



## Histopathological and the Dose Depended Effects of Aspartame toxicity on Liver and Kidney of Rats

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### ABSTRACT

Aspartame is a commonly employed artificial sweetener used by hyperglycemic patients and in food management. Its danger depends on the outcome of previous studies that revealed controversy. The purpose of this study was to look into the histopathological effects of aspartame on renal and hepatic organ tissues in laboratory albino rats. This study used thirty albino rats that were 3 to 4 months old and weighed between 250 and 325 g. They were divided into three groups (ten animals for each group); Group 1 was a control group (food and water ad-libitum). Groups 2 and 3 were treated with aspartame at doses of 40, 80 mg/kg, respectively. All the treatments were administered by using oral gavage once a day for 120 days after the end of the experiment, the organs were collected for histopathological examination. According to dose, results showed the histopathological changes were varied in both the liver and kidney as a result of aspartame administration compared to the control group. The results show that the toxic effects of aspartame in rats treated with 80 mg/kg are greater than those in rats treated with 40 mg/kg, this indicates that the aspartame needs a high dose to create pathological effects. The study concluded that aspartame became more hepatotoxic and nephrotoxic by increasing its dose.

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### INTRODUCTION

The public is progressively more concerned with fitness and physical health, and thus many low-fat, non-weight-bearing dietary choices have been required, including aspartame (Abd Elfatah *et al.*, 2012; Abhilash *et al.*, 2013). No-caloric sweeteners are commonly used nowadays to avoid rising rates of obesity and hyperglycemia and to treat these patients, acting as important tools in helping control caloric ingestion. Aspartame stands out in the middle of all the others (Magnuson *et al.*, 2016). Aspartame is one of the sugar substitutes for diabetics, as well as being used in the desalination of soft drinks and in the manufacturing of anti-ulcer drugs (Fagherazzi *et al.*, 2013; Finamor *et al.*, 2017; Lebda *et al.*, 2017), as well as being a derivative of a dipeptide (L-aspartyl L-phenylalanine methyl ester) that is globally used in diet and beverages to avoid elevating blood sugar and obesity (Butchko *et al.*, 2002).

After the oral ingestion of aspartame, it's absorbed from the intestinal lumen and hydrolyzed to

phenylalanine (50%), aspartic acid (40%), and methanol (10%) (Ranney *et al.*, 1976). Although the Food and Drug Administration (FDA) has approved aspartame for human consumption, it is still considered controversial (Ghosn, 2006). On the other hand; some research indicates that aspartame may cause cancer in mice as a food additive (Liu, 2003; Iman, 2011; Goljan, 2011; Ikpeme *et al.*, 2017).

Aspartame consumption lasts approximately 90 days and causes severe hepatic toxicity by decreasing antioxidant capacity, such as glutathione reduction in the liver (Liu, 2003; Ghosn, 2006; Magnuson *et al.*, 2007; Goljan, 2011; Ikpeme *et al.*, 2017). Histologically, some lesions appeared as a result of aspartame administration, such as congestion of hepatocytes in the region of the central vein with dilatation of the blood sinusoids, death of several hepatocytes, presence of vacuoles in the cytoplasm of hepatocytes, emphysema, hypertrophy of the bile duct, and fibrosis near the vesicles (Parthasarath *et al.*, 2006; Okasha, 2016; Adaramoye and Akanni, 2016; Pandurangan *et al.*, 2016a; Pandurangan *et*

*al., 2016b*). Some studies showed that the hepatic and hereditary system modifications in the liver and bone marrow of white female mice and their newborns result from aspartame consumption (*Pragasam et al., 2005; Parthasarathy et al., 2006*). The kidney is regarded as the organ that plays an important role in the excretion of different waste metabolite products, thus studies have increased on the composition and role of the kidney to estimate the toxic effect of aspartame (*Moubarz et al., 2018; Harpaz et al., 2018*).

Aspartame, on the other hand, is the most contentious simulated sweetener due to its potential toxicity. Under different studies, it was harmless and led to various health problems (*Saad et al., 2014*). It causes acute problems like headache, mood change, dry mouth, dizziness, nausea, and vomiting, it reduces the seizure threshold, and it causes persistent problems like lymphomas and blood cancer. Also, it has been confirmed that neurotoxicity (*Kirkland and Gatehouse, 2015*), genotoxicity (*Smith et al., 2016*), and carcinogenicity (*Finamor et al., 2016*) occurred due to aspartame. Besides, it exerts toxic effects on various sections and organs, excluding the liver (*Ardalan et al., 2017*), kidney (*Dang, 2019*), and pancreas (*Finamor et al., 2014*). In addition, aspartame can cause diabetes (*Martinez-Morales et al., 2015; Choudhary, 2018.*), neurologic and behavioural disorders (*Alkafafy et al., 2015*), and liver cell lesions (*Prokić et al., 2015*).

Moreover, the continual consumption of ASP might cause hypersensitivity reactions and stiffness of blood vessels (*Choudhary and Devi, 2015*). One more study revealed that ASP raises lipid peroxidation and nitric oxide levels, inducing the creation of free radicals that change homeostasis. Also, aspartame has an effect on the reproductive hormones by decreasing the levels of luteinizing hormone, follicular stimulating hormone, and testosterone (*Azeez, 2021*).

The majority of studies have observed that using aspartame for a long time is responsible for oxidation and renal-hepatic toxicity, therefore, the aim of this work was to verify the pathological lesions of the kidney and liver caused by the administration of different doses of aspartame.

## **MATERIALS AND METHODS**

### **Animals**

Male Wistar rats weighing between 250 and 325 g were obtained from the animal house of the Department of Pathology and Microbiology, College of Veterinary Medicine, University of Duhok. The rats were kept in ventilated cages, and their temperature

was kept at 22 ± 2 °C during light and dark cycles. Food and water were given daily. Rats' management and treatment were according to the strategy for laboratory animal care and use (*Azeez et al., 2020*). The study was accepted by the Animal Ethics Committee of the College of Veterinary Medicine, University of Duhok (DR1996919CV approved on June 11, 2019).

### **Experimental Design**

Thirty (30) rats were divided into three groups (10 animals for each group); group 1 was a control group (only received food and water), while groups 2 and 3 were treated with aspartame from Alfa Aesar, Thermo Fisher Scientific, Germany, at a dose of 40 and 80 mg/kg, respectively (*Azeez et al., 2020*). For 120 days, all of the rats were given a single dose orally via gavage.

### **Histopathological Analysis**

After the end of the experiment, the specimens of both liver and kidney from different groups of rats were fixed in 10% neutralized buffered formalin. Then the tissues were dehydrated in ascending concentrations of alcohol, and then in xylene for clearing. For the preparation of paraffin blocks, tissues with a melting point of 54–56 °C were embedded in a pure white paraffin wax. The processed and embedded tissue sections were cut at 4–5 µm with a rotary microtome (Leica, Germany). Finally, the slides were stained with Hematoxylin and eosin (H&E) stains (Luna, 1968). The stained sections will be examined under a field microscope and photographed using a digitally computerized canon camera (Leica, Germany). The histopathological alterations will be analysed and interpreted.

## **RESULTS**

Histological tissue sections with Hematoxylin and eosin from normal kidneys revealed that the kidneys consist of the cortex cortices, which appears as a granular structure because it includes renal pellets, renal tubules, the medulla, and renal hoops. While the renal tubules are characterized by proximal and distal convoluted tubules with a narrow cavity lined by epithelial cells based on a basement membrane (Fig. 1.A). The normal histological structure of the liver of control rats represents the lobular pattern of the central vein, from which radiate the hepatic cords divided by blood sinusoids. The structure of the periphery of the hepatic lobule and the portal tract appears as three regular structures: a branch of the portal vein, bile duct, and hepatic artery. The shape of the hepatocytes appears as a large, polyhedral, and slightly eosinophilic granular cytoplasm (Fig. 1.B).

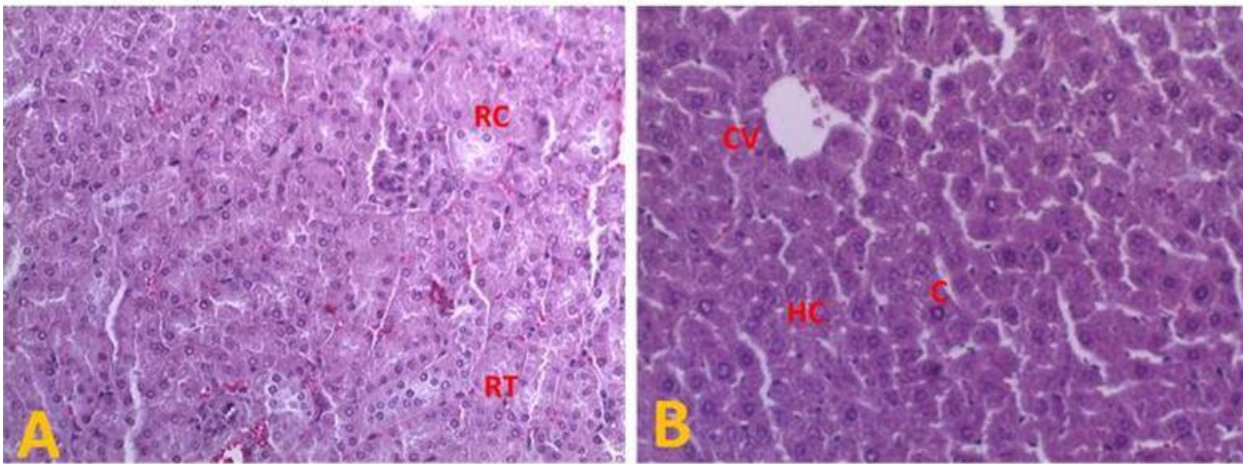


Figure 1: Microphotography of normal kidney tissues. (A) showed normal renal cortex(RC), a medullary rays which are a collection of renal tubules that drain into a single collecting duct that they are formed of close and distant convoluted renal tubules(RT) . Normal liver tissues, (B) showed normal structure of the liver tissues with normal central vein(CV) surrounded by a numbers hepatic cells (HC) and confines among the sinusoids(C).H&E. 100x

The effect of aspartame treatment was evident on the kidney section, which progressed from mild to severe as the dose of aspartame increased from 40 to 80 mg/kg. In groups treated with aspartame 40 mg/kg, mild lesions were evident, consisting of hemorrhage, degeneration of renal tubules, and necrosis with focal infiltration of inflammatory cells between the renal tubules (Fig. 2.A), whereas in section (Fig. 2.B), the effects of aspartame were more clear on the glomeruli specially in the cortex area as hemorrhage, focal necrosis and infiltration of inflammatory cells between the tubules with glomerular tuft.

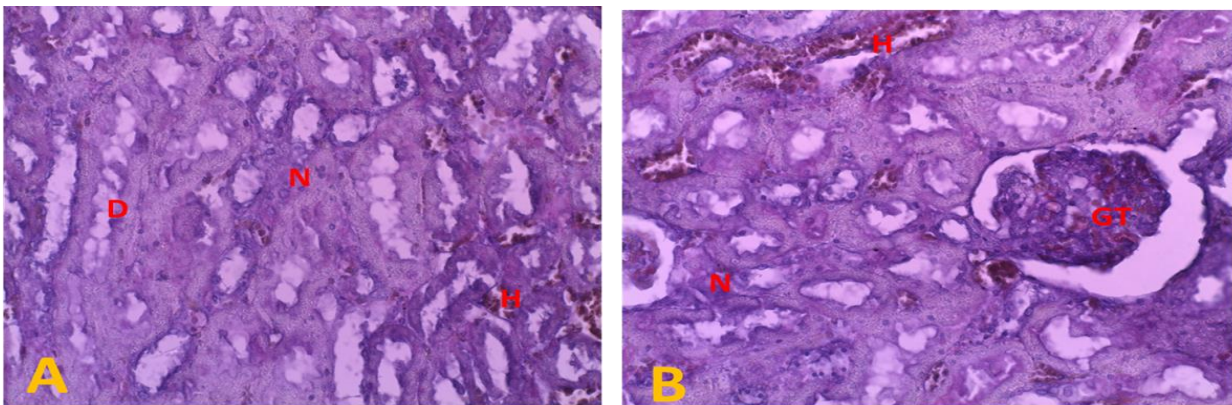


Figure 2: Microphotography of kidney tissues showed microscopical changes of aspartame treated rats with 40mg/kg showed hemorrhage(H) and degeneration (D) in tubular cells lining epithelium, focal necrosis with focal infiltration of inflammatory cells (N) between the tubules and blood vessels in part (A) . congestion and Hemorrhage in stromal cortical blood vessels (H) with focal necrosis(N) and infiltration of inflammatory cells between the tubules, blood vessels of glomerular tuft (GT) in part (B).H&E 200X

The histopathological observation of liver rats received aspartame 40 mg/kg, results showed the degradation and alteration in the structure, with congestion and hemorrhage of sinusoids and central venous as shown in Fig. 3.A as well as there was enlargement, hemorrhage of the liver sinusoids, necrosis of hepatocytes and sever infiltration of inflammatory cells around the central vein as shown in Fig. 3.B. Conversely, in groups of rats that received a higher dose (80 mg/kg) of aspartame, the results revealed more pathological changes such as severe destruction of tissue, severe haemorrhage and necrosis beside severely infiltration of inflammatory cells between tubules and blood vessels as shown in Fig. 4.A. However, the glomerular effects represented as atrophic glomeruli, with widening of their lumens in addition to necrosis, congested of stromal cortical blood vessels and proliferation of inflammatory cells as shown in Fig.4.B.

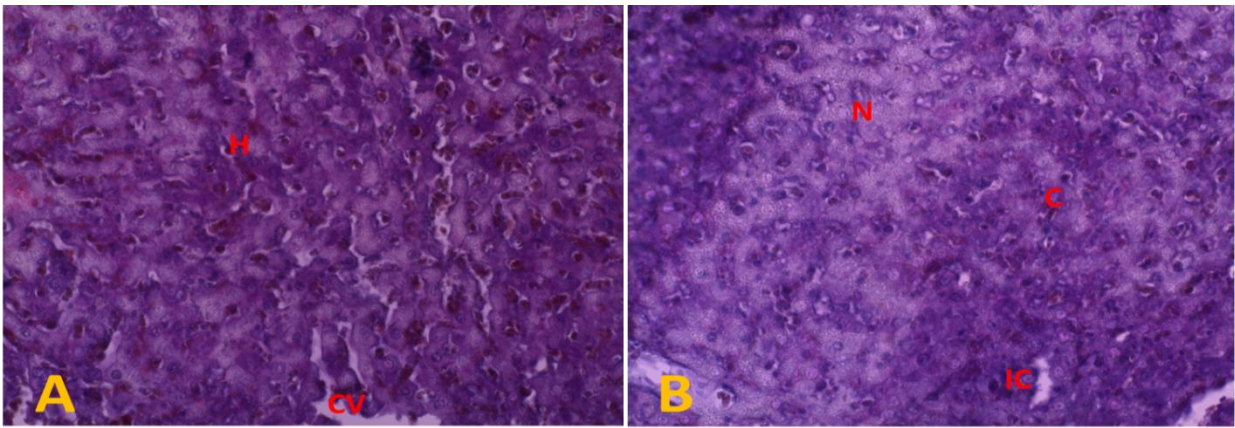


Figure 3: Microphotography of liver tissues showed microscopical changes of liver treated with aspartame 40mg/kg showed congestion and Hemorrhage(H) of sinusoids and central venous(CV) in part (A) with necrosis (N) of liver cells with inflammatory cells (IC)around the central vein, Hemorrhage and enlargement of the hepatic sinusoids(C) in part (B). H&E 200x

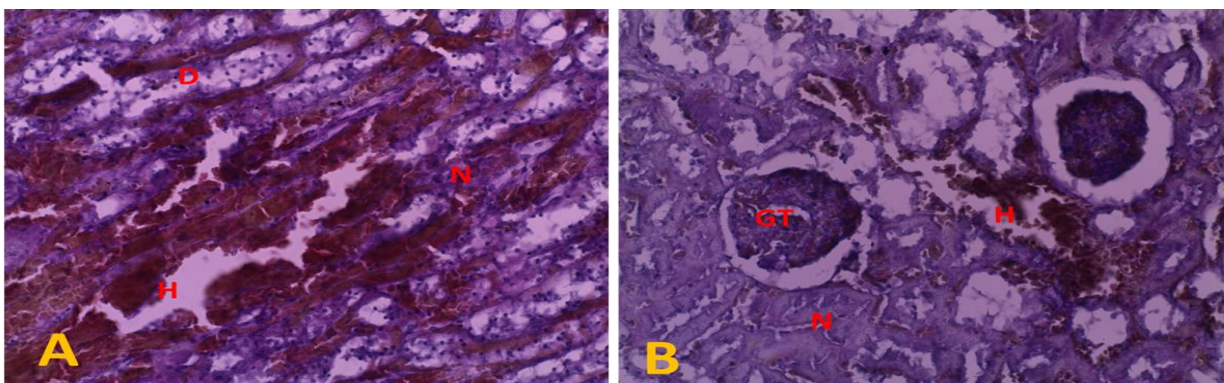


Figure 4: Microphotography kidney tissues showed microscopical changes of aspartame treated rats with 80mg/kg showed sever Hemorrhage(H), sever degeneration (D) in renal tubules, focal necrosis (N) with focal infiltration of inflammatory cells between the tubules and blood vessels in part (A ) and severe congestion and Hemorrhage (H) in stromal cortical blood vessels with focal necrosis (N) and infiltration of inflammatory cells between the tubules, blood vessels of glomerular tuft (GT) in part (B).H&E 200X

Whereas these histological lesions were more manifested in liver sections from rats that received higher doses of aspartame (80 mg/kg), which is represented by severe damage, severe congestion and severe haemorrhage of the sinusoids and central venous (Fig. 5.A) furthermore, the pathological changes showed presence of vacuolar degeneration, local necrosis and saver infiltration of inflammatory cells in some areas around the central vein beside the hemorrhage and enlargement of the hepatic sinusoids (Fig. 5.B).

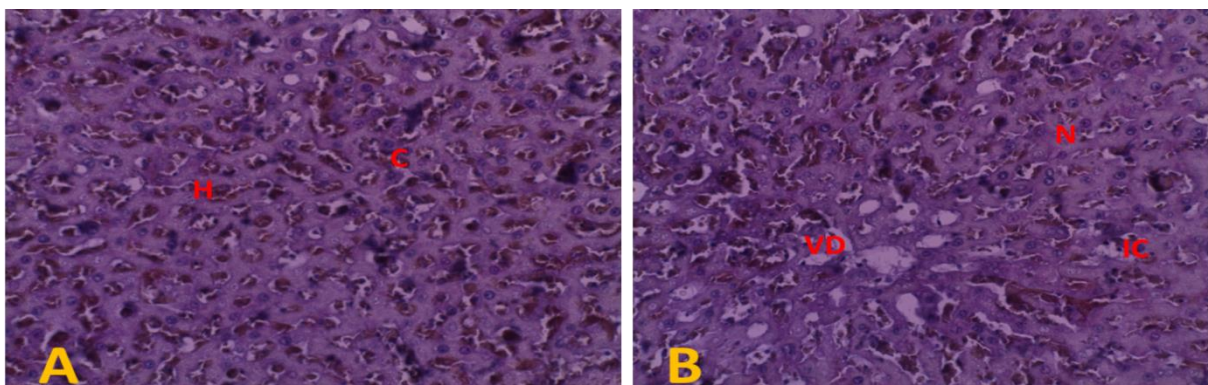


Figure 5: Microphotography of liver tissues showed microscopical changes of liver treated with aspartame 80mg/kg showed sever congestion(C) and Hemorrhage(H) of sinusoids and central venous in part (A) with necrosis (N) and vascular degeneration of liver cells (VD) with inflammatory cells (IC) around the central vein and bleeding and enlargement of the hepatic sinusoids in part (B). H&E 200x

## DISCUSSION

Globally, aspartame is used in diet and beverages to avoid blood sugar elevation and obesity, acting as a tool to aid in caloric intake control; additionally, aspartame is present in over 6,000 food products (Butchko *et al.*, 2002). Therefore, the majority of aspartame consumers are unaware of its potentially negative metabolites and controversial safety (Abhilash *et al.*, 2011). According to past results, from many of researchers was observed that the metabolism of aspartame in the body produces many harmless substances during metabolism that are responsible for oxidation and lead to renal and hepatic toxicity and this is also supported by the results of (Ikpeeme *et al.*, 2016; Pandurangan *et al.*, 2016).

In this research, the treated rats with aspartame at two different doses of 40 mg/kg and 80 mg/kg body weight for 120 days showed high cellular damage, especially in the liver and kidney, as well as it being reported by (Othman and Bin-Jumah, 2019) that oxidative stress plays an essential role in the injury of hepatic and renal cells. The results of the current study revealed that the effects of aspartame were more visible in the kidney section, where there is hemorrhage, narrowing in the glomerular hollow, and extensive destruction in some areas of renal tissues due to congestion of renal tubules as a result of free radical initiation and decline of antioxidant power of the cells through decreasing cellular antioxidant enzymes (Ebaid *et al.*, 2013; Ghosn, 2006). These results are in agreement with the research of Gabr *et al.*, (2011) who conducted that the main side effect of aspartame is nephrotoxicity. Beside the study created by Ashok and Sheeladevi (2015) who confirmed that using of aspartame eating for a long time (90) days caused histopathological alteration in the rat kidney.

The occurrence of most histopathological observation of this study as hemorrhage, congestion and necrosis which is occurred between tubules and blood vessels as well as in the cortical cortex may be due to injury of cells that happened resulted from long time intake of aspartame and this is an agreement with previous study (Othman and Bin-Jumah, 2019) which is showed that these changes can related due to elevated of free-radical creation which can lead to injure to the cell membrane during the peroxidation of unsaturated fatty acids in phospholipids in the cell membrane although another causes of cell death may be due to cell swelling which is concord with (El Haliem and Mohamed, 2011) who reported that aspartame metabolism produce many reactive oxygen species which they exposed to cause harm of cellular DNA and proteins. Damage to mitochondria was also discovered, which causes increased membrane permeability, and ion concentration disturbances occurred in organelles and cytoplasm. This damage

was finally followed by an increase of sodium in the cytoplasm, which later built up water in the cytoplasm and caused cell swelling then cellular necrosis.

The pathological variation of lesions between organs of study via the use of different doses of aspartame includes congestion, haemorrhage of sinusoids and central venous with necrosis, and vascular degeneration of hepatocytes and these may be caused by metabolism of aspartame in the liver, which generates many toxic substances that result in hepatic injury, This is in agreement with (Ikpeeme *et al.*, who have observed that the metabolism of aspartame in the body creates massive lethal agents, the most important being methanol which may be methanol itself or constituents contributing to alterations in the progress of antioxidants and pathological changes in the liver. Adaramoye and Akanni (2016) found that doses of 35 and 70 mg/kg body weight of aspartame caused severe necrosis, severe infiltration of inflammatory cells, congestion, and dilation of the sinusoids in male Wistar rats' liver cells.

However, it was also established that the by-products of aspartame metabolism lead to liver damage by producing reactive oxygen species that harm the composition and function of cell components through oxidation (Fernandez-Checa *et al.*, 1997). This study concluded that the pathological effect of aspartame on liver and renal tissue is dose dependent toxicity.

## CONCLUSION

Although aspartame may have a positive effect on obesity as a low-calorie, non-weight-bearing dietary alternative, histopathological observations for affected tissues confirmed that it has severe cellular toxic effects on the liver and kidney, and that dose is important. The cellular toxic effect was analyzed experimentally which through is observed severe hemorrhage, degenerative changes and necrosis were observed. Therefore, this data is recommended that when using aspartame, it should be taken under medical supervision.

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## Conflicts of interest

The authors acknowledge that there is no conflict of interest regarding the research data and tools used with this study.

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