Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v31i4.5715

"EXPLORING THE CONTROVERSIAL LINK BETWEEN ARTIFICIAL SWEETENERS AND CANCER RISK: A NARRATIVE REVIEW"

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ABSTRACT:
Aspartame is a widely consumed non-sugar sweetening agent used in more than ninety different countries. It is a methoxycarbonyl of apeptidyl of aspartic acid and phenylalanine. It is many times more saccharine than sugar but has very less calories therefore it is widely used in diet or zero-sugar food products. When metabolized in our body it is broken down into diketopiperazine, aspartyl phenylalanine, and phenylalanine. It is a frequently used and studied synthetic sweetening agent. However, there is a controversy related to its possible carcinogenic effect. Some studies have shown it to have some genotoxic and carcinogenic effects. But others have shown no genotoxic or carcinogenic effects of aspartame when ingested. The possible carcinogenic effect of aspartame is controversial for a long time. As aspartame is widely used in daily use dietary products, finding out whether it is safe for human consumption is extremely important. This literature review/study's sole objective is to know about aspartame's possible carcinogenic roles. The search engine used to find articles related to the possible carcinogenic effects of aspartame is PubMed. The keywords used for searching the articles are; aspartame, carcinogenesis, metabolism of aspartame in humans, aspartame as a carcinogen, genotoxicity, genotoxicity induced by aspartame, and artificial sweeteners. The articles are further filtered by the timeline (articles from 2013 – 2023 only). Articles from only the past 10 years are included, which consist of systemic reviews, meta-analyses, research articles, and literature reviews. 27 articles are studied.

Keywords: Aspartame, carcinogen, genotoxicity, artificial sweetener, intake, safe use

INTRODUCTION

Aspartame is a synthetic sugar substitute that is about two hundred times greater in sweetness than sugar. For more than three decades, it has been used as a sweetener in lots of food and beverage items. Chemically it is N-(L-Aspartyl)-L-phenylalanine,1-methyl ester. (1) Over 90 nations have currently authorized aspartame to be consumed as an artificial sweetening agent in different food products.

The U.S. Food and Drug Administration (FDA) defines a food additive as any material that is purposefully added to food. Unless competent experts for their intended use commonly recognize them as safe, or unless their use comes under an exception from the definition of a food additive, such compounds must go through premarket evaluation and clearance by the FDA before they may be used in food products. (2) Despite the fact that natural sweeteners' safety cannot be completely guaranteed, it has become more common to use them due to their purported safety benefits.Aspartame , sucralose, sodium saccharin, and steviol glycosides stand out as among the most widely favored sweetening agents. (3)

The phrase "contains phenylalanine" must be printed on the label of food items that contain aspartame. For those who have phenylketonuria (PKU), this knowledge is crucial. People with PKU, who have a restricted capacity to handle phenylalanine, are cautioned against taking this non-caloric sweetener as one of the byproducts of aspartame metabolism is phenylalanine. Aspartame is widely used as a sweetener and should include a warning on the package that it shouldn't be used in baking or cooking. (4)

Aspartame's genotoxicity and carcinogenicity are now the subject of conflicting research, raising questions about its safety. In order to have a more complete and precise knowledge of its safety profile, it is essential to conduct further genotoxicity and carcinogenicity investigations. (5)

Processing of aspartame within the human body's metabolic system

The Food and Drug Administration and Joint FAO/WHO Expert Committee on Food Additives have formed different acceptable daily intake (ADI) levels for aspartame. The FDA sets its ADI at 50 mg/kg of body weight per day, however JECFA has set it at 40 mg/kg of body weight per day. (6) Aspartame is a dipeptide of L-phenylalanine and L-aspartic acid. It is hydrolyzed in the enteric system with the help of enzymes called esterase and peptidases, and as a result, aspartyl phenylalanine and methanol are formed. Than after further digestion methanol (10%), aspartic acid (40%), and phenylalanine (50%) are formed as by products.These elements are taken up through the mucosal lining of the intestines. (7) Within the liver, methanol is first metabolized into formaldehyde, which subsequently transforms into formic acid. (7) However, this process may lead to the accumulation of harmful substances within cells. (6) Moreover, the conversion of methanol to formaldehyde generates superoxide anions and hydrogen peroxide, causing protein denaturation and changes in enzymatic activity. (8).The primary metabolic pathway of phenylalanine involves its conversion into tyrosine, accompanied by minor quantities of phenylethylamine and phenylpyruvate. Conversely, aspartic acid undergoes metabolism yielding alanine and oxaloacetate. (9) Some individuals are born with phenylketonuria, a genetic condition that impairs the conversion of phenylalanine to tyrosine, and they need to avoid consuming aspartame. In order to guarantee the well-being of individuals with phenylketonuria, the FDA mandates aspartame-containing products to display a tag indicating phenylalanine presence in the product, along with relevant cautionary information. (7)

Genotoxic role of aspartame

For several years, there has been an ongoing debate regarding the potential genotoxic risks of aspartame for humans.Genotoxicity encompasses diverse types of DNA harm, including mutagenicity. Compounds exhibiting genotoxic properties are those that engage with DNA, its associated biological constituents (like the spindle apparatus), or enzymes (such as topoisomerases). (6) The research findings regarding the genotoxicity of aspartame have exhibited inconsistencies. (10)A single investigation examined 24 evaluations documented in 15 scientific publications, primarily employing chromosomal aberration tests. The findings of this study indicated a moderate level of genotoxic risk associated with aspartame. (6) On the other hand, other studies and evaluations, consistently support the notion that aspartame does not possess genotoxic properties. This is further reinforced when considering the collective evidence from more recent publications. (11) In vivo studies, such as bone marrow micronucleus, chromosomal aberration, and comet assays, showing substantial evidence supporting that aspartame has no genotoxic effect in the somatic tissues of animals exposed to it. (12) According to some reports, aspartame exhibited a genotoxic effect on

human lymphocytes when examined using chromosomal aberration and the micronucleus test. The Ames Salmonella microsome test, on the other hand, revealed no mutagenic effect. (10)

Type of Study	Strain & species (number per group)	Route/dose/duration	Parameters evaluated	Genotoxic Findings	Comments	References
Bacterial Mutagenicity Assay	For the Ames mutagenicity testing, Tester strains of Salmonella typhimurium TA97a and TA100 were used. S9 was prepared as well.	Different concentrations of the test chemicals, including ASP, ASK, and saccharin (10, 100, 250, 500, 1,000, and 10,000 g/plate), were then dissolved in distilled water.	**Mutagenicity**	The sweeteners were not mutagenic to either of the S. typhimurium strains TA 97a or TA 100either without S9 or when it is present.	No mutagenic effects on the TA 97a and TA 100 S. typhimurium strains.	(Bandyopadhyay et al., 2008)
Bacterial mutation (Ames) assays	*S. typhimurium* T A98, TA100	50 to 2000 µg/plate. Inclusion of plates in two distinct trials with or without S9.	Mutagenicity	No appreciable increases in the number of TA98 revertants; insignificant increases in the number of TA100 revertants (maximum 1.4-fold, dose-unrelated); biologically relevant	a negligible and not biologically significant increase in TA100 revertants	(Rencüzoğullari et al., 2004)
Bacterial mutation (Ames) assay	5,000 lg per plate of the test strains of S. typhimurium TA98, TA100, TA1535, TA1537, and TA1538 were found both in the presence and the absence of metabolic activation.	10–5000 g per plate. Two distinct experiments used the pre-incubation technique: - & + S9.	Base pair substitution and frame-shift mutation	There was no toxicity, and revertant counts didn't significantly rise.	Genotoxicity was absent.	(Yılmaz & Uçar, 2014)
Micronucleus (MN) tests in bone marrow or blood	Male rat bone marrow (5 males per group)	500–2000 mg/kg/day given orally. Three doses every day, marrow samples taken 24 hours after the final dosage, and 2000 PCE/rat scored for MN	Acute toxicity of the bone marrow	No definite proof of bone marrow toxicity was found, and treated mice didn't develop more MNs.	Rat bone marrow was examined, and no toxicity was discovered.	(Kirkland & Gatehouse, 2015)
Chromosomal aberrations (CA)	Rats of the Holtzman strain's spermatogonia (10 males per group)	400–1600 mg/kg/day administered gastrically. spermatogonia were sampled approximately 29 hours after the last dose, and 500 cells per group were scored for CA.	Chromosomal aberrations	There have been no statistically significant increases in the CA frequency	Absent genotoxicity	(Kirkland & Gatehouse, 2015)
DNA damage (alkaline comet) assays	ddY mice (4 males per group) with glandular spleen, colon, liver, kidney, urinary bladder, lung, brain, and bone marrow	Oral route; 2000 mg/kg. Animals were slain 3 and 24 hours after receiving a single dose, and 50 organs/nuclei/animals were evaluated for comet tail length.	DNA damage	In any of the 8 tissues, DNA migration did not increase.	Absent genotoxicity	(Sasaki et al., 2002)

Carcinogenic role of aspartame:

Aspartame consumption has been linked to potential carcinogenic effects in the body due to its conversion to formaldehyde, a harmful substance known for its carcinogenic properties (13). When an individual consumes 1 liter of diet soda, approximately 600mg of aspartame is converted into about 60mg of formaldehyde (14–16). This amount exceeds formaldehyde's acceptable daily intake (ADI), which is set at 0.15 mg/body weight(kilograms).

Several studies have investigated the potential effects of aspartame on cancer cells. Although it did not induce the HeLa cells lysis at any experimented amounts, it was found to influence gene expression in these cells. Aspartame led to increased the bcl-2 gene (an anti-apoptotic gene) mRNA expression while decreasing the apoptotic genes (p53 tumor suppressor gene and the bax gene) mRNA expression. Furthermore, markers of proliferation, Ki 67, and PCNA, were markedly positively stimulated the mRNA and protein levels, indicating an increase in cancer cell proliferation, a common characteristic of cancer cells(17).

In a study on mice, exposure to aspartame resulted in increased expression of certain oncogenes and the p53 tumor suppressor gene within the kidney, bone marrow, and lymphoid tissues. Elevated gene expression was also observed in the liver, spleen, and lungs, but just with the highest amounts tested (200 mg per kg of body weight). These findings align with previous research indicating an increased incidence of malignant neoplasms, suggesting a potential carcinogenic effect of aspartame (18).

Additional proof seconding the potential cancer causing properties of aspartame was gathered from studies involving rats exposed to aspartame from prenatal age to adulthood. This early-life exposure appeared to enhance the carcinogenic effect of aspartame. Moreover, in rats fed with aspartame, the expression of the H-ras gene manifesteded a dose-dependent rise, while the P27 gene's expression is reduced in liver tissue in comparison to the control group (19,20).

Regarding pancreatic cancer in rodents, aspartame did not seem to influence its occurrence and may even reduce the risk of pancreatic cancers when used as a substitute for glucose. However, there is still ongoing debate about the overall impact of aspartame on cancer risk (21,22)(23).

In men, higher activity of ADH (alcohol dehydrogenase), involved in aspartame metabolism, was linked to a higher vulnerability for non-Hodgkin lymphoma (NHL) and multiple-myeloma. These findings suggest a potential link between aspartame consumption and elevated chances of having NHL and multiple myeloma among males, as well as an increased leukemia risk for both males and females (16).

It is important to note that although studies on rodents and gene expression have raised concerns about the potential carcinogenic properties of aspartame, most research conducted on humans has not definitively established an association between aspartame consumption and cancer risk (21,24). Therefore, while some evidence points to possible carcinogenic effects, the link is not conclusive, and further research is necessary to fully comprehend the impact of aspartame on human health (25)

On the other hand, certain studies have reported that sweeteners, including aspartame (ASP), do not have genotoxic and carcinogenic effects. Specific tests have shown that ASP did not exhibit mutagenic properties for Salmonella typhimurium strains TA98 and TA100, with and without the S9 mix. Additionally, ASP did not cause sister chromatid exchange (SCE) in human lymphocytes, indicating no genotoxicity (26).

Study Type	Strain and species (number per group)	Route, dosage and duration	Parameters assessed	Carcinogenic results	Comments	References
Oral administration	100,442 male & female in CPS-II Group	Beverage intake (Carbonated)	Diet, lifestyle assessment over a follow up span of 10 year	Regular consumption of beverages with artificial carbonation has not been associated with a higher risk of NHL (Non-Hodgkin's lymphoma).	Aspartame consumption did not appear to be associated with an increased risk of NHL (RR:1.02; Cl:0.84, 1.24; P-trend 0.69, top vs bottom quintile).	J Nutr 2014; 144:2041-9
Oral administration	Male & female Albino rats	Given at 0, 1, 2, 4, or 8 g/kg/day; in the high dose group, there was an increase at week 16 from 6 to 7 g/day and at week 144 from 7 to 8 g/kg/day. The study comprised 104 weeks.	Exposure included 60 days of mating, females during gestation and lactation, and exposure to food.	In female rats, no tumor responses associated with exposure to APM were found.	Unrelated to treatment, dosage, or gender, isolated cases of intracranial neoplasms have been reported.	Reno et al., 1973
Full carcinogenicity, oral administration	Albino rats (male and female), Body weights ranging 75 to 108 g for male and 80-102g of female	Weeks 16 and 44 saw increases in the high dose group from 6 to 7 g/kg and 7 to 8 g/kg-bw, respectively. The entire study term lasted 104 weeks.	The consideration of weight applied to both female and male rats.	Both male and female rats had benign and malignant tumors.	Minor reduction in weight	Belpoggi et al., 2006
Cancer Bioassay, oral administration	Male and female Sprague-Dawley rats, 100–150 per sex/group	0, 80, 400, 2000, 10000, 50000, or 100000 (0,4,20,100,500, 2500, 500mg/kg bw); Duration: daily until natural death	Weight	Dysplastic papillomas occurring in the female ureter and renal pelvis. Furthermore, trend analysis showed that the incidence of hyperplasia in the olfactory epithelium increased statistically significantly in both males and females.	There has been a noticeable increase in the trend of malignant tumors, especially lymphomas/leukemia and neoplastic lesions of the ureter and renal pelvis. This increase in tumor incidence occurred within the dosage range of 400 to 10,000 ppm.	Soffritti et al., 2006
Oral administration	Rat, SLC Wistar (Male and Female) 6 weeks of age	0, 1000, 2000, 4000mg/kg/day 104 weeks. Rats who survived were killed at 104 weeks	Organ weight, body weight, hematology, clinical chemistry, tissue assessment, and urinalysis	No tumor responses were associated with exposure to APM in the initial or subsequent exams.	The model involved the expression of the SV40 large T Antigen, which is regulated by the Elastase-1 acinar cell promoter, in the context of neoplastic lesions in order to induce spontaneous formation of pancreatic cancer. Every animal showed signs of tumor growth.	Shibui et al., 2019

Oral administration	Mice (male and female) 50 each	5% m/v through hydration (intake totaling 395.7 g/kg). administered from the fifth to the thirty-sixth week of the trial Duration lasted for 96 weeks.	Body weight, urinalysis, blood biochemistry and organ weight	Tragacanth gum did not demonstrate carcinogenic properties in B5CF mice of either gender	There were no reports of either neoplastic or non-neoplastic lesions	Hagiwara et al., 1984
Oral administration	Mouse, C57BL/6 Ela1-Tag (Male)	Perinatal and transplacental exposure followed by oral administration 0.035% APM is present in drinking water. 21-week period of time	Weight, blood glucose	The author reported that there was no significanr effect on the development, growth, or mortality of pancreatic acinar carcinoma.	Lung bronchiolar/alveolar carcinoma: Male: 15/117, 15/103, 14/62, 15/64, 17/83 (p-value less than 0.05 when compared to control group) Female: 11/102, 19/122, 9/73, 9/64, 6/62	Dooley et al. (2017)
Oral administration		0, 500, 1000, 2000 mg/kg/day Single administration (gavage), animals were evaluated for 24 hours and 48 hours after dosing	Exposure of the bone marrow and body weight	Negative results were reported	Aspartame was reported as non-genotoxic and non-mutagenic	Otobe et al. (2018)

Further investigations using wing spot and comet assays on Drosophila supported these findings, demonstrating that ASP was not genotoxic (27).

Comprehensive reviews assessing the cancer causing and gene damaging influences of aspartame consistently showed that ASP does not cause mutations in bacterial mutation tests and does not exhibit genotoxicity in somatic cells when assessed through bone marrow micronucleus tests, chromosomal aberration tests, and Comet assays (5,28). These findings provide evidence suggesting that aspartame does not pose a genotoxic or carcinogenic risk under the tested experimental conditions. (2)

Regarding epidemiological data, there has been no consistent association with the intake of aspartame (ASP) and the occurrence of hematogenic cancers, brain neoplasms, cancers in gastrointestinal system, breast cancer, prostate cancer, and various other types of neoplasms. Likewise, a study by Marinovich et al. in 2013 indicated that low-calorie sweeteners, including aspartame, were not linked to an increased risk of vascular events and preterm deliveries. These findings suggest that there is no substantial evidence supporting a direct connection between the use of aspartame and these specific health outcomes based on epidemiological findings (29)

As shown by the study conducted by Soffritti et al. in 2014 (30), focusing on the potential carcinogenic effects of aspartame (ASP), the authors emphasize the urgency of reevaluating the current stance taken by international regulatory agencies on this matter. They stress that such a reassessment is essential for public health considerations. The research findings call for a thorough review and reconsideration of existing regulatory positions to address any potential risks associated with aspartame consumption.

Studies investigating the physiological outcomes of small quantities of synthetic sweeteners on cells have showed that aspartame can induce programmed cell death in PC12 cells in a dosage-dependent partner. This process involves an increase in the expression of caspases 8 and 9, as well as cytochrome c. The induction of this programmed cell death is believed to be associated with an enhanced release of cytochrome c in the cytosol through the mitochondrial pathway, which is known to be involved in apoptosis as a response to oxygen toxicity. Additionally, it has been suggested that at higher concentrations, aspartame could also cause the programmed cell death through the death receptor pathway(31).

In a systemic review conducted in 2023, exceeding forty observational researches on humans, twelve experimental animal cancer studies, and over 1360 assay endpoints have been analyzed assessing the potential mechanistic activity of aspartame, comprising of various gene damaging studies adhering to Good Laboratory Practice and test guidelines. The comprehensive body of evidence from these studies does not provide any conclusive or consistent indications of an association between aspartame exposure and the development of any specific type of neoplasm. Furthermore, no biologically plausible mechanism has been found to suggest a causal link between aspartame consumption and carcinogenicity. These findings apply to studies conducted on humans, experimental animals, as well as in vitro mechanistic assays (32)

METHODS:

In this study, we have reviewed 32 articles. The search engine used for data collection is PubMed. We have included all the articles from 2013 to June 2023 (a period of the past 10 years) related to the carcinogenic effects of aspartame. All types of articles are included (systemic reviews, literature reviews, meta-analyses, and experimental research papers). Any article not fitting in the timeline is not included in our research. The terms used for searching the articles include aspartame, carcinogenesis, metabolism of aspartame in humans, aspartame as a carcinogen, genotoxicity, genotoxicity induced by aspartame, artificial sweeteners, and safe use of aspartame.

CONCLUSION:

Aspartame is a widely consumed low-calorie synthetic sweetening agent in a lot of diet/zero-calorie food products. Because of its vast consumption, evaluating the safety of its consumption is extremely important. It is one of the most studied artificial sweeteners and its role in genotoxicity and carcinogenesis has been a topic of interest for a long time. But despite all this, we are not so sure about its genotoxic and carcinogenic roles, as some studies show aspartame consumption to be linked with possible genotoxicity and carcinogenesis while others show no evidence of both. So, further research needs to be done in this regard.

CONFLICT OF INTEREST:

There is no conflict of interest of any of the authors

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