



(RESEARCH ARTICLE)



## Current approaches to the use of artificial sweetener aspartame

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### Abstract

With the recommendation of the World Health Organization (WHO) to reduce the sugar consumption of children and adults to less than 10% of the total energy intake, many people turned to sweeteners. Aspartame (E951), an artificial sweetener, is synthesized from L-phenylalanine or methyl ester of L-phenylalanine with L-aspartic acid. It is an amphoteric dipeptide composed of aspartic acid and phenylalanine. Apart from chemical peptide synthesis, aspartame can also be synthesized enzymatically commercially. 1 gr of it gives 4 Kcal energy. The taste perception of aspartame appears delayed and lasts a long time. Since it is not heat resistant during cooking, it can only be used as a sweetener in cold drinks and food, coffee, tea. Although there were some scientific objections after the introduction of aspartame to the market, animal and human experiments and investigations started to increase. In another study; Consumption of 40, 75, 500 mg/kg/day aspartame have increased oxidative stress parameters and has been reported to damage liver antioxidant capacity. Also, in some other studies in which negative effects on experimental animals were discussed, 250, 500, 1000 mg/kg/day aspartame consumption was found to significantly increase the liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Besides, studies showing that aspartame does not have negative effects on health, 240 mg/kg/day aspartame consumption did not make a significant difference in alanine aminotransferase (ALT) value, and there was no significant difference between the groups in fasting blood glucose with 4% aspartame solution daily consumption. On the other hand, studies on aspartame toxicity also have conflicting results. Some studies using in vivo and in vitro tests have shown that aspartame does not cause genotoxicity, DNA damage, and mutagenesis, but does stimulate chromosome aberrations and micronucleus formation. Many studies have been done to show the safety of aspartame. The European Food Safety Authority stated in its 2013 re-evaluation that aspartame is safe for human consumption at current exposure levels. In a review evaluating the data obtained from aspartame studies, it is supported that aspartame is a safe sweetener when used within the recommended dose limits. For aspartame, this value (ADI) has been recommended as 40 mg/kg body weight/day.

Considering its association with age, gender, personal metabolism, and metabolic diseases, it was concluded that the use of aspartame is safe, with the fact that it has some harmful effects depending on the exposure time and dose.

**Keywords:** Aspartame; Sweetener; Artificial; Dose

### 1. Introduction

With the recommendation of the World Health Organization (WHO) to reduce the sugar consumption of children and adults to less than 10% of the total energy intake, many people turned to sweeteners. Especially diabetics and people with weight problems tend to use sweeteners instead of sugar. Although they are about 200-300 times sweeter than sugar, the low glycemic index and calorie values of artificial sweeteners have made them an alternative to sugar (10).

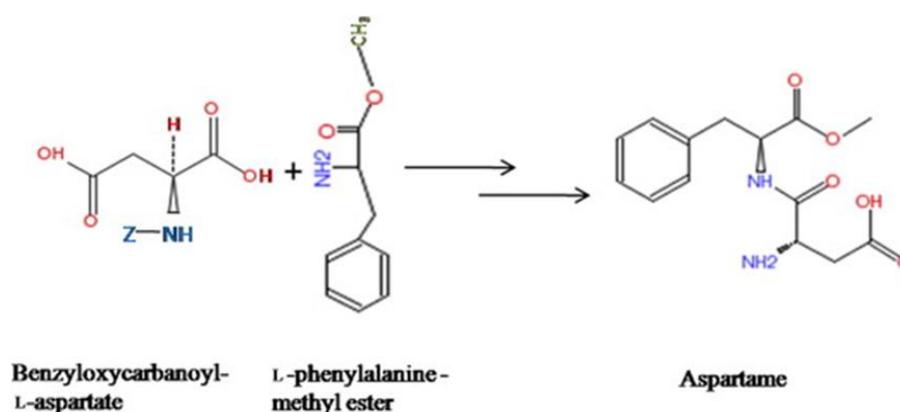
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Aspartame, an artificial sweetener, was discovered in 1965 by James M. Schlatter. Its reliability has been a matter of debate for a long time after it was approved in the USA in 1974. It was approved for use in food products by the FDA for the first time in 1981 as a result of the fact that it has no proven harm in researches (22). Since 2002, the European Food Safety Authority (EFSA) has regularly reviewed the safety of aspartame and has published various opinions on studies on this sweetener in scientific panels. According to EFSA recommendations, the acceptable daily intake (ADI) of aspartame in humans is reported as 40 mg/kg/day. However, this ADI value provided by EFSA is not valid for patients with phenylketonuria, since it is mandatory to follow a diet containing low phenylalanine in patients with phenylketonuria (PKU) (27). After the introduction of aspartame, there were some scientific objections and these objections were examined by animal and human experiments. As before it was approved, these objections focused largely on the hypothetical toxicity that could occur with the administration of extremely high doses of metabolic components and included the potential neurotoxicity of aspartic acid, the potential effects of phenylalanine on brain function, and the potential toxicity of the methanol metabolite formate. Although these objections were resolved satisfactorily by official institutions around the world before the approval of aspartame, preclinical safety paradigms were revised with additional studies after the approval; The ratio of aspartame consumption to the acceptable daily consumption level, its metabolism, aspartate and excitotoxicity, phenylalanine and neurochemistry, methanol toxicity, other adverse effects associated with aspartame, its use in susceptible populations, its effects on weight control were studied (16).

## 2. Aspartame Chemical Structure and Properties

Aspartame (C<sub>14</sub>H<sub>18</sub>N<sub>2</sub>O<sub>5</sub>) (E951), an artificial sweetener, is synthesized from L-phenylalanine or the methyl ester of L-phenylalanine with L-aspartic acid. It is an amphoteric dipeptide composed of aspartic acid and phenylalanine.



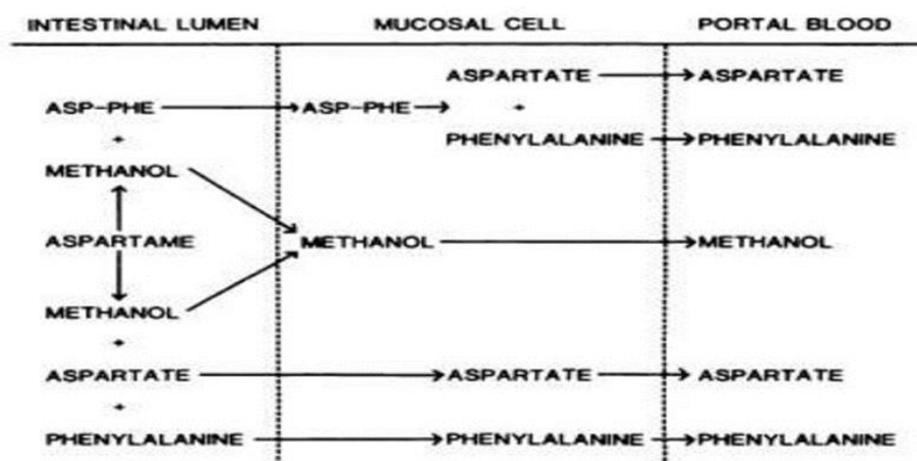
**Figure 1** Aspartame synthesis (13).

**Table 1** General Properties of Aspartame (19)

Chemical Name	N-(L- $\alpha$ -Aspartyl)-L-phenylalanine, 1-methyl ester
Chemical Formula	C <sub>14</sub> H <sub>18</sub> N <sub>2</sub> O <sub>5</sub>
Molecular Weight	294.31 g/mol
Cas Number	[22839-47-0]
Melting point	246-247 °C
Regulatory Status	Often approved as a flavoring and flavor enhancer in foods
Sweetness Intensity Compared to Sucrose	200 x
Glycemic Index	0
Energy (kcal/g)	4
Glycemic Index Acceptable Daily Intake Level (ADI) (mg/kg)	40

1 gr of it gives 4 Kcal energy. The taste perception of aspartame appears delayed and lasts a long time. Since it is not heat resistant during cooking, it can only be used as a sweetener in cold drinks and food, coffee, and tea (7). It is 180 times sweeter than tea sugar. Aspartame dissolves very little in water (1% level at 25 °C). Isoelectric point is pH = 5.2. Its solubility in water is pH-dependent, it has low solubility (1g / 100mL) at and above the isoelectric point. The stability of aspartame is affected by factors such as pH, temperature, and humidity, and aspartyl phenylalanine and methanol form as ester bond hydrolysis in high temperature and acidic environments. Since the products formed during the removal of methanol do not have a sweet taste, the food also causes a loss of sweetness (2). Therefore, the use of aspartame is recommended for products that do not require high temperatures and long-term storage. Considering the humidity and storage, aspartame deterioration was detected in 30 °C and 70% relative humidity for 6 months storage. Also, it was observed that there is less than 2% deterioration when stored at 20 °C and 40% relative humidity for 1 year (7).

Aspartame is metabolized by digestive esterases and peptidases into three normal dietary elements: aspartic acid and phenylalanine the amino acids and methanol. Hydrolysis of the methyl group by intestinal esterases yields methanol oxidized to CO<sub>2</sub> in the one-carbon metabolic pool. The resulting dipeptide is cleaved by dipeptidases on the mucosal surface, and free amino acids are absorbed into the blood (21).



**Figure 2** Aspartame Metabolites (28)

Blood aspartic acid, phenylalanine, and methanol concentrations are well below the level considered potentially harmful. The toxic effects of methanol in humans are due to the accumulation of its metabolite formate. Inhibition of the conversion of phenylalanine, one of the metabolic products of aspartame, to tyrosine is an indicator of an inherited metabolic disorder. Therefore, the individual cannot convert phenylalanine to tyrosine. As a result, different catabolites of phenylalanine occur in the body, and phenylacetic acid is produced. Phenylacetate combines with glutamine in the liver and is excreted in the urine as phenylacetylglutamine. This phenomenon causes mental retardation in phenylketonuria patients and especially in infants. Therefore, these patients should be fed with foods with very low phenylalanine content (26). Studies in phenylketonuria heterozygotes have shown that plasma phenylalanine concentrations are safe even in amounts that are well above the 90% consumption level of aspartame; showed that when these people were given high doses of aspartame for more than 12 weeks, there was no difference in cognitive function and EEG compared to placebo. It has been claimed that phenylalanine in the composition of aspartame can change brain functions, resulting in headache, convulsive (shock) seizures, behavioral, and mood changes. Several metabolism studies in adult humans have shown that administering much higher than typical consumption levels of aspartame (100 times that of the 90% consumption group) results in safe plasma phenylalanine concentrations, with no effect on brain chemistry (5, 23). It was thought that aspartame, especially when taken with foods containing monosodium glutamate, would increase the plasma concentration by combining aspartate and glutamate, which could pose a risk in terms of brain lesions. As a result of the studies, brain lesions in neonatal mice could only be created with extremely high glutamate or aspartate doses; Many human metabolism studies have shown that even if a person always consumes products containing aspartame, even taking it with monosodium glutamate, it is impossible for the plasma aspartate/glutamate/aspartate + glutamate concentration to reach the concentration seen in neonatal mice (5). To produce any increase in blood methanol concentrations, at least 50 mg/kg of aspartame should be taken orally. There was no increase in blood formate concentration, the toxic metabolite of methanol, at 200 mg/kg bolus and 75 mg/kg/day long-term aspartame doses. These aspartame doses are equivalent to an adult consuming 28 liters of soft

drink flavored with 100% aspartame as a bolus and consuming 10 liters of soft drink flavored with 100% aspartame per day for 6 months. In other words, it is impossible for a person to consume the necessary aspartame to increase the blood formate concentration to toxic levels (25).

### 3. Experimental Studies on Aspartame

In a study investigating the effect of aspartame on changes in acetylcholinesterase (AChE) activity in liver, lung, kidney, and brain tissues, rats were given 50, 100, and 200 mg/kg aspartame intraperitoneally. AChE activities were significantly higher in the liver and kidney at all doses at 12 hours following injection. But the same high values were not observed in the lungs and brain. However, activities in the liver and kidney were similar to the control 24 hours after the administration of 200 mg/kg (20). In a study where the adverse effects on experimental animals were discussed, it was found that 250, 500 and 1000 mg/kg/day aspartame consumption significantly increased the liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) (19). In another study; It has been determined that 5-7 mg/kg/day aspartame consumption causes glucose intolerance and impairs insulin sensitivity (18). Contrary to this study, another study found that aspartame, which is used as a low-calorie sweetener, has no negative effects on individuals with diabetes (14). In a study with pregnant mice, mice were given sucrose, saccharin, and aspartame. Plasma glucose, total and LDL cholesterol increased in the Aspartame group compared to the control group. An increase in total and LDL cholesterol was also observed in the sucrose group. Phenylalanine, released as a result of aspartame metabolism, may accumulate in the brain during prenatal development, resulting in permanent changes in hyperphenylalaninemia and neuronal glucose homeostasis in offspring. But; Many metabolism studies in humans have shown that it is impossible for a person to always consume aspartame-containing products, even taking them with monosodium glutamate, to achieve plasma aspartate or glutamate or aspartate + glutamate concentrations to the concentrations seen in neonatal rats (5). Potential carcinogenic effects were detected in the brain of rats following high doses of oral aspartame. In chronic toxicity studies conducted with 0, 1, 2, and 4 g / kg/day aspartame, the incidence of brain tumors in rats given 4 g / kg/day aspartame (6.3%) was found to be higher than the control group (0.8%). In another group, in the chronic toxicity study conducted at the same dose and duration, no difference was found with the control group (24). The risk ratio of developing bladder cancer at a daily dose of all artificial sweeteners (saccharin, cyclamate, aspartame, acesulfame) is given as 2, 12 depending on the use of 10 years or more (3). Analyzes of aspartame and allergic-type reactions have been performed in controlled clinical studies and it has been conclusively shown that aspartame is not an allergen. Animal experiments and in vitro experiments showed that aspartame has no secretory effect on mast cells or basophils; proved to have no effect on inflammation parameters such as connective tissue formation and adjuvant arthritis (6). Since the number of studies on the relationship between aspartame and headache is limited, no definite conclusion can be drawn about the mechanism of action and the risky level. More research is needed on this subject (17). In a study on oxidative stress, aspartame consumption of 40, 75, 500 mg/kg/day increased oxidative stress parameters and was found to damage liver antioxidant capacity. (4, 15). In a study investigating whether daily oral aspartame administration (40 mg/kg) for 2, 4 and 6 weeks caused oxidative stress in the liver and kidneys of male albino rats have studied lipid peroxidation (LPO), glutathione (GSH) levels, superoxide dismutase (SOD), glutathione-S-transferase (GST) and catalase (CAT). A significant increase in the LPO levels was seen in liver tissue. In the kidney, LPO level was low in the 2nd week, while a significant increase was observed in the LPO level at the end of the 6th week. SOD activity decreased in both liver and kidney in all weeks. Catalase activity is decreased in the liver. As a result of this study, it was stated that aspartame may cause oxidative stress in the liver and kidney tissues of male albino rats (9). Ahmad et al. (2020), in a study investigating the effects of aspartame and sucralose on the intestinal microbiome; explained that the daily consumption of oral beverages sweetened with 136 mg/day sucralose or 425 mg/day aspartame in healthy participants did not affect the gut microbiota measurably and, in addition, did not alter the gut microbiota structure. Kanietha Priya and Ganesh Prasath (2018) applied a water-dissolved aspartame diet to volunteer women and men aged 20-30 for two months, and at the end of the study, they showed that systolic and diastolic blood pressure and heart rate increased significantly in subjects consuming aspartame compared to the control group.

### 4. Conclusion

Studies conducted in the early years on the use of aspartame have yielded highly contradictory results. Although many studies have been conducted to date, its effect on human metabolism is still controversial. Phenylalanine formation as a result of metabolic degradation is harmful to people with phenylketonuria disease. For this reason, the FDA has required the warning "Contains phenylalanine" on products containing aspartame (12). Aspartame does not contain calories, making it an attractive alternative for individuals looking to reduce their sugar intake. Although responsible organizations and authorities around the world approve of aspartame consumption, the possibility of gradual emergence of effects due to long-term use should be considered. Its controlled use is recommended against possible

metabolic sensitivity. Experimental studies that will reveal health problems related to aspartame consumption should continue and the results of the studies should be shared with both authorities and consumers.

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## Compliance with ethical standards

### *Disclosure of conflict of interest*

All authors declare that they have no conflict of interest.

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