperplasia, was observed in treated groups.

Results

After careful examination of the body weight assessment, sampling, biochemical assays, and other variable, it is found that aspartame and saccharin led to significant biochemical changes, including elevated enzyme activities and decreased antioxidant levels, histological liver damage, and gene expression alterations indicative of potential cancer risk. Specifically, the study observed overexpression of the oncogene h-Ras and downregulation of the tumor suppressor gene P27 in rats treated with both sweeteners (Alkafafy et al., 2015).

While the current study shares one area of interest with many other studies carried out to investigate the safety of artificial sweeteners, it is distinguished by its exhaustive look into gene expression changes, histopathological features in the liver, and the attentive consideration of both ADI-level and high-dose exposure. It gives deeper insight at the molecular level with respect to chronic consumption of artificial sweeteners in possible carcinogenic risks and liver damage; therefore, it fits into the literature in a rather interesting way.

Conclusion

As the use of aspartame is prominent in most of the population's daily lives, it is important to know the health risks as well as its potential cancer-causing risks. This paper investigates the potential health risks associated with artificial sweeteners, focusing specifically on aspartame. While it is deemed safe by regulatory agencies within acceptable daily intake limits, the evidence from this study suggests that high doses may have adverse effects associated with cancer risks such as oxidative stress, liver damage, and altered gene expression. However, further research is required to elucidate the precise biochemical and molecular mechanisms through which artificial sweeteners might contribute to cancer development. Even though some evidence is not as direct as others, there is still a potential correlation between aspartame and cancer.

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