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The Harmful Effects of Aspartame as a Food Additive on Some Body Organs in Laboratory Animals: A Review Study

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التأثيرات الضارة للأسبارتام كمضاف غذائي على بعض أعضاء الجسم في حيوانات التجارب: دراسة مرجعية

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Abstract

Aspartame is among the most frequently used synthetic sweeteners worldwide, appreciated for its intense sweetness and negligible caloric content. Structurally, it consists of a dipeptide formed by the combination of aspartic acid and methyl ester of phenylalanine. During metabolism, it breaks down into three primary components: aspartic acid, phenylalanine, and methanol. Prolonged or excessive intake of these metabolites has been linked to various toxic responses and potential carcinogenic risks.The present review aims to consolidate findings from experimental animal studies concerning the harmful impacts of aspartame on vital organs, particularly the liver, kidneys, and testes, with attention to both physiological alterations and histopathological manifestations. Reported data indicate a marked elevation in hepatic enzyme activities (AST, ALT, ALP) and renal function indicators (urea, creatinine, uric acid), as well as disturbances in electrolyte balance (Na^+, K^+, Ca^{2+}). In contrast, a reduction in reproductive hormones (FSH, LH, and testosterone) was consistently observed when compared with control groups.Histopathological assessments revealed noticeable degenerative and necrotic lesions in hepatic, renal, and testicular tissues, manifested as cellular degeneration, vascular congestion, inflammatory infiltration, and atrophy of seminiferous tubules. Overall, the available evidence demonstrates that aspartame exerts toxic effects that are dependent on both dose and duration of exposure. The study emphasizes the necessity for further in-depth research to elucidate the biochemical mechanisms underlying these toxicities and advocates for the adoption of safer natural sweetening alternatives.

Keywords: Aspartame, Liver, Kidney, Testis, Artificial Sweetener, Laboratory Animals.

الملخص
يُعدّ الأسبارتام من أكثر المُحلّيات الصناعية استخدامًا على مستوى العالم نظرًا لدرجة حلاوته المرتفعة وانخفاض قيمته الحرارية مقارنة بالسكروز. ويتكون الأسبارتام كيميائيًا من ثنائي الببتيد الناتج عن ارتباط حمض الأسبارتيك بإستر ميثيل للفينيل ألانين، وينتج عن عملية أيضه في الجسم ثلاثة مكوّنات رئيسة هي: حمض الأسبارتيك، والفينيل ألانين، والميثانول. وقد أشارت تقارير علمية متعددة إلى أن الإفراط في استهلاك هذه النواتج قد يسبب تأثيرات سمّية ويُحتمل ارتباطه بخصائص مسرطنة. تهدف هذه الدراسة المرجعية إلى تحليل الأدلة التجريبية المتوفرة حول التأثيرات السُمّية للأسبارتام بوصفه مضافًا غذائيًا على بعض الأعضاء الحيوية في الحيوانات المختبرية، مع التركيز على الكبد والكلى والخصيتين من الجانبين الفسيولوجي والنسيجي المرضي. أظهرت نتائج الدراسات المستعرَضة زيادة ملحوظة في أنشطة إنزيمات الكبد(*AST* ، *ALT*، *ALP*)، وارتفاع مؤشرات وظائف الكلى مثل اليوريا، والكرياتينين، وحمض البوليك، بالإضافة إلى اضطراب مستويات الإلكتروليتات (Na^{+} ، K^{+}، Ca^{+2}) . كما لوحظ انخفاض في تركيز الهرمونات الجنسية(*FSH* ، *LH*، والتستوستيرون) مقارنةً بالمجموعات الضابطة. وعلى المستوى النسيجي، بينت الدراسات حدوث تغيرات مرضية واضحة في أنسجة الكبد والكلى والخصيتين تمثلت في تنكس الخلايا، واحتقان الأوعية الدموية، وارتشاح الخلايا الالتهابية، وضُمور الأنابيب المنوية. وتشير هذه النتائج مجتمعةً إلى أن سمّية الأسبارتام تعتمد على كلٍّ من الجرعة ومدة التعرض. وتخلص الدراسة إلى ضرورة إجراء بحوث مستقبلية معمقة للكشف عن الآليات الجزيئية المسؤولة عن هذه التأثيرات، مع التوصية بتقليل استهلاك الأسبارتام وتفضيل استخدام المُحلّيات الطبيعية الأكثر أمانًا على المدى الطويل.

الكلمات المفتاحية: الأسبارتام، الكبد، الكلية، الخصية، المحليات الصناعية، الحيوانات المختبرية.

Introduction

Food additives are substances intentionally incorporated into food products to improve their flavor, appearance, texture, or shelf life. Among these additives, artificial sweeteners have gained remarkable popularity because they provide intense sweetness with minimal caloric value. Aspartame, one of the most extensively used artificial sweeteners, is estimated to be about 180–200 times sweeter than sucrose, with an energy value of approximately 17 KJ per gram. It is commonly consumed by the general population, particularly individuals with diabetes, athletes, and children. Aspartame is found in over 6,000 commercial products such as jams, chewing gums, soft drinks, baked items, powdered beverages, dairy products, and even more than 500 pharmaceutical formulations (Lohner *et al*., 2017; Al-Hamdani and Al-Kazzaz, 2018; Moubarz *et al*., 2018; Azab *et al*., 2022).

On product labels, it is identified either by name or by the code E951 (Shaher *et al*., 2023), and it is marketed under several trade names including Diet Sweet, NutraSweet, and Canderel. According to both the U.S. Food and Drug Administration (FDA) and the European Food Safety Authority (EFSA), the acceptable daily intake of aspartame ranges between 40–50 mg/kg of body weight to minimize potential toxic effects (Griebsch *et al*., 2023).

Once ingested, aspartame undergoes rapid metabolism in the gastrointestinal tract, yielding aspartic acid, phenylalanine, and methanol. Methanol is subsequently oxidized to formaldehyde and formic acid, both of which are toxic metabolites. Formaldehyde, in particular, is recognized as a potent carcinogen capable of inducing oxidative stress and impairing normal cellular functions. Long-term consumption of aspartame contributes to the overproduction of reactive oxygen species (ROS) and free radicals, which may lead to cellular damage, particularly in renal tissues (Kashif *et al*., 2020). Numerous studies have linked chronic aspartame exposure to metabolic disorders, obesity, fatigue, neurological impairments, and hepatic as well as renal toxicity. Additionally, it has been implicated in carcinogenic processes (Ragi *et al*., 2021). Histopathological findings have demonstrated several hepatic abnormalities, including vascular congestion, hepatocyte swelling and necrosis, fibrosis, and bile duct hyperplasia. Furthermore, aspartame-induced hepatotoxicity has been associated with a decline in antioxidant defenses such as glutathione activity in the liver (Azez *et al*., 2023).

Given its extensive presence in a wide range of food and pharmaceutical products, consumers frequently consume aspartame in considerable amounts, often unknowingly. Hence, regulatory authorities require labeling that states “Contains phenylalanine” to warn individuals with phenylketonuria (PKU), a rare genetic disorder caused by phenylalanine hydroxylase deficiency, against its consumption (Czarnecka *et al*., 2021). For the same reason, aspartame is not recommended for use in high-temperature cooking or baking, since heat can alter its chemical stability. Moreover, excessive intake has been associated with neurological disturbances such as reduced motor activity and neuromuscular imbalance (Zafar *et al*., 2017).

This review was conducted to explore the toxicological consequences of aspartame on key organs, namely the liver, kidneys, and testes, through the synthesis of experimental evidence from recent studies. It highlights both the biochemical and histopathological alterations associated with aspartame exposure in laboratory animals. Relevant studies were collected from databases including PubMed, ScienceDirect, and Google Scholar using the keywords Aspartame, Toxicity, Liver, Kidney, Testes, and Experimental Animals, focusing on research published between 2015 and 2025. The inclusion criteria encompassed peer-reviewed experimental studies assessing biochemical and histological parameters of the aforementioned organs following aspartame administration. Understanding the toxicological implications of aspartame is crucial not only for safeguarding public health but also for advancing Sustainable Development Goal 3 (Good Health and Well-Being), which aims to reduce exposure to harmful chemicals and promote safer food consumption practices in support of sustainable human development.

Chemical and physical properties of aspartame:

Chemically known as N-L-α-aspartyl-L-phenylalanine methyl ester (Butchko *et al*., 2002), has a molecular formula of $C_{14}H_{18}N_2O_5$ Figure (1), and is a white, crystalline powder with a strong, sweet taste. It is composed of two essential amino acids, aspartic and phenyl, and has a molar mass of 294.31 g/mol. Its density is 1.347 g/cm³ and it has a high melting point of 246–247 °C. It decomposes under both alkaline and strongly acidic conditions. Its solubility is affected by changes in pH and temperature, with it dissolving more rapidly in acidic solutions at elevated temperatures (Zafar *et al*., 2017).

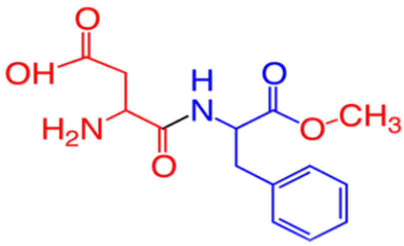

Figure (1): Chemical structure of aspartame (Zafar *et al*., 2017).

Effects of aspartame on body organs:

Children and adults unintentionally consume aspartame in quantities exceeding the FDA-approved limit (Oyama *et al*., 2002), leading to serious health complications due to its metabolites. Aspartame is a unique molecule that is metabolized into three common nutrients (i.e., aspartic acid, phenylalanine, and methanol) by digestive esterase and peptidase enzymes (Harriett *et al*., 2001). The methanol moiety of aspartame is released through the hydrolysis of methyl esters by pancreatic chymotrypsin and is immediately absorbed in the small intestine (Gombos *et al*., 2007). Although methanol itself is not inherently toxic at low doses, its metabolites such as formaldehyde and formic acid have been associated with cellular toxicity in experimental studies (Ells *et al*., 2000; Prokic *et al*., 2014). These metabolites engage with the cytochrome c oxidase enzyme located within the mitochondria, leading to increased microsomal proliferation and the formation of free oxygen radicals (Parthasarathy *et al*., 2006). With the widespread use of aspartame in the modern diet, there is growing interest in understanding its effects on various body systems, including its effect on the fertility of testicular tissue (Magnuson *et al*., 2007), liver tissue, and kidney.

The Effect of Aspartame on the Kidneys:

Several experimental studies have documented the nephrotoxic potential of aspartame through alterations in biochemical and histological parameters. Aruchi *et al*. (2022) reported that Swiss rats administered 50 mg/kg of aspartame daily for 30, 60, and 90 days exhibited elevated electrolyte levels throughout the experimental period. Specifically, potassium, calcium, and sodium ion concentrations were significantly higher in the treated rats than in the control group. Conversely, chloride and bicarbonate levels declined after 30 days of exposure, while bicarbonate concentrations increased after 90 days. These findings suggest that prolonged aspartame intake may disrupt electrolyte homeostasis, potentially contributing to metabolic imbalances among regular consumers.

In another investigation, Usman *et al*. (2022) administered aspartame at doses of 50 and 500 mg/kg daily for seven weeks. Their results revealed a marked rise in serum creatinine and urea levels, particularly at the 500 mg/kg dose, indicating impaired renal function. Moreover, microscopic examination showed mesangial cell proliferation in the kidneys of rats treated with the lower dose (50 mg/kg), whereas those exposed to the higher dose (500 mg/kg) exhibited interstitial lymphoid infiltration, reflecting inflammatory renal injury. Hozayen *et al*. (2014) demonstrated that rats receiving 1000 mg/kg of aspartame by oral gavage every other day for three months showed a significant elevation in serum urea, creatinine, and potassium levels, accompanied by a notable reduction in sodium concentration compared with healthy controls. Histopathological analysis revealed congestion in the sclerotic cortical blood vessels and swelling of the epithelial cells lining the renal tubules, confirming that high-dose aspartame exposure induces marked renal structural damage.

Experimental research consistently demonstrates that aspartame exerts dose-dependent nephrotoxic effects, leading to structural and biochemical disturbances in kidney tissues. According to Azez *et al*. (2023), rats exposed to 40 and 80 mg/kg of aspartame daily for 120 days developed progressive renal lesions. At the lower dose (40 mg/kg), histological analysis revealed mild pathological changes, including tubular necrosis, intertubular hemorrhage, and localized inflammatory cell infiltration. These effects were particularly evident in the glomeruli of the cortical region, where focal necrosis and capillary congestion were observed. In contrast, rats receiving the higher dose (80 mg/kg) exhibited extensive renal tissue damage characterized by widespread necrosis, severe hemorrhage, marked inflammatory infiltration, and glomerular atrophy accompanied by dilated cavities and vascular congestion.

Similarly, Ashok *et al*. (2014) reported that administering 75 mg/kg of aspartame daily for 90 days resulted in significant glomerular degeneration and loss of normal cortical architecture. The renal cortex displayed reduced glomerular volume, while the epithelial lining of the proximal and distal convoluted tubules showed irregular, brush-like deformities, indicating cellular stress and tubular degeneration. Further evidence was provided by Abdel-Ghaffar *et al*. (2021), who administered 40 mg/kg of aspartame orally in drinking water for six months. The treated rats exhibited a substantial rise in serum urea and creatinine levels in both males and females compared to controls. Histopathological observations revealed hemolysis of the glomerular tuft and necrosis of renal tubular epithelium, signifying functional and structural renal impairment. Othman and Bin-Jumah (2019) demonstrated that exposing mice to 500 mg/kg of aspartame in drinking water for one month caused pronounced renal injury. Most renal cells underwent necrosis or degeneration, with others showing chromatin condensation, glomerular shrinkage, and luminal narrowing. Severe congestion, hemorrhage, and partial destruction of the tubular walls were also evident, indicating acute renal toxicity.

Attiya *et al*. (2019) found that rabbits treated with 250 mg/kg of aspartame daily for eight weeks developed markedly elevated serum urea, creatinine, and uric acid levels relative to control animals, confirming the systemic biochemical impact of aspartame on renal function. Consistent findings were also reported by Allam *et al*. (2019), who treated rats with 100 mg/kg of aspartame dissolved in water and administered by gavage for 90 days. Biochemical assays revealed significantly elevated urea and creatinine levels, while histological assessment showed widespread interstitial inflammation, tubular necrosis, and hydropic degeneration. The renal glomeruli appeared atrophic with dilated urinary spaces, and many interstitial blood vessels exhibited dilation, congestion, and occasional thickening of the vascular walls, reflecting chronic kidney injury induced by prolonged aspartame exposure.

Exposure to high doses of aspartame has been shown to induce marked renal dysfunction and structural alterations in male albino rats. Boughdady *et al*. (2025) reported that rats treated with 200 mg/kg daily for six weeks exhibited significant increases in serum urea and creatinine levels, indicating impaired kidney function. Histological examination revealed extensive changes in both renal corpuscles and tubules. Many glomeruli appeared shrunken with dilated Bowman's capsules, while tubules displayed luminal dilation and hollow cytoplasm with punctate nuclei. In some tubules, individual epithelial cells showed degenerated nuclei and eosinophilic staining. Discontinuity of brush borders and basal lamellae was observed in most tubules, glomeruli, and the parietal layer of Bowman's capsule, reflecting widespread structural damage.

Likewise, Desouky *et al*. (2019) observed that administration of 500 mg/kg of aspartame daily for six weeks led to pronounced degenerative changes in renal tissues. The study reported shrinkage of renal corpuscles, destruction of glomerular capillaries, irregularity and dilation of Bowman's capsule, and partial destruction or coalescence of some tubules. Vascular congestion was evident between tubules, and the brush border of proximal convoluted tubules (PCT) was partially lost. Semi-thin section analysis confirmed extensive degeneration, including glomerular capillary destruction, expanded Bowman's space, and widespread loss of tubular brush borders. These findings collectively indicate that high-dose aspartame exposure can severely impair renal architecture and function, with both glomerular and tubular structures being affected.

The effect of aspartame on the liver:

The liver is the central organ responsible for detoxifying, metabolizing, and eliminating both naturally occurring and foreign compounds from the body (Hodgson, 2004). Consequently, any impairment in its normal activity can result in hepatotoxicity and various health disorders. Upon ingestion, aspartame and its metabolites circulate in the bloodstream at elevated levels (Ghanem *et al*., 2023). The liver serves as the main site for their biotransformation, as it plays a crucial role in processing xenobiotic, including drugs and other chemical substances. Continuous intake of aspartame has been linked to the accumulation of methanol and its by-products, which promote oxidative stress in hepatic tissues (Ashok and Sheeladevi, 2012).

Experimental studies further confirm these findings. Usman *et al*. (2022) reported that rats administered 50 or 500 mg/kg of aspartame exhibited significantly higher serum levels of liver enzymes (AST, ALT, and ALP) indicating hepatocellular damage. Histopathological observations revealed marked structural alterations in the liver, including inflammation around portal and lobular hepatocytes, accompanied by lymphocytic infiltration near the portal vein.

Azez *et al*. (2023) found that rats receiving 40 or 80 mg/kg of aspartame displayed hemolysis and pronounced hepatic tissue damage, such as sinusoidal congestion, central vein hemorrhage, hepatocyte necrosis, and infiltration of inflammatory cells. The pathological alterations were more severe in the higher-dose group (80 mg/kg), characterized by widespread congestion, hemorrhage, vacuolar degeneration, localized necrosis, and sinusoidal hyperplasia surrounding the central vein.

Several experimental studies have demonstrated that long-term oral exposure to aspartame may induce various histopathological and biochemical alterations in liver tissues. According to Ashok *et al*. (2014), male Wistar white rats administered 75 mg/kg of aspartame dissolved in sterile saline daily for 90 days exhibited distinct hepatic changes. These included neutrophil infiltration, cytoplasmic microvacuolation, and nuclear condensation within hepatocytes. Similarly, in another experiment where rats received aspartame at 40 mg/kg in drinking water for six months, elevated serum glucose, albumin, total protein, and hepatic enzyme levels (ALP and ALT) were recorded in both sexes. However, AST activity increased significantly only in females. Histological analyses revealed vascular inflammation, endothelial cell degeneration, thrombus formation, hepatic edema with expanded Disse's spaces, and activated Kupffer cells (Abdel-Ghaffar *et al*., 2021). Comparable hepatic toxicity patterns were reported by Hekimoğlu *et al*. (2022), who treated rats with 50 mg/kg and 250 mg/kg of aspartame for ten weeks. Both groups displayed increased serum ALT and AST levels, sinusoidal dilation, and heterogeneity in hepatocyte nuclei. The high-dose group exhibited more severe sinusoidal enlargement and evidence of necrosis, suggesting that prolonged intake of elevated aspartame doses may trigger oxidative stress–induced hepatocellular injury. In another study, Othman and Bin-Jumah (2019) administered 500 mg/kg of aspartame to mice for one month and observed pronounced hepatocyte degeneration and necrosis. The findings included endothelial disruption in hepatic veins, chromatin condensation, cytoplasmic vacuolation, and hemolysis, as well as congestion of the central vein and narrowing of hepatic sinusoids. Lipid droplet accumulation was also evident, indicating the onset of hepatic steatosis accompanied by inflammatory cell infiltration.

Further confirmation of these hepatotoxic effects was reported by Attiya *et al*. (2019), who found that rabbits treated orally with 250 mg/kg of aspartame for eight weeks exhibited elevated serum ALT, AST, and ALP activities, together with increased total protein and decreased albumin levels. Ghanem *et al*. (2023) also reported comparable outcomes in pregnant rats exposed to 40 mg/kg of aspartame from early gestation until weaning. Histological sections revealed damaged hepatocytes with fatty vacuolation, dilated sinusoids, hemorrhagic areas, increased Kupffer cells, and inflammatory infiltration around the congested portal vein. Mild degenerative changes were also detected in the liver tissue of the offspring. El-Shinnawy and Abd Elmageid (2017) observed time-dependent hepatic alterations in male albino rats receiving 75 mg/kg of aspartame for 30 and 90 days. Early lesions included degenerative changes, mild hemorrhage, inflammatory infiltration, and Kupffer cell proliferation, while prolonged exposure caused extensive necrosis, loss of hepatic architecture, multinucleated hepatocytes, lymphocytic accumulation, cytoplasmic vacuolation, and nuclear membrane degeneration. Persistent vascular dilation, endothelial destruction, and hemostasis were also prominent features. It is worth noting that similar hepatic injury patterns have been reported for other hepatotoxic agents. For example, Moubarz *et al*. (2018) found that female rats treated with 50 mg and 150 mg of fentanyl for six months displayed marked hepatic disorganization, degeneration of hepatocytes, cytoplasmic vacuolation, and nuclear necrosis. Although the compound investigated differed, the resulting hepatic histopathology resembles that observed with aspartame exposure; reinforcing the view, that chronic intake of certain xenobiotics can lead to progressive structural and functional liver impairment.

The effect of aspartame on the testicles:

Male fertility is a multifactorial biological process that relies on the coordinated function of the reproductive organs, particularly the testes, which serve as the site of spermatogenesis. Any disturbance in the physiological or biochemical integrity of this system can adversely affect reproductive capacity (Sharpe, 2010). Aspartame, once ingested, undergoes complete intestinal metabolism, yielding aspartic acid, phenylalanine, methanol, and diketopiperazine as its main metabolites. Among these, methanol is subsequently oxidized to formaldehyde and formic acid, compounds known for their high toxicity. Methanol and its derivatives are capable of damaging several organs, including the liver, kidneys, testes, and even the nervous and visual systems (Pohanish, 2002). Experimental evidence indicates that the testes are particularly vulnerable to excessive exposure to aspartame metabolites, notably aspartic acid and methanol, which interfere with spermatogenic activity. Such interference manifests as a reduction in testicular mass and seminiferous tubular diameter, along with the suppression of steroid hormone synthesis in Leydig cells (Nandi *et al*., 1999). Furthermore, increased generation of reactive oxygen species (ROS) in testicular tissue and seminal plasma has been associated with oxidative stress, leading to impaired sperm function and structural damage Gil-Guzman *et al*., 2001).

Several studies have investigated the effects of aspartame on male reproductive function, revealing significant endocrine and histopathological alterations. Hozayen *et al*. (2014) reported that rats administered 1000 mg/kg body weight of aspartame orally every other day for three months exhibited a marked reduction ($P < 0.01$) in serum levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), and testosterone compared to controls. Additionally, aspartame exposure was associated with sperm crystallization within the lumina of certain seminiferous tubules, indicating impaired spermatogenesis.

El-Alfy *et al*. (2023) assessed the histological impacts of aspartame in 25 male albino mice divided into a control group and four experimental groups receiving 250, 500, 750, and 1000 mg/kg orally once daily for one month. The study revealed dose-dependent testicular damage, including seminiferous tubule atrophy, irregular tubule contours, cytoplasmic vacuolation, germ cell exfoliation, and interstitial edema. Higher doses corresponded to more pronounced histological alterations, highlighting a clear relationship between aspartame intake and testicular tissue injury. Similarly, Anbara *et al*. (2020) examined the long-term reproductive effects of aspartame in 36 adult male mice allocated to four groups: a control group and three groups receiving 40, 80, or 160 mg/kg of aspartame daily for three months. The findings demonstrated that prolonged exposure induced significant histochemical changes in testicular tissue, accompanied by alterations in sperm parameters, serum testosterone levels, oxidative stress markers, and histomorphometric indices. Collectively, these results indicate that chronic aspartame consumption can compromise male reproductive function, primarily through mechanisms involving oxidative stress.

Conclusion:

The findings of this review study highlight the need for caution in aspartame consumption, as evidence from multiple experimental studies indicates that excessive or prolonged intake may negatively affect key organs, including the liver, kidneys, and testes. Accordingly, the study recommends moderation in the use of aspartame and suggests considering natural sweeteners as safer alternatives for long-term consumption. Furthermore, these results emphasize the importance of conducting additional experimental and clinical research to elucidate the underlying mechanisms of aspartame's biological effects and to establish safe consumption limits tailored to different age groups and health conditions. Collectively, the findings underscore the necessity of raising public awareness about the potential risks associated with excessive intake of artificial sweeteners, thereby promoting healthier dietary habits and preventing possible adverse health outcomes.

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