Protective Role of Quercetin on Hippocampus Inflammatory and Oxidative Damage Induced By Monosodium Glutamate in Rats

Shereen Ahmed El-Khateeb¹*, Abeer Ramzy Mahmoud¹, Nahla E. Ibrahem²

ABSTRACT

The aim of the current study was to investigate the possible protective role of quercetin against monosodium glutamate (MSG) induced oxidative stress and inflammation on the brain hippocampus of adult male albino rats. Thirty adult male albino rats were equally divided into 5 groups; Group I (control), group II received 1 ml/ kg/ day of 0.5% of Dimethyl sulfoxide (DMSO), group III received 50 mg of quercetin/ kg/ day, group IV received 1.6 g/ kg/ day of MSG, group V received quercetin and after one hour, rats received MSG as previously mentioned. All treatments were given orally for 8 weeks. Then rats were anesthetized, sacrificed and specimens from the brain hippocampus were taken for biochemical and histological studies. MSG exposure showed deleterious effects on Y-maze discrimination learning and memory, significantly increased tissue malondialdehyde (MDA), inducible nitric oxide synthase (iNOS), interleukin-1 beta (IL-1β), tumor necrosis factor-α (TNF-α), glutamate level and acetyl cholinesterase (AChE) activity with significant depletions of catalase (CAT) activities and reduced glutathione (GSH) content. This was accompanied with alteration in the structure of the brain hippocampus. Co-administration of quercetin along with MSG ameliorated the above mentioned effects. The results of this study have shown that quercetin has protective effects against MSG-induced toxicity in rat brain hippocampus.

Introduction

Monosodium Glutamate (MSG) is used in commercial foods all over the world. It is found in many different ingredients and processed foods obtainable in every market. It gives a special taste to processed foods (Veni et al., 2010). Therefore, most of canned and fast food as marinated meats, frozen foods, flavored chips, bottled soy, tuna and canned and packed soups contain variable concentrations of MSG (Bojanić et al., 2009). The MSG effect was firstly described in 1968 as Chinese restaurant syndrome. Earlier researches reported that MSG has neurotoxic effects (Onishi and Xavier, 2010). It was reported that MSG may influence the memory recovery, cognition as well as capacity to learn (Pilgrim et al., 2012 and Abu-Taweel et al., 2014). Monosodium glutamate induces oxidative stress and disturbance in the antioxidant homeostasis in various organs (Sadek et al., 2016).

Experimental studies reported that toxicity of MSG can be overcome by the substances which could inhibit oxidative damage. Authors investigated the role of
lycopene, ginger, vitamin E, selenium and propolis to avert the neurotoxic effects of MSG in rats (Sadek et al., 2016; Hussein et al., 2017). Quercetin (3,5,7,30,40-pentahydroxyflavone), is one of the flavonoids of polyphenols that is present in fruits, onions, apples and blueberries, black and green tea, citrus fruits and red grapes. Previous studies investigated its beneficial effects on human health and reported that quercetin has antioxidant and anti-inflammatory effects (Mythri et al., 2012; Anand David et al., 2016). Quercetin has been shown to maintain integrity of blood-brain barrier by active oxygen scavenging (Lapi et al., 2012). Also, quercetin has been revealed to be a multi-target therapeutic tool for protecting the brain where it can be a direct inhibitor of monoamine oxidase- A in nerve cells by targeting mitochondria (Bandaruk et al., 2014).

Based on these findings, the aim of our research was to explore the potential protective role of quercetin against MSG induced oxidative stress and inflammation in the brain hippocampus of adult male albino rats.

Materials and Methods

Chemicals and Reagents:

Monosodium glutamate (MSG) (C5H9NO4 Na; purity >98%) was obtained from Al-Dawlya Chemicals Co. (Cairo, Egypt), Quercetin (C15H10O7; CAS Number: 117-39-5); was provided as a yellow powder (≥98% HPLC), and Dimethyl sulfoxide (DMSO); CAS Number: 67-68-5) were obtained from Sigma-Aldrich chemical company (St Louis, MO, USA). The rest of chemicals and reagents were obtained from Sigma-Aldrich (St Louis, MO, USA) and Biodiagnostics (Cairo, Egypt).

Animal treatment and experimental design:

Thirty adult male Wister albino rats were used. Each rat was 180-200 grams weight, 7-8 weeks old. They were housed in polypropylene cages and fed standard pellet diet and water, given ad libitum in the departmental animal house of Faculty of Medicine, Zagazig University, Egypt and kept with a 12-h light/dark cycle at controlled temperature (22 ± 2°C). This research was done according to the guiding principles for the animal use and care and approved by The Institutional Animal Care and Use Committee, Zagazig University with approval code ZU-IACUC/2/F/212/2019.

Experimental design:

Animals were divided into 5 groups each one has six rats. Total duration of experiment was 8 weeks. Group I served as control (fed on balanced diet and water). Group II received 0.5% Dimethyl sulfoxide (DMSO) at a daily dose of 1 ml/kg body weight/day by oral gavage. Group III received quercetin dissolved in 0.5% DMSO at a dose 50 mg/kg body weight/day through oral gavage (El-Beltagi and Ahmed, 2016; Rahvar et al., 2018). Group IV administered MSG orally as 1.6 g/kg body weight/day (1/10 LD50) where 100 g of MSG were dissolved in 300 ml tap water and given by oral gavage as 0.95 ml/rat for 8 weeks. The LD50 of MSG in rats is 15-18 g/kg bw based on previous studies (Joint FAO/WHO Expert Committee on Food Additives, 1988; Walker and Lupien, 2000). Group V orally received quercetin dissolved in 0.5% DMSO at a dose 50 mg/kg body weight and after one hour, rats administered MSG and dissolved in tap water at a dose of 1.6 g/kg bw/day.

Cognitive test to assess hippocampal function (Test of Y-Maze Discrimination Learning):

This test was done after 8 weeks of treatment. It was especially designed at the Physiology Department. It consists of three similar arms, which are differentiated by colored spots at their ends. The main mission is to learn a thirsty rat the correct direction.
(right side) in order to acquire a drop of water (Borbély et al., 2013). The rats were thought to have learnt the task when they did 9 of the 10 tests. The rate of learning was evaluated by how many trials needed for obtaining the response. After 24 hours, the test was repeated; memory was measured as the percentage of correct responses.

Sample preparation for biochemical analysis:
At the end of the experiment, rats were anesthetized then sacrificed by decapitation. The brains were obtained immediately. In each rat; the hippocampus of one hemisphere was removed, isolated, rinsed in ice-cold isotonic saline, dried, homogenized, centrifuged and the resultant supernatant was stored at -20°C until used for biochemical measurements. The hippocampus of the other hemisphere was divided into 2 halves; one half was stored at -80°C and used for real-time polymerase chain reaction (RT-PCR). The other part was used for histopathological examination.

Assessment of Oxidative stresses markers level:
1. Measurement of lipid peroxidation (LPO) as oxidative stress indicator: Malondialdhyde (MDA) was assessed according to Ohkawa et al. (1979) using commercial available kit.
2. Measurement of reduced glutathione (GSH): Reduced glutathione (mmol/g) was assessed as described by Beutler et al. (1963) using commercially available kit.
3. Determination of catalase (CAT) enzymes activity: Catalase activity (U/g tissue) was assessed in brain hippocampus according to Aebi (1984). The absorbance was measured at 510 nm.
4. Inducible nitric oxide synthase (iNOS): Nitric oxide assay was done according to (Montgomery and Dymock, 1961). Total nitrate/nitrite is measured in two steps that first nitrate is converted to nitrite. Secondly, nitrite is converted to a deep purple azo compound that has a bright reddish-purple color.

Determination of Acetylcholinesterase (AChE; EC 3.1.1.7.) activity in hippocampus
Acetyl cholinesterase (AChE) activity was measured as done by Ellman and Callaway (1961). The activity was expressed as μmoles of acetylthiocholine hydrolyzed/min/mg tissue.

Determination glutamate Level in hippocampus
Glutamate measurement were done using rat glutamate enzyme linked immunesorbent assay (ELISA) kit (No: MBS047402, MyBioSource, Canada) by a microplate reader (Tecan, Infinite 200 PRO, Switzerland) at 450 nm. Glutamate levels were assessed by the standard curve as reported by the manufacturer.

Analyses of Gene Expression of ILI-β and TNF-α by Real Time PCR
Total RNA was extracted from brain hippocampus homogenate using a Qiagen RNA isolation kit (RNeasy, Qiagen Ltd, Crawley, West Sussex, UK) according to the manufacturer’s protocol. The total RNA was quantified by the measured absorbance at 260 nm in a spectrophotometer. After that, RNA is converted into complementary DNA (cDNA) by reverse transcriptase (QuantiTect Reverse Transcription Kit, QIAGEN, # 205310, Germany). This extracted RNA was used for assessment of expression of ILI β and TNF-α. All the specimens were run in duplicates. PCR amplification consisted of 40 cycles of denaturation at 95°C for 10 s, annealing at 55°C for 10 s, and extension at 72°C for 20 s. The primers were designed by the web based tool, Primer 3 (http://www-genome.
wi.mit.edu/cgi-bin/primer/primer3 www.cgi) based on the published rat sequence. The sequence of the primers used is as follow: *IL-1β* forward, 5' - CACCTCTCAAGCAGACAG -3'; *IL-1β* reverse, 5' - GGGTCCATGGTAAGCTCAAC-3; *TNF-α* forward 5'- AAATGGGCTCCCTCATCAGTTC 3'; *TNF-α* reverse, 5' - TCTGCTTGGTGGTTGCTACGAG -3; glyceraldehyde 3-phosphate dehydrogenase (GAPDH) forward, GTATTGGGCGCCTGGTCACC 3'; GAPDH reverse, 5' - CGCTCCTGGAAGATGGTGATGG -3'. The amount of cDNA in the reactions was normalized with an internal control, the constitutively expressed gene glyceraldehyde 3-phosphate dehydrogenase (GAPDH). Relative gene expression was calculated from the formula: $2^{\Delta\Delta CT}$; ($\Delta\Delta CT = CT_{GAPDH} - CT_{target}$).

**Histopathological studies:**
Specimens (1 cm thick) were fixed in 10% buffered formalin solution and processed to obtain paraffin sections of 5 µm thickness. The sections were stained with haematoxylin and eosin (Bancroft and Gamble, 2008).

**Morphometrical analysis:**
The thickness of the granular cell layer in the dentate gyrus and the pyramidal cell layer in CA1, CA1 and CA3 were measured. Lines were drawn vertically; the lines were then measured by the software. Moreover, the surface area of granular cells in the dentate gyrus and pyramidal cells in CA1, CA2 and CA3 were measured. For each animal, five non-overlapping high-power fields (×400) from five different sections were randomly chosen. Five separate readings from each of the photos taken were recorded and the mean was calculated for each specimen. All data have been collected using a Leica Qwin 500 image analyzer computer system (UK) at the Histology and Cell Biology Department, Faculty of Medicine, Cairo University.

**Statistical analysis:**
Data were analyzed by Statistical Package of Social Science (SPSS), software version 20 (SPSS Inc., 2011). Data were normally distributed and summarized as mean ± Standard deviation. Differences among the groups were analyzed through One way analysis of variance (ANOVA) followed by post-hoc Tukey HSD Test for inter-group comparisons difference.

**Results**

**Y- maze test:**
Administration of MSG had affected Y-maze discrimination learning and memory in rats as the number of trials needed to learn was more than that of control ($p<0.01$), the duration of all responses was more than the control ($p<0.01$). The proper rate one day after was less than the control denoting lack of ability to learn and deteriorated memory. Rats treated with MSG and quercetin showed considerably enhanced learning and memory in Y- maze test ($p>0.01$) (Table 1).
Table (1): Comparison of Y-maze discrimination learning and memory in different groups.

<table>
<thead>
<tr>
<th>Groups (n= 6)</th>
<th>Number of training sessions Mean ± SD</th>
<th>Duration (sec)</th>
<th>% of Correct response after 24 hours Mean± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I (negative control)</td>
<td>16.5± 1.37</td>
<td>910</td>
<td>72±1.2</td>
</tr>
<tr>
<td>Group II (DMSO)</td>
<td>16.5± 1.1</td>
<td>912</td>
<td>71± 2.3</td>
</tr>
<tr>
<td>Group III (Quercetin)</td>
<td>16.17± 1.04</td>
<td>915</td>
<td>71± 1.6</td>
</tr>
<tr>
<td>Group IV (MSG)</td>
<td>24.7± 2.8#</td>
<td>1800</td>
<td>63±2.4</td>
</tr>
<tr>
<td>Group V (Quercetin + MSG)</td>
<td>18.3± 1.5##</td>
<td>950</td>
<td>73±1.4</td>
</tr>
</tbody>
</table>

$p$- value: $p<0.01$

SD: standard deviation; n: number; # $p<0.01$ is significant as compared with control group; ## $p<0.01$ is significant as compared with MSG treated group; sec: seconds MSG: monosodium glutamate; DMSO: Dimethyl sulfoxide

Assessment of oxidative stress in treated groups:

Administration of MSG elevated MDA in hippocampus ($p < 0.01$). A decrease in GSH content, and CAT activity was observed in MSG administered rats as compared to control ones. Co-administration of quercetin with MSG obviously attenuated oxidative stress by ameliorating MDA and increasing GSH content and CAT activity in hippocampus as compared to MSG group ($p < 0.01$). Regarding iNOS level, it was increased in MSG treated rats in comparison with control group. Quercetin co-administration with MSG decreased the level of iNOS ($p < 0.01$) (Table 2).

Table (2): Comparison of the antioxidant status in brain hippocampus of different Studing groups.

<table>
<thead>
<tr>
<th>Groups (n= 6)</th>
<th>MDA (nmol/ g tissue) Mean ± SD</th>
<th>GSH (nmol/ g tissue) Mean ± SD</th>
<th>CAT (U/ g tissue) Mean ± SD</th>
<th>iNOS (nmol/ g) Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I (negative control)</td>
<td>11.48± 1.17</td>
<td>4.64 ±0.37</td>
<td>16.5 ±0.84</td>
<td>21.50 ± 0.97</td>
</tr>
<tr>
<td>Group II (DMSO)</td>
<td>11.92± 1.17</td>
<td>4.64 ±0.37</td>
<td>16.38 ±1.7</td>
<td>21.14± 1.17</td>
</tr>
<tr>
<td>Group III (Quercetin)</td>
<td>10.23± 0.91</td>
<td>5.18 ±0.41</td>
<td>17.33± 2.1</td>
<td>20.70 ± 1.00</td>
</tr>
<tr>
<td>Group IV (MSG)</td>
<td>16.42± 2.35#</td>
<td>2.59 ±0.62##</td>
<td>11.62± 2.1 #</td>
<td>35.44 ± 3.16</td>
</tr>
<tr>
<td>Group V (Quercetin + MSG)</td>
<td>10.8±1.7##</td>
<td>4.81 ± 0.57####</td>
<td>18.14 ± 2.4 ##</td>
<td>18.40± 0.58####</td>
</tr>
</tbody>
</table>

$p$- value: $p<0.01$

SD: standard deviation, n: number of rats in each group; # $p<.01$ is significant versus control group; ## $p<.01$ is significant versus MSG treated group; MDA: malondialdehyde; GSH: reduced glutathione; CAT: catalase; iNOS: inducible nitric oxide synthase,MSG: monosodium glutamate; DMSO: Dimethyl sulfoxide
Assessment of AChE activity and glutamate level in brain hippocampus of treated groups

Rats treated with MSG showed a significant increase in AChE activity \((p<0.01)\) as compared to control group. However, administration of quercetin along with MSG revealed reduction in AChE activity \((p<0.01)\) as compared to MSG treated rats (Figure 1). Assessment of glutamate neurotransmitter showed significant elevation \((p < 0.01)\) in MSG treated group versus ordinary control. However, supplementation with quercetin returned glutamate level in the brain to almost normal (Figure 2).

**Fig. (1):** Acetyl cholinesterase (Ach E) level in the studied groups; a: significant as compared with control group; b: significant as compared with monosodium glutamate (MSG) treated group.

**Fig. (2):** Glutamate level in the studied groups; a: significant as compared with control group; b: significant as compared with monosodium glutamate (MSG) treated group.
mRNA expression of *IL-1β*, *TNF-α*

Administration of MSG for 8 weeks revealed increasing in mRNA expression of pro-inflammatory cytokines *IL-1β*, *TNF-α*. This was reduced by administration of quercetin along with MSG (Figure 3).

![Graph showing mRNA expression of IL-1β and TNF-α](image)

**Fig. (3):** Tissue interleukin (*IL-1β*), tumor necrosis factor-α (*TNF-α*). a: significant as compared with control group; b: significant as compared with monosodium glutamate (MSG) treated group.

**Histological examination**

Histological examination of hematoxylin and eosin stained sections of brain hippocampus taken from the control, DMSO and quercetin groups showed normal structure which is formed of Cornu Ammonis (CA) parts as CA1, CA2, CA3 & CA4 regions and C shape dentate gyrus (DG) enclosing CA4 (Figure 4A). Dentate gyrus is formed of three layers; the granular layer contains granule cells, the molecular layer and the polymorphic layer (Figure 4 B). The CA1 and CA2 formed of zone of closely packed small pyramidal cells, CA3 and CA4 formed of zone of large pyramidal triangular cells (Figures 4 C, D, and E).
Monosodium glutamate treated group showed alteration in the structure of dentate gyrus where granule and small pyramidal cells showed small dark stained nuclei. Granular and polymorphic layers showed areas of cell loss, vacuolation, dilated blood capillaries and increased neuroglial cells (Figure 5 A). Morphometric analysis revealed decrease in the mean surface area of granular cells and mean thickness of granular layer in comparison to control group ($p < 0.001$) (Tables 3 and 4). Regarding CA1, CA2, CA3 areas, they showed severely damaged pyramidal cells in the form of pyknotic, shrunken, darkly stained nuclei, vacuolation, and dilated blood vessels (Figures 5 B, C and D). Morphometric analysis revealed statistically significant ($p < 0.001$) decrease in surface area of pyramidal cells and thickness of pyramidal layer in CA1, CA2 and CA3 of MSG group ($p<0.001$) as compared to control (Tables 3 and 4).
Fig. (5): Sections from hippocampus of rats received monosodium glutamate (MSG) 1.6 g/kg. bw/ day showing (A): Dentate gyrus reveals granule cells and pyramidal cells with small dark stained nuclei (arrow head)& (curved arrow) respectively with areas of cell loss (*), vacuolation (v), dilated blood capillaries (c) and neuroglial cells (arrow) are observed. (B) CA1 area, (C): CA2 area, (D): CA3 area, all showing many of pyramidal cells shrunken with darkly stained nuclei and wide peri-cellular spaces (arrow). (H&E×200); ML; molecular layer; GL; granular layer.

Examination of H&E stained sections of rats treated with quercetin and MSG revealed nearly normal hippocampus. Dentate gyrus showed granule cells with vesicular nuclei and reduced vacuolation, while there were still small dark nuclei in some granule cells. The picture was near to normal regarding CA1, CA2 and CA3 areas (Figures 6; B, C and D). Morphometric analysis revealed statistically significant ($p < 0.001$) increase in the mean surface area of granule cells and pyramidal cells, increase mean thickness of granular layer of dentate gyrus pyramidal layer of CA1, CA2 and CA3 than in the MSG group ($p<0.001$) (Tables 3 and 4).
Fig. (6): Sections from hippocampus of rats received monosodium glutamate (MSG) at dose 1.6 g/kg. bw/ day and quercetin at dose 50 mg/kg. bw/ day showing (A): dentate gyrus reveals apparently normal structure. Granular layer (GL) showing normal cells (arrow head) while others have small dark nuclei (red arrow). (B): CA1 area, (C): CA2 area and (D): CA3 area look more organized (H&E×200), (arrow): normal pyramidal cells; (curved arrow): cells with darkly stained nuclei, (c): dilated blood capillaries. ML; molecular layer; GL; granular layer.

Table (3): Comparison of the mean surface area of pyramidal cells (µm²) in CA1, CA2 and CA3 and granular cells in dentate gyrus of different studied groups.

<table>
<thead>
<tr>
<th>Surface area</th>
<th>Group I (negative control)</th>
<th>Group II (DMSO)</th>
<th>Group III (Quercetin)</th>
<th>Group IV (MSG)</th>
<th>Group V (Quercetin+ MSG)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA1</td>
<td>227.89 ± 26.70</td>
<td>226.54 ± 29.50</td>
<td>228.41 ± 28.30</td>
<td>99.71 ± 16.15&lt;</td>
<td>218.6 ± 25.6&lt;</td>
</tr>
<tr>
<td>CA2</td>
<td>223.42 ± 27.80</td>
<td>222.71 ± 25.6</td>
<td>224.13 ± 29.9</td>
<td>107.8 ± 18.75&lt;</td>
<td>213.5 ± 29.07&lt;</td>
</tr>
<tr>
<td>CA3</td>
<td>221.70 ± 24.09</td>
<td>223.12 ± 21.05</td>
<td>222.50 ± 23.20</td>
<td>113.34 ± 18.41&lt;</td>
<td>198.5 ± 25&lt;</td>
</tr>
<tr>
<td>Dentate gyrus</td>
<td>148.96 ± 15.16</td>
<td>146.7± 15.95</td>
<td>147.51 ± 16.62</td>
<td>50.73 ± 8.99&lt;</td>
<td>116.9 ± 14.74&lt;</td>
</tr>
</tbody>
</table>

SD: standard deviation; n: number of rats; < p<.001 is significant versus control; ### p<.001 is significant versus MSG treated group; CA: Cornu Ammonis; MSG: monosodium glutamate
Table (4): Comparison of mean thickness in pyramidal layer (µm) in CA1, CA2 and CA3 and granular layer (µm) in dentate gyrus of different groups of the study.

<table>
<thead>
<tr>
<th>Thickness</th>
<th>Groups (n= 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean± SD</td>
<td>Group I (negative control)</td>
</tr>
<tr>
<td>CA1</td>
<td>119.05±18.76</td>
</tr>
<tr>
<td>CA2</td>
<td>126.25±25.63</td>
</tr>
<tr>
<td>CA3</td>
<td>134.46±17.51</td>
</tr>
<tr>
<td>Dentate gyrus</td>
<td>132.66±19.14</td>
</tr>
</tbody>
</table>

SD: standard deviation; n: number of rats; # p<.001 is significant versus control; ## p<.001 is significant versus MSG treated group; CA: Cornu Ammonis; MSG: monosodium glutamate

Discussion

Monosodium glutamate activates of both ionotropic and metabotropic glutamate receptors (iGluR and mGluR) in the central nervous system. Over activation of these receptors had led to excitotoxicity and neuronal death (Pavlovic et al., 2009).

Quercetin was found to have the capacity to crosses the blood-brain barrier (Paulke et al., 2006). Further, the role of quercetin against MSG induced brain hippocampus toxicity was not well researched. The objective of this research was to assess the possible protective role of quercetin against MSG induced oxidative stress and inflammation on the brain hippocampus of adult male albino rats.

In the present study, administration of MSG induced profound negative effects in the brain hippocampus. This was assured from enhanced lipid peroxidation, pro-inflammatory cytokines (IL-1β, TNF-α), increased glutamate level and AChE activity associated with concomitant decrease in antioxidant defense system in brain hippocampus. Quercetin co-administration along with MSG attenuated MSG induced neurotoxicity through modulation of oxidative damage and inflammation in brain hippocampus.

Assessment of oxidative stress markers in the present study revealed a significant increase in the MDA level and reduction in the total GSH content and CAT antioxidant enzyme activity in the brain hippocampus of MSG treated rats. Moreover iNOS level was increased. On the same context, Shivasharan et al. (2013) and Hussein et al. (2017) reported enhanced oxidative stress in the kidney and brain of rats after MSG intake. GSH depletion indicates tissue degeneration (Andersen, 2004; Mahmoud and Hussein, 2014). Catalase (CAT) has a basic role in getting ride of hydrogen peroxide (Singh et al., 2008; Bjorklund and Chirumbolo, 2017). The histopathological results of this research confirmed the negative effects of MSG on the brain hippocampus where MSG treated rats showed alteration in the structure of dentate...
gyrus, CA1, CA2 and CA3 areas. Hashem et al. (2012) reported that MSG administration induced degeneration in neurons and astrocytes in cerebellar cortex of rats. Also, Dief et al. (2014) evaluated the neurodegenerative effect of MSG and illustrated that cyclic AMP-activated protein kinase (AMPK) level was reduced and (Fas ligand) that mediate apoptosis showed two folds increase in the hippocampus of MSG treated rats.

Quercetin is a naturally occurring flavonoid compound that is characterized by the presence of multiple phenol rings, C to C double bonds and hydroxyl groups (Myhrstad et al., 2002). The hydroxyl groups are critical for antioxidant activity, and scavenge free radicals and ROS by donation of a proton (Justino et al., 2009). Co-administration of quercetin along with MSG ameliorated oxidative stresses, decreased MDA level, produced an inhibitory effect on iNOS and restored the antioxidant enzymes confirming its antioxidant property. These protective effects were assured by histopathological examination of the brain hippocampus. Co-administration of quercetin preserved hippocampal cell architecture. These results can be matched with Kanter et al. (2016) who concluded that quercetin inhibited neuronal apoptosis, and raised antioxidant enzyme activity of the hippocampal tissue resulted from cadmium toxicity. The results of the present study were consistent with preceding studies (Sharma et al., 2013; Sharma et al., 2016). Yang et al. (2013) stated that pre-treatment of mouse hippocampal neuronal cells (HT22) with quercetin significantly inhibited formation of reactive oxygen species by about 77.89% compared with that of glutamate-treated cells. Also, Bao et al. (2017) reported that PC-12 cells pretreated with quercetin showed improved cell viability, decreased H2O2-enhanced ROS formation and mitigated lipoperoxidation of cell membranes.

The present results showed increased levels of IL-1β, TNF-α in brain hippocampus of MSG treated rats. This was in line with Khalil and Khedr (2016) who stated that co-administration of quercetin along with MSG induced an anti-inflammatory response through significant decrease in mRNA expression of pro-inflammatory cytokines IL-1β, TNF-α. This also was in agreement with previous studies where quercetin decreased the formation of iNOS, COX-2, PGE2, and IL-1β (Kang et al., 2013; Vargas-Restrepo et al., 2018).

Stimulation of glutamate receptors may cause excitation and death of neurons (Zhou and Danbolt, 2014). In this study, MSG administration was found to increase the level of glutamate in the brain hippocampus of treated rats. This increase was consistent with the outcomes of (Hussein et al., 2017). On the other hand, quercetin supplementation along with MSG restored the brain glutamate level to nearly normal. Lu et al. (2013) suggested that quercetin suppress glutamate release and linked this to the reduction in presynaptic voltage-dependent Ca^{2+} entry and to the inhibition of protein kinase C and protein kinase A activity.

As a neurotransmitter, acetyl choline is involved in behavior, learning, memory and neurodegeneration. The results of this study have shown that MSG enhanced hippocampus AChE activity in rats. Increased AChE activity may reduce cholinergic neurotransmission effect secondary to reduction in acetyl choline level in the synaptic cleft that might enhance progressive cognitive deterioration (Khalil and Khedr, 2016). Abu-Taweel et al. (2014) interpreted the enhanced AChE activity by oxidative stress. In this research, co-administration of quercetin together with MSG reduced AChE activity. Moreover, quercetin ameliorated oxidative stresses. In a research to assess the impact of quercetin on toxicity caused by cadmium, Abdalla et al. (2013) noted that quercetin inhibited the rise in AChE activity.
Administration of MSG showed negative effects on Y-maze discrimination learning and memory in rats. This was coincided with Zhang et al. (2012). The hippocampus has a basic function in controlling memory and learning functions (Compton, 2004). The impairment in working memory seen at MSG treated rats was explained secondary to the combined effect of slight elevation of glutamate and glutamine coupled with increased oxidative stress (Onaolapo et al., 2016). Other studies have shown that the memory impairment might be through inhibition of the cholinergic system (Park et al., 2000; Perez-Lloret and Barrantes, 2016). On the same context, the results of our study revealed increased oxidative stress, AChE activity and glutamate level in MSG-treated group versus the normal control.

Quercetin is considered as a cognitive enhancer in traditional medicine (Suganthy et al., 2016). Co-administration of quercetin with MSG improved Y-maze discrimination learning and memory. Pu et al. (2007) reported that quercetin ameliorated the neuronal death in the hippocampus leading to enhanced learning and memory. The enhanced learning and memory of Y-maze discrimination could be secondary to the improvement of oxidative stress, anti-inflammatory impact and reduction of AChE.

Conclusion and Recommendation

From all these results, it is concluded that quercetin had positive effects on brain hippocampus and improved the cognitive impairment in rats treated with MSG by alleviating oxidative stress, suppressing inflammation and maintaining AChE level. During MSG consumption, quercetin may be suggested as a supplement to improve the related neurotoxicity.

Conflict of interest

There is no conflict of interest.

References


Pu, F.; Mishima, K.; Irie, K.; et al. (2007): “Neuroprotective effects of quercetin and rutin on spatial memory impairment in an 8-arm radial maze task and neuronal death induced by repeated cerebral


تأثير الكيرسيتين على الأضرار الانتهائية والتأكسدية لحصين الدماغ التي يسببها الالتهابات décisionية الصوديوم في الجرذان

شيرين أحمد الطيب، عبير رفيق محمود، نبيلة إبراهيم

قسم الطب الشرعي و السموم الأكلينيكية، قسم علم الأنسجة والبيولوجيا الخلية
كلية الطب النسائية - جامعة الزقازيق

كان الهدف من الدراسة الحالية هو بحث الدور الوقائي المحتمل للكيرسيتين ضد الإجهاد التأكسدي والالتهابات التي تسبب الالتهابات décisionية الصوديوم على الحصين الدماغي لذكر الجرذان البيضاء البالغة.

تم تقسيم ثلاثين من ذكور الجرذان البالغين البيضاء بالتناسلي إلى 5 مجموعات: المجموعة الأولى (المجموعة الضابطة)، المجموعة الثانية تلقى 1 مل / كجم / يوم 0.5% من ثنائي ميثيل سلفوكسيد، المجموعة الثالثة تلقى 50 مجم من الكيرسيتين / كجم / يوم، المجموعة الرابعة تلقى 100 مجم / كجم / يوم من الجلوليات أحادية الصوديوم، المجموعة الخامسة تلقى كيرسيتين وبعد ساعة واحدة، تلقى الجرذان الجلوليات أحادية الصوديوم كما ذكر سابقا. تم إعطاء جميع العلاجات بالفم لمدة ثمانية أسابيع، ثم تم تخدير الفئران وذبحها، وأخذت عينات من الحصين لإجراء دراسات كيميائية ونسيجية.

أظهر التعرض لمادة الجلوليات أحادية الصوديوم تأثيرات ضارة على التعلم والذاكرة للتمييز في مساحة Y، زيادة ملحوظة في الملالونديا الدهني، خفافة أكسيدي النتريلك، والإنترولوكين -1 بيتا، وعامل نخر الورم، مستوى الجلوليات، ونشاط لاستيل كولين. استغلال كبير لأنشطة الكاتالاز وانخفاض محتوى الجلوليات. وقد صاحب ذلك تغيير في بنية الحصين. أدى إعطاء الكيرسيتين مع الجلوليات أحادية الصوديوم إلى تحسن التأثيرات المذكورة أعلاه.

أظهرت نتائج هذه الدراسة أن الكيرسيتين له تأثيرات وقائية ضد السمية التي تسببها الجلوليات أحادية الصوديوم في الحصين في دماغ الجرذان.