INTRODUCTION

Food Additives are of two types, Natural: extracted from plants and animals, (usually considered harmless), artificial (these are harmful) comprised of several different types of additives [1]. Food additives are used to improve food quality such as color, taste or appearance [2,3]. Food preservatives are also classified into two main groups: antioxidants and antimicrobials. Antioxidants are compounds that delay or prevent the deterioration of foods by oxidative mechanisms. Antimicrobial agents inhibit the growth of spoilage and pathogenic microorganisms in food [4].

Aspartame is one of the most widely used sweeteners, discovered in 1965, produced commercially from the methyl ester of two amino acids, L-aspartic and L-phenyl alanine [5]. It is approved in Egypt since 1981 [6,7]. However, food and drug administration (FDA) presented a warning label regarding the potential toxicity of aspartame in patients with phenylketonuria and liver diseases [2]. The accepted daily intake recommended by the FDA is 50 mg/kg body weight/day [8].

Monosodium Glutamate (MSG), is the sodium salt of naturally occurring non-essential amino acid L-form of glutamic acid, constitutes about 20% of total amino acids found in natural protein source [9]. MSG is one of the worlds most extensively used food additives, which is ingested as part of commercially processed food [10]. MSG serves as an energy source for certain tissues and as a substrate for glutathione synthesis. Excessive consumption of MSG may cause many symptoms as brain damaging potential, stunted skeletal development, behavioral aberration, neuro-endocrine disorders, and hyperglycemia [9].

The oxidative stress elicited by aerobic metabolism, is a generator for animal and human cells to develop a pervasive antioxidant defense system, which consists of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and glutathione reductase together with a number of low molecular-weight antioxidants such as ascorbate, α-tocopherol and glutathione (GSH), cysteine, thioredoxin, vitamins, etc. [11,12]. Abhilash et al. [13] showed that the activity of reduced glutathione (GSH) was significantly...

ABSTRACT

The objective of the present study is to evaluate the effect of food additives as aspartame (ASP) and monosodium glutamate (MSG) either individually or in combination on body indices and antioxidant parameters, of adult male albino rats. Only ASP treated group showed significant increase in body weight gain and kidney index compared to control. Superoxide dismutase (SOD) and catalase (CAT) activities in the liver were significantly increased in rats of the most treated groups of the tested food additives. Malonaldehyde (MDA) and glutathione (GSH) contents in the liver showed significant reduction in MSG, ASP+MSG and ASP treated groups compared to the control, respectively. The lone administration of ASP and MSG induced marked decrease in the kidney MDA content, compared to the control group. The kidney GSH content was significantly decreased only in ASP+MSG treated group compared to control. The kidney CAT activity was significantly increased in case of rats given mixture of ASP and MSG, while it was not affected in the rest of groups. Positive significant correlation coefficient (r=0.908) between kidney CAT and MDA was observed only for ASP treated group. Brain SOD, CAT and MDA and kidney SOD levels were not varied statistically from the control due to food additives consumption. On contrary, the brain SOD activity was significantly inhibited from the control after treatment with MSG. Therefore, the consumption of the tested food additives induced harmful changes in the antioxidant status of the rat. So, its consumption should be restricted.

Keywords: Aspartame, Monosodium glutamate, Body weight, Antioxidant parameters.
reduced in the liver of rats received aspartame, but no significant changes were observed in (SOD) and catalase (CAT) activity. On the other hand Mourad found that daily oral administration of ASP (40 mg/kg) for 6 weeks induced oxidative stress in the liver and kidney of male albino rats with concomitant increased SOD activity and reduced GSH content in the liver tissue. Prokic et al. [14] reported that chronic ASP administration to rats, caused enhancement in the concentration of reduced GSH and the activity of CAT, which is an indication of oxidative stress in erythrocytes. It also induced a significant increase in the activity of SOD, glutathione peroxidase levels (GPx), and CAT activity [15]. While Saleh and Finamor et al. [16,17] found that there was a decrease in GSH levels induced by long-term consumption of the artificial sweetener. Lebda et al. [18] found that rats treated with ASP showed significant increase in the hepatic MDA concentration, significant decrease, in the hepatic GSH concentration, CAT and SOD in rats that received ASP, compared to control.

Elsabagh et al. [19] showed that there are pathological changes in the brain of rat increased from mild to severe by increasing the concentration of MSG which led to damage of the brain cells. Abdel-Reheim et al. [20] found that there is a decrease in CAT, GSH, and SOD in liver and kidney of MSG treated rats. Some investigators reported that ingestion of MSG induced oxidative stress and halt the antioxidant defense [21-25].

The available data exploring the antioxidant defense of rat given ASP and MSG at or below the acceptable daily intake is insufficient. Furthermore, that of their combination is unavailable. Therefore, the present work was carried.

**MATERIALS AND METHODS**

**Experimental Animals**

The present study was carried out on adult male albino rats, (weighing 120 ± 10 g). The animals were obtained from Helwan Farm of Egyptian Organization for Vaccine and Biological Preparations. They were acclimatized for 10 days in well-ventilated room under controlled laboratory conditions. After that, rats were randomly divided into 4 experimental groups (5 in each) and supplied with diet and water ad libitum. Animals were handled in the laboratory following the standard principles of laboratory animal care.

**Experimental Groups and Tissue Sampling**

**Group I (control group):** Rats in this group received a daily oral dose of 1 ml of distilled water for one month.

**Group II (ASP treated group):** Rats in this group received a daily oral dose of ASP 0.13 g (dissolved in 1 ml of distilled water) per kg of body weight for one month.

**Group III (MSG treated group):** Rats in this group received a daily oral dose of MSG 0.13 g (dissolved in 1 ml of distilled water) per kg of body weight for one month.

**Group IV (ASP+MSG treated group):** Rats in this group received a daily oral administration of ASP 0.13 g + MSG 0.13 g (dissolved in 1 ml distilled water) per kg of body weight for one month.

The examined food additives structure and sources were described earlier by El-Ezaby et al. [26]. At the end of the experimental period, rats were fasted overnight. The animals of each group were weighed, anaesthetized by ether inhalation and then blood samples were collected in dry glass tube using a syringe. Serum was separated by centrifugation at 3000 rpm for 15 min, then it was stored at -20°C until analysis.

**Determination of Body Weight Gain and Relative Organ Weights**

The average body weight of the animals was recorded at the beginning of the experiment and at the end of the experimental time, the difference between them is the body weight gain (g). Organs (Brain, Liver and kidney) were removed at the end of the experimental period, weighed and relative organ weights were calculated as follows: Relative organ weight=(weight of each organ by g / total body weight by g) × 100.

**Determination of Antioxidant Parameters**

Liver, kidneys and brain were removed from dissected rats. Two hundred and fifty mg of each tissue was kept in 1 ml of phosphate buffer saline (PBS) and homogenized by using homogenizer, then centrifuged by using cooling centrifuge (at -4°C, and 10000 rpm), then supernatant was removed for antioxidant parameters determination.

Determination of superoxide dismutase (SOD, U/g) activity was determined according to Nishikimi et al. [27] by using SOD Biodiagnostik and Research Reagent Colorimetric Method Assay Kit. Determination of reduced glutathione (GSH, mg / tissue) content was determined according to Beutler et al. [28] using GSH Biodiagnostik and Research Reagent Colorimetric Method Assay Kit. Determination of catalase (CAT, U / g) activity was determined according to Aebi [29] using CAT Biodiagnostik and Research Reagent Colorimetric Method Assay Kit. Determination of Lipid Peroxide Malondialdehyde (MDA, nmol / g fresh tissue) activity was determined according to Ohkawa et al. [30] using MDA Biodiagnostik and Research Reagent Colorimetric Method Assay Kit.

**Statistical Analysis**

The data expressed as mean ± SE. It was analyzed using analysis of variance (ANOVA) followed by Duncan’s multiple range test.
Person correlation coefficient was computed between every two parameters. Differences were considered significant at P<0.05. All statistical analysis was done using SPSS software version (V20).

RESULTS

Effect of Food Additives on Body Weight

The data of body weight and weight gain was presented in Table 1. The treatment with the tested food additives induced increase in the final body weight. The highest increase (41.29%) was recorded for ASP treated rats that was significantly varied from the control one. While, treatment with MSG or ASP+MSG induced non-significant increase in rat body weight. The body weight gain revealed increased values of about 6.6%, 36.4%, 18.6% and 10% for group 1 until group 4, respectively. The analysis of variance (ANOVA) for the data of body weight gain in Table 1, showed that there was significant difference between the control and ASP treated group. The highest weight gain was recorded for ASP treated group being 451.51% above control value.

Effect of Food Additives on Liver, Kidney and Brain Indices

The data of the liver, kidney and brain indices were presented in Table 1. Analysis of variance for liver, kidney and brain relative weight showed non-significant increase in all treated groups except the kidney relative weight for rat treated with ASP showed significant increase for those of control.

Table 1. Body weight, liver, kidney, and brain indices of male albino rat orally administered with aspartame (0.13 g/Kg b.w.), monosodium glutamate (0.13 g/Kg b.w.) and their combination (Monosodium glutamate + Aspartame 0.13 g/Kg b.w.) for one month.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Parameters</th>
<th>Control</th>
<th>Aspartame (ASP)</th>
<th>Monosodium glutamate (MSG)</th>
<th>ASP + MSG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>Mean ± SE</td>
<td>114 ± 3.70 b</td>
<td>134 ± 5.28 a</td>
<td>118.2 ± 3.56 ab</td>
<td>112.4 ± 9.71 b</td>
</tr>
<tr>
<td>Weight</td>
<td>%Of Change</td>
<td>-</td>
<td>17.54%</td>
<td>3.68%</td>
<td>-1.40%</td>
</tr>
<tr>
<td>Final</td>
<td>Mean ± SE</td>
<td>120.6 ± 1.16 b</td>
<td>170.4 ± 16.32 a</td>
<td>136.8 ± 3.38 b</td>
<td>122.4 ± 6.86 b</td>
</tr>
<tr>
<td>Weight</td>
<td>%Of Change</td>
<td>-</td>
<td>41.29%</td>
<td>13.43%</td>
<td>1.49%</td>
</tr>
<tr>
<td>Gain (g)</td>
<td>%Of Change</td>
<td>6.60 ± 2.67 b</td>
<td>36.40 ± 11.28 a</td>
<td>18.60 ± 0.40 ab</td>
<td>10 ± 3.46 b</td>
</tr>
<tr>
<td>Liver</td>
<td>Mean ± SE</td>
<td>3.79 ± 0.11 a</td>
<td>4.30 ± 0.47 a</td>
<td>3.66 ± 0.05 a</td>
<td>3.93 ± 0.06 a</td>
</tr>
<tr>
<td>Index</td>
<td>%Of Change</td>
<td>-</td>
<td>13.45%</td>
<td>-3.43%</td>
<td>3.69%</td>
</tr>
<tr>
<td>Kidney</td>
<td>Mean ± SE</td>
<td>0.36 ± 0.2 b</td>
<td>0.52 ± 0.2 a</td>
<td>0.39 ± 0.4 b</td>
<td>0.44 ± 0.5 ab</td>
</tr>
<tr>
<td>Index</td>
<td>%Of Change</td>
<td>-</td>
<td>44.44%</td>
<td>8.33%</td>
<td>22.22%</td>
</tr>
<tr>
<td>Brain</td>
<td>Mean ± SE</td>
<td>0.9 ± 0.05 a</td>
<td>1 ± 0.11 a</td>
<td>0.8 ± 0.17 a</td>
<td>0.9 ± 0.3 a</td>
</tr>
<tr>
<td>Index</td>
<td>%Of Change</td>
<td>-</td>
<td>11.11%</td>
<td>-11.11%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Number of animals in each group=5.
Data were presented as mean ± SE.
% Of change = [(Value of treated – Value of control) / Value of control] × 100.
In the same row: Similar letters mean non-significant difference.

Antioxidant Parameters

Liver

Rats treated with either ASP or MSG showed significant increase in SOD activity and non-significant increase for their combination compared to control (Table 2). Treatment with ASP showed non-significant decrease in MDA activity, but treatment with MSG and the mixture of ASP+MSG showed significant decreases in its content compared to control. Treatment with ASP showed significant decrease in GSH activity compared to control and non-significant differences in other treated groups. The data of CAT activity showed that all treated groups have significant enhancement over the control value. The data tabulated in Table 3, showed no correlation between the tested parameters in the liver tissue.

Table 2. Antioxidant parameters in liver tissue (Superoxide dismutase activity, SOD U/gm, malonealdehyde content, MDA nmol/g, glutathione content, GSH mg/g, catalase activity, CAT U/g) of male albino rats orally administered with aspartame (0.13 g/Kg b.w.), monosodium glutamate (0.13 g/Kg b.w.) and their combination (Monosodium glutamate + Aspartame 0.13 g/Kg b.w. for each) for one month.

<table>
<thead>
<tr>
<th>Groups /Parameters</th>
<th>Control</th>
<th>Aspartame (ASP)</th>
<th>Monosodium glutamate (MSG)</th>
<th>ASP + MSG</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOD</td>
<td>Mean ± SE</td>
<td>1086.20 ± 68.96 c</td>
<td>1427.41 ± 22.47 a</td>
<td>1332.59 ± 17.88 a</td>
</tr>
<tr>
<td>(U/g)</td>
<td>% Of Change</td>
<td>31.41%</td>
<td>22.68%</td>
<td>12.69%</td>
</tr>
<tr>
<td>MDA</td>
<td>Mean ± SE</td>
<td>533.04 ± 76.83 a</td>
<td>399.59 ± 26.07 b</td>
<td>275.35 ± 44.50 a</td>
</tr>
<tr>
<td>(nmol/g)</td>
<td>% Of Change</td>
<td>-25.03%</td>
<td>-48.34%</td>
<td>-40.45%</td>
</tr>
<tr>
<td>GSH</td>
<td>Mean ± SE</td>
<td>56.61 ± 7.16 a</td>
<td>16.21 ± 1.71 b</td>
<td>50.46 ± 2.35 a</td>
</tr>
<tr>
<td>(mg/g)</td>
<td>% Of Change</td>
<td>-71.36%</td>
<td>-10.86%</td>
<td>3.51%</td>
</tr>
<tr>
<td>CAT</td>
<td>Mean ± SE</td>
<td>35.28 ± 4.12 a</td>
<td>292.13 ± 25.72 a</td>
<td>231.59 ± 73.08 a</td>
</tr>
</tbody>
</table>

Number of animals in each group=5.
Data were presented as mean ± SE.
% Of change = [(Value of treated – Value of control) / Value of control] × 100.
In the same row: Similar letters mean non-significant difference.
Number of animals in each group=5
Data were presented as mean ± SE
% Of change=((Value of treated–Value of control) / Value of control) × 100
In the same row: Similar letters mean non-significant difference

Table 3. Correlation coefficient of the tested antioxidant parameters in the liver of different groups.

<table>
<thead>
<tr>
<th>Groups/Parameters</th>
<th>Control</th>
<th>ASP</th>
<th>MSG</th>
<th>ASP+MSG</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOD × CAT</td>
<td>0.517</td>
<td>-0.839</td>
<td>-0.672</td>
<td>-0.848</td>
</tr>
<tr>
<td>SOD × GSH</td>
<td>0.218</td>
<td>0.152</td>
<td>0.241</td>
<td>0.393</td>
</tr>
<tr>
<td>SOD × MDA</td>
<td>-0.568</td>
<td>0.462</td>
<td>-0.169</td>
<td>0.118</td>
</tr>
<tr>
<td>CAT × GSH</td>
<td>-0.232</td>
<td>-0.152</td>
<td>0.028</td>
<td>0.393</td>
</tr>
<tr>
<td>CAT × MDA</td>
<td>-0.327</td>
<td>-0.22</td>
<td>0.123</td>
<td>-0.344</td>
</tr>
<tr>
<td>MDA × GSH</td>
<td>0.093</td>
<td>0.735</td>
<td>0.801</td>
<td>-0.454</td>
</tr>
</tbody>
</table>

Significant at P<0.05

Kidney

The data of antioxidant parameters in the kidney of rats exposed for one-month to oral administration of the examined food additives were presented in Table 4. In SOD activity, all treatments induced non-significant changes from the control. ASP and MSG treated groups exhibited significant decrease in MDA content (maximum difference was -47.17% from the control), while the ASP+MSG combinations have non-significant decrease. Treatment with ASP and MSG caused non-significant decrease for GSH content, and significant decrease in ASP+MSG treated group compared to control one. Catalase activity (CAT) was not affected in rats given either ASP or ASP+MSG. While the treatment with MSG showed significant rise of CAT (being 172.96% over the control value (4). Worthy to mention that kidney CAT × MDA was high proportionally correlated (r=0.908) for ASP treated rat. The rest of parameters showed non-significant correlation (Table 5).

Table 4. Antioxidant parameters in kidney tissue (Superoxide dismutase activity, SOD U/gm, maleonalesahide content, MDA nmol/g, glutathione content, GSH mg/g, catalase activity, CAT U/g) of male albino rats orally administered with aspartame (0.13 g/Kg b.w.), monosodium glutamate (0.13 g/Kg b.w.) and their combination (Monosodium glutamate + Aspartame 0.13 g/Kg b.w. for each) for one month.

<table>
<thead>
<tr>
<th>Groups/Parameters</th>
<th>Control</th>
<th>Aspartame (ASP)</th>
<th>Monosodium glutamate (MSG)</th>
<th>ASP + MSG</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOD Mean ± SE</td>
<td>1279.31 ± 40.21a</td>
<td>1385.34 ± 78.04a</td>
<td>1316.09 ± 22.99a</td>
<td>1224.13 ± 68.96a</td>
</tr>
<tr>
<td>% Of Change</td>
<td>-</td>
<td>8.28%</td>
<td>2.87%</td>
<td>-4.31%</td>
</tr>
<tr>
<td>MDA nmol/gm Mean ± SE</td>
<td>357.26 ± 36.62a</td>
<td>231.58 ± 40.53b</td>
<td>188.71 ± 25.02b</td>
<td>249.70 ± 30.42ab</td>
</tr>
<tr>
<td>% Of Change</td>
<td>-</td>
<td>-35.17%</td>
<td>-47.17%</td>
<td>-30.10%</td>
</tr>
<tr>
<td>GSH mg/tissue Mean ± SE</td>
<td>72.95 ± 3.07c</td>
<td>69.11 ± 1.75a</td>
<td>60.05 ± 3.69b</td>
<td>43.29 ± 11.90b</td>
</tr>
<tr>
<td>% Of Change</td>
<td>-</td>
<td>-5.26%</td>
<td>-17.68%</td>
<td>-40.65%</td>
</tr>
<tr>
<td>CAT Mean ± SE</td>
<td>77.30 ± 13.23c</td>
<td>64.23 ± 6.09b</td>
<td>211 ± 30.86a</td>
<td>109.56 ± 21.30b</td>
</tr>
<tr>
<td>% Of Change</td>
<td>-</td>
<td>-16.90%</td>
<td>172.96%</td>
<td>41.73%</td>
</tr>
</tbody>
</table>

Significant at P<0.05

Brain

Brain SOD, CAT activities and MDA content showed that treatment with the tested food additives caused non-significant fluctuations compared to control (Table 6). But rats treated with MSG showed significant decreased values in the tested parameters compared to control and other treated groups. The data highlights that all treated groups (ASP, MSG and ASP+MSG) showed significant increase in GSH activity compared to control one. Its maximal increase was recorded for MSG treated group (Table 6), being 128.09% over the control value. Person correlation coefficient presented in Table 7, showed weak correlation between all the tested parameters for all tested groups (Table 8).

Table 6. Antioxidant parameters in brain tissue (Superoxide dismutase activity, SOD U/gm, maleonalesahide content, MDA nmol/g, glutathione content, GSH mg/g, catalase activity, CAT U/g) of male albino rats orally administered with aspartame (0.13 g/Kg b.w.), monosodium glutamate (0.13 g/Kg b.w.) and their combination (Monosodium glutamate + Aspartame 0.13 g/Kg b.w. for each) for one month.
In contrary Tawfik and Al-Bader [40] found that MSG induces significant increase in relative liver weight. The increased CAT activity recorded for MSG may be an indication of oxidative stress generated both enzymatic and non-enzymatic strategy, and are essential for the cellular metabolism and function (ROS). In order to prevent the potential effects of ROS, organisms have evolved multiple systems of antioxidant defense including the control value, with a percentage of 181.81% from the control. Previous data indicated such weight enhancement for MSG as food additives [36,37].

It was explained that MDA level is increased as a product of lipid peroxidation occurred by ROS action on lipids of cellular membranes. Lipid peroxidation is a major indicator of oxidative damage initiated by ROS and causes impairment of membrane function.

The stimulation of appetite has been suggested to result from enhanced energy demand [34]. On contrary to our results, it was found that ASP administration induced significant reduction in weight gain of rats [35]. This is possibly related to that ASP can affect energy (Lipids and Carbohydrates) metabolism, increasing energy outflow [33]. The present study indicates that MSG induces triple fold increase in weight gain over the control value, with a percentage of 181.81% from the control. Previous data indicated such weight enhancement for MSG as food additives [36,37].

The animals during their life exposed to various stressors. Some of them generate free radicals, reactive oxygen species (ROS). In order to prevent the potential effects of ROS, organisms have evolved multiple systems of antioxidant defense including both enzymatic and non-enzymatic strategy, and are essential for the cellular metabolism and function [42].

In regards to the control, the present study revealed significant increase in SOD and CAT activities in the liver for rats treated with the examined food additives. The increased CAT activity recorded for MSG may be an indication of oxidative stress [43]. On the other side, the liver reduced GSH and MDA contents showed significant reduction for rats treated with ASP and MSG and their combination, compared to the control, respectively. The reduction of antioxidant metabolites (GSH and MDA) in rat as an effect of food additives was previously recorded [44]. In contrast, enhanced MDA was reported for rat given food additives [39]. Lipid peroxidation is a major indicator of oxidative damage initiated by ROS and causes impairment of membrane function [45]. It was explained that MDA level is increased as a product of lipid peroxidation occurred by ROS action on lipids of cellular membrane.

**DISCUSSION**

The present study indicates that MSG induces triple fold increase in weight gain over the control value, with a percentage of 181.81% from the control. Previous data indicated such weight enhancement for MSG as food additives [36,37]. This is related to increase in energy intake resulted from MSG [38], with the possibility of values fatness [39] or change the levels of carbohydrates, lipids and proteins in rats [38].

The relative organ weight recorded in the present study explores non-significant increase in the liver and brain for rats given the tested food additives. In contrary to our results, it was found that ASP administration induced significant reduction in weight gain of rat [7,35]. This is possibly related to that ASP can affect energy (Lipids and Carbohydrates) metabolism, increasing energy outflow [33]. The present study indicates that MSG induces triple fold increase in weight gain over the control value, with a percentage of 181.81% from the control. Previous data indicated such weight enhancement for MSG as food additives [36,37].

The increase of body weight gain was reported for all groups only those of ASP showed significant difference from the control. This results is in agreement with those reported by Feijo et al. [32], as they reported increased body weight and fluid intake in a group treated with ASP. This could be explained as ASP increases the appetite in rats [34]. The present study indicates that MSG induces triple fold increase in weight gain over the control value, with a percentage of 181.81% from the control. Previous data indicated such weight enhancement for MSG as food additives [36,37]. This is related to increase in energy intake resulted from MSG [38], with the possibility of values fatness [39] or change the levels of carbohydrates, lipids and proteins in rats [38].

The relative organ weight recorded in the present study explores non-significant increase in the liver and brain for rats given the tested food additives. In contrary Tawfik and Al-Bader [40] found that MSG induces significant increase in relative liver and kidney weight. The present study indicates general increase over the control value in relative kidney weight, due to administration of the tested food additives with significant increase for ASP group. This result was in agreement with Tawfik and Al-Bader, which reflect increase in the activity of inflammatory agents that could result to inflammation of liver and kidney [41].

The animals during their life exposed to various stressors. Some of them generate free radicals, reactive oxygen species (ROS). In order to prevent the potential effects of ROS, organisms have evolved multiple systems of antioxidant defense including both enzymatic and non-enzymatic strategy, and are essential for the cellular metabolism and function [42].

In regards to the control, the present study revealed significant increase in SOD and CAT activities in the liver for rats treated with the examined food additives. The increased CAT activity recorded for MSG may be an indication of oxidative stress [43]. On the other side, the liver reduced GSH and MDA contents showed significant reduction for rats treated with ASP and MSG and their combination, compared to the control, respectively. The reduction of antioxidant metabolites (GSH and MDA) in rat as an effect of food additives was previously recorded [44]. In contrast, enhanced MDA was reported for rat given food additives [39]. Lipid peroxidation is a major indicator of oxidative damage initiated by ROS and causes impairment of membrane function [45]. It was explained that MDA level is increased as a product of lipid peroxidation occurred by ROS action on lipids of cellular

**Table 7.** Correlation coefficient of the tested antioxidant parameters in brain of different groups.

<table>
<thead>
<tr>
<th>Groups/Parameters</th>
<th>Control</th>
<th>ASP</th>
<th>MSG</th>
<th>ASP+MSG</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOD × CAT</td>
<td>0.438</td>
<td>0.516</td>
<td>0.349</td>
<td>0.09</td>
</tr>
<tr>
<td>SOD × GSH</td>
<td>0.246</td>
<td>-0.1</td>
<td>0.603</td>
<td>0.742</td>
</tr>
<tr>
<td>SOD × MDA</td>
<td>-0.457</td>
<td>0.35</td>
<td>-0.787</td>
<td>-0.652</td>
</tr>
<tr>
<td>CAT × GSH</td>
<td>-0.698</td>
<td>-0.51</td>
<td>0.671</td>
<td>-0.524</td>
</tr>
<tr>
<td>CAT × MDA</td>
<td>0.3</td>
<td>-0.492</td>
<td>-0.844</td>
<td>-0.004</td>
</tr>
<tr>
<td>MDA × GSH</td>
<td>-0.553</td>
<td>0.509</td>
<td>-0.717</td>
<td>-0.739</td>
</tr>
</tbody>
</table>

Significant at P<0.05

Table 8. Correlation coefficient of the tested antioxidant parameters in different tissues regardless the treated groups.

<table>
<thead>
<tr>
<th>r-value</th>
<th>Liver</th>
<th>Kidney</th>
<th>Brain</th>
<th>Overall r-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOD × CAT</td>
<td>0.133</td>
<td>0.174</td>
<td>0.36</td>
<td>0.198</td>
</tr>
<tr>
<td>SOD × GSH</td>
<td>-0.131</td>
<td>0.099</td>
<td>0.243</td>
<td>0.11</td>
</tr>
<tr>
<td>SOD × MDA</td>
<td>-0.157</td>
<td>0.154</td>
<td>-0.22</td>
<td>-0.111</td>
</tr>
<tr>
<td>CAT × GSH</td>
<td>0.111</td>
<td>-0.246</td>
<td>-0.06</td>
<td>-0.026</td>
</tr>
<tr>
<td>CAT × MDA</td>
<td>-0.135</td>
<td>0.168</td>
<td>-0.21</td>
<td>-0.123</td>
</tr>
<tr>
<td>MDA × GSH</td>
<td>-0.09</td>
<td>-0.296</td>
<td>-0.3</td>
<td>-0.222</td>
</tr>
</tbody>
</table>

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membrane. The disturbed oxidative stress biomarkers in the liver tissue reported in the present study are an indication of liver impairment.

Although some information is available on the aspartame induced toxicity at various levels, the studies on the effect of long-term oral exposure of aspartame on liver antioxidants are insufficient. Moreover, most of studies on aspartame have been carried out to understand the mechanisms of neurotoxicity and cancer. Aspartame-induced liver inflammation and necrosis is associated with GSH depletion and a decrease in glutathione peroxidase and glutathione reductase activities. Aspartame also provokes adrenal cell apoptosis in vitro and brain apoptosis in vivo. Hence, GSH depletion and changes in GSH-related enzymes are considered main features linked to aspartame-induced oxidative stress and injury. Moreover, methanol may cause oxidative stress and is considered the major contributor to ASP toxicity upon administration. Subchronic consumption of aspartame significantly increased lipid peroxidation products in the brain, liver, and kidneys with a concomitant depletion of enzymatic (GST, GPx, SOD, and CAT) and non-enzymatic (GSH) antioxidant levels. This finding was consistent with the result of the present study, explaining another mechanism of hepatic damage induced by aspartame other than lipid alterations. Alwaleedi reported that a 60-day aspartame treatment significantly increased lipid peroxidation with a remarkable reduction in antioxidant status in the liver and kidney tissues of rats. Aspartame-induced oxidative stress may be attributed to its methanol content, a hallmark of aspartame toxicity, and the free radicals produced during aspartame metabolism that cause lipid peroxidation and depletion of antioxidant enzymes.

The present study recorded elevated activities of SOD and CAT in kidney of rat treated with the tested food additives. Similar results were reported by Tawfik et al. Also, the recorded data highlighted reduction in renal MDA and GSH, which are an indication of renal oxidative damage induced by food additives. Such harmful effect was previously recorded by Tawfek and Al-Badr. The extent of oxidative stress-induced damage depends not only on the nature and amount of ROS involved but also on the duration of ROS exposure and ROS scavengers.

The recorded data in the present undertaken indicated significant reduction of brain SOD activity for rat treated with MSG compared to the control. The brain GSH content showed significant increase in all treated groups compared to the control. These significant changes of the antioxidant biomarkers reflect the generation of the oxidative stress in the brain. This is in agreement with those reported by for ASP.

Oxidative stress is the general phenomenon of oxidant exposure and antioxidant depletion, or oxidant-antioxidant balance. The central nervous system is vulnerable to free radical damage because of brain’s high oxygen consumption, its abundant lipid content, and the relative paucity of antioxidant enzymes as compared with other tissues. Tawfek et al. found that significant increase in MDA and lipid peroxidation could also be due to the increases in the blood glutamate and glutamine, which are reported to favor lipogenesis. Glutamate is poorly transported across cell membranes and could accumulate intracellular, altering the redox state of the cell. In this altered redox state, the cell favors lipid synthesis and tends to shut down lipolysis. The increased level of glutamate increases the concentration of glutamine, which may cause toxicity in various organs of body, especially brain.

**CONCLUSION**

The present study concluded that administration of ASP and MSG either individually or in combination caused oxidative stress and weekend the antioxidant potentiality of rat body. It also explores the potentiality of the ASP and MSG mixture to induce interactive toxicity. So, the present study recommend staying away from using MSG and ASP in our foods.

**REFERENCES**


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