

# Nephrotoxic Effect of Aspartame as an Artificial Sweetener

## A Brief Review

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Aspartame is one of the most popular artificial sweeteners over the world. Although its consumption is considered to be safe in acceptable daily intake ranges which were set by the United States Food and Drugs Administration and other regulatory agencies, there are lots of controversies regarding its safety nowadays. Some of the recent experimental and epidemiological studies showed that consumption of aspartame may causes some adverse health effects including obesity, metabolic syndrome, and alteration in gut microbiota. Moreover, studies on the nephrotoxic effect of aspartame have increased. A search of several literature databases for publications on adverse effects of aspartame on the kidney function from 1980 to 2016 showed that long-term consumption of aspartame led to a dose-dependent increased production of free radicals in renal tissues as well as kidney injury, based on several studies on animals. However, given the lack of clinical data in this area, it is difficult to make a definitive conclusion regarding nephrotoxic effect of aspartame. Overall, consumers should be aware of the potential side effects of aspartame and other artificial sweeteners. At present it may be recommended that only a minimal amount of them would be consumed.

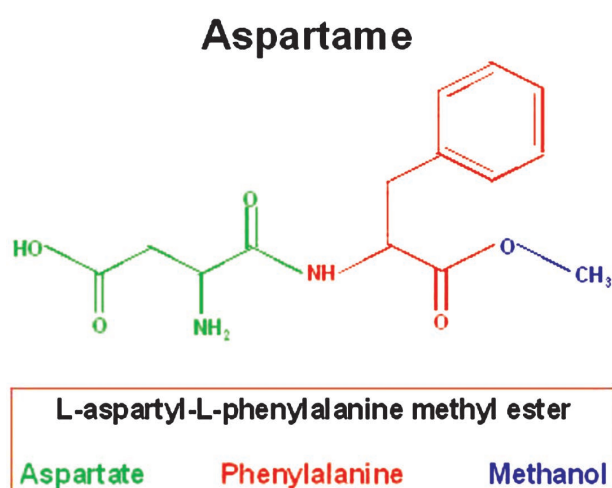
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### INTRODUCTION

Artificial sweeteners are a class of food additives that provide sweet taste without increasing caloric intake. They are also named as 'nonnutritive sweeteners,' 'high-intensity sweeteners,' and 'low caloric sweeteners'.<sup>1-3</sup> Aspartame (L-aspartyl-L-phenylalanine methyl ester) also known as 'NutraSweet,' is one of the most popular synthetic artificial sweeteners over the world (Figure). The global production of aspartame is assumed to be more than 16 000 tons per year.<sup>4</sup> Aspartame is a white, odorless powder, approximately 200 times sweeter than sucrose.<sup>5-7</sup> It is unstable during prolonged heating; therefore, it cannot be used for cooking.<sup>7,8</sup> It was discovered in 1965 and got its initial approval from the US Food and Drugs Administration in 1974.

The Food and Drugs Administration and other advisory agencies have set an acceptable daily intake for each nonnutritive sweetener.<sup>9</sup> The acceptable daily intake of aspartame is 50 mg/kg and 40 mg/kg per day, respectively, based on the United States and the European Union recommendations.<sup>9,10</sup> Although consumption of artificial sweeteners is considered to be safe in acceptable daily intake range, the results of some experimental and epidemiological studies showed that their consumption may cause some adverse health effects including obesity,<sup>11-15</sup> metabolic syndrome,<sup>14-17</sup> alteration in gut microbiota,<sup>18-21</sup> cancer,<sup>22,23</sup> and adverse neurobehavioral effects.<sup>24</sup>

As the kidney has an important role in excretion of various waste metabolites from the body, studies on nephrotoxic effect of artificial sweeteners,



The structure of aspartame.

especially aspartame, have recently increased,<sup>25-31</sup> The present article review summarizes the results of most relevant studies concerning the nephrotoxic effect of aspartame as the most popular artificial sweetener.

### NEPHROTOXIC EFFECT OF ASPARTAME

According to some experimental studies, consumption of aspartame has been linked to kidney dysfunction.<sup>25-31</sup> Saleh<sup>28</sup> and Bahr and Zaki<sup>32</sup> showed that oral administration of drinking water containing 0.25 g/L of aspartame for 60 days significantly increased blood urea nitrogen, serum creatinine, and potassium levels in male rats. Similar findings were also reported by Waggas and coworkers in female rats fed with 50 mg/d and 150 mg/d of aspartame for 6 months, along with significant structural changes in their renal tubules compared to a control group.<sup>30</sup> Moreover, Martins and Azoubel showed that orogastric administration of 14 mg/kg of aspartame to female rats on the 9th, 10th, and 11th days of pregnancy led to some alterations in the development of fatal renal structures.<sup>25</sup> In addition, karyometry and stereology analyses of fetal rats suggested the toxicity of glomerulus, proximal and distal convoluted tubules, and to a lesser degree, the collecting ducts of their kidneys.<sup>25</sup>

To the best of our knowledge such adverse effects by aspartame intake have not been assessed in humans. There are just few conflicting results on the association of artificially sweetened soda with chronic kidney disease. However, it should

be considered that soda is generally acidified using phosphoric acid, which seems to affect the risk of chronic kidney disease.<sup>33,34</sup> Moreover, Chamberlain and colleagues demonstrated that a mixture of aspartame versus sucrose-based liquid with oral sodium phosphate solutions used in colonoscopy had no significant effect on serum sodium, serum potassium, blood urea nitrogen, serum creatinine, and blood urea nitrogen-creatinine ratio. Whereas, serum phosphorous significantly increased in the aspartame-based group compared to the sucrose, which may be due to increasing the phosphate absorption by aspartame or its amino acids.<sup>35</sup>

In contrast to the abovementioned nephrotoxic effects of aspartame, there are some evidence from the in vitro and a few animal studies that aspartame may protect against the cytotoxic and genotoxic effects of mycotoxins such as ochratoxin A in the kidney and other tissues.<sup>36-38</sup> Ochratoxin A inhibits protein synthesis by competition with phenylalanine, which is its structural analogue, as well as induces lipid peroxidation in the tissue. It was reported that aspartame may be effective in washing out the toxin and preventing the morphological and histological damages of the kidney induced by the ochratoxin A in vivo.<sup>36</sup> The protective effects of aspartame on ochratoxin A-induced nephrotoxicity could be mainly due to the delivery of phenylalanine by its cleavage and also the direct effect of the aspartame on the bending capacity and transport of the toxin.<sup>37-38</sup> However, future studies are needed to investigate the direct effect of aspartame and other artificial sweeteners on human's kidney function.

### ASPARTAME AND OXIDATIVE STRESS

Results of experimental studies showed that the administration of aspartame induced oxidative stress and significantly decreased the activity of antioxidant enzymes including superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase in both hepatic and renal tissues of rats.<sup>27-32</sup> Interestingly, some of these articles examined the effect of antioxidant agents such as aqueous extract of Majoram leaves,<sup>30</sup> flaxseed oil and coenzyme Q10,<sup>32</sup> *Pimpinella anisum* oil,<sup>39</sup> and *Zingiber officinale* extract<sup>40</sup> in combination with the aspartame to decrease the observed prooxidant and nephrotoxic effects of aspartame in rodents.

Oxidative stress is characterized by increased level of pro-oxidants such as reactive oxygen species and reactive nitrogen species or decreased level of antioxidants that could lead to cell dysfunction and degradation.<sup>41</sup> It seems that the decreased activity of antioxidant enzymes in aspartame-fed animals might be due to methanol production or some other metabolites. Once ingested, aspartame is metabolized to aspartic acid, phenylalanine, and methanol in the ratio of 50:40:10, respectively, and also a small amount of aspartyl phenylalanine diketopiperazine, especially during its heating.<sup>25</sup> Methanol further oxidized to formaldehyde, which is accompanied by the formation of superoxide anion and hydrogen peroxide in the kidney and some other organs like liver and brain.<sup>2,10, 42-44</sup> The other metabolite, diketopiperazine, seems to be a carcinogen.<sup>45</sup>

Iyyaswamy and Rathinasamy reported a significant increase of plasma methanol level and free radical production after aspartame administration.<sup>46</sup> Moreover, Szponar and colleagues reported a 61-year-old man with suspected methanol poisoning transferred to the Regional Center of Clinical Toxicology, the laboratory tests of whom showed metabolic respiratory acidosis, and investigations revealed that a few days prior to the hospitalization the patient was drinking a great amount of fruit juices sweetened with aspartame and milk (more than 12 liters per day). They concluded that excessive consumption of aspartame might lead to methanol poisoning in this patient.<sup>47</sup>

It seems that humans are more sensitive to the toxic effects of methanol because of the slow methanol oxidation and low liver folate content compared to the other animals, such as rodents.<sup>48</sup> In a recent study, Saleh reported a significant decrease in glutathione level and the activity of glutathione peroxidase and catalase in the kidney tissue of aspartame-fed rats, which was significantly reversed during the administration of folic acid and N-acetyl cysteine.<sup>28</sup> Similarly, Finamor and associates showed the protective effect of N-acetyl cysteine against the oxidative damage of the brain in long-term aspartame-fed rats.<sup>49</sup>

Overall, most of the current data on the nephrotoxic effect of aspartame are based on the results of experimental studies and such adverse effects have not been assessed in humans.

Moreover, one limitation of those animal studies was oral treatment with a high dose of aspartame, consumption of which seems to be unusual by humans. However, future epidemiological studies and clinical trials are needed to investigate the adverse effects of long-term consumption of aspartame at the acceptable daily intake.

In conclusion, based on these observations long-term or high-dose consumption of aspartame may lead to a dose-dependent increase in free radical production and some adverse health effects, including kidney injury, especially in some conditions such as diabetes mellitus, older ages, and intense and prolonged exercise with innately increased production of free radicals. Therefore, consumers should be aware of the potential side effects of aspartame, albeit there is not a conclusive clinical data about those adverse effects.

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#### CONFLICT OF INTEREST

None declared.

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