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Full length Research Article

Phoenix dactylifera and Polyphenols Ameliorated Monosodium Glutamate toxicity in the Dentate Gyrus of Wistar Rats

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Summary: Monosodium glutamate (MSG) has been known to cause neurodegeneration, due to its ability to trigger excitotoxicity, and the hippocampus is one of the most affected regions. Therefore, *Phoenix dactylifera* (*P. dactyliferaa*) and polyphenols were employed in this study to mitigate on the deleterious effect of monosodium glutamate on the dentate gyrus of Wistar rats. Forty-eight male Wistar rats weighing between 120-150g was used for the study. The Wistar rats were grouped into eight, (n=6). Groups 1-8 received 1.6mL/kg normal saline, 4000mg\kg monosodium glutamate for 7-days, 4000mg\kg monosodium glutamate for 7-days and 100mg\kg caffeic-acid for 14-days concurrently, 4000mg\kg monosodium glutamate for 7-days and 100mg\kg *P. dactyliferaa* for 14-days concurrently, 4000mg\kg monosodium glutamate for 7-days and 100mg\kg luteolin for 14-days concurrently, 100mg\kg. caffeic-acid for 14-days followed by 4000mg\kg monosodium glutamate for 7-days, 100mg\kg *P. dactyliferaa* for 14-days followed by 4000mg\kg monosodium glutamate for 7-days and 100mg\kg luteolin for 14-days followed by 4000mg\kg monosodium glutamate for 7-days respectively. After the treatments, the rats underwent behavioural test (Y-maze test), and subsequently, the brain tissues were processed for histological (Hematoxylin & Eosin stain) and biochemical (superoxide dismustase, glutathione peroxidase and malondialdehyde) analyses. The activities of *P. dactyliferaa* and polyphenols ameliorated the deleterious effect of monosodium glutamate, through increased spontaneous alternation of the experimental animals, dominant matured granule cells of the dentate gyrus and modulated the activities of superoxide dismutase, glutathione peroxidase and malondialdehyde in the male Wistar rats. Therefore, this study revealed that *P. dactyliferaa* and polyphenols ameliorated monosodium glutamate toxicity in the dentate gyrus of Wistar rats.

Keywords*: Glutamate toxicity, Dentate gyrus, Phoenix dactylifera, Oxidative stress, Neurodegeneration*

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INTRODUCTION

Glutamate is the main constituent of dietary protein and is also consumed in many foods as additive and flavourings in homes and restaurants, in the form of monosodium glutamate (Airaodion *et al*., 2019). It is made of a nutritionally indispensable amino acid, glutamic acid (Zehra *et al*., 2017). Despite its deleterious effect, it remains the major food addictive in most low-income countries. Glutamate is the excitatory neurotransmitter in the mammalian Central Nervous System (CNS) playing an important role in both physiological and pathological processes (Airaodion *et al*., 2019). Receptors of glutamate are dispersed throughout the CNS especially in the amygdala, hippocampus and hypothalamus where they regulate many vital metabolic and autonomic functions. Monosodium glutamate (MSG) is a sodium salt of glutamic acid and has almost same structure with glutamate, the difference is that one hydrogen atom at the carboxylic chain has been replaced with a sodium atom, hence, the name (Airaodion *et al*., 2019). Monosodium glutamate has a meaty taste and due to this, many food producers use MSG to enhance the flavour of their products. Monosodium glutamate could cause neurodegeneration due to its ability to trigger excitotoxicity when consumed in high amount, and the hippocampus is one of the most affected regions, the granule cells of the dentate gyrus being its major input area (Abdel *et al*., 2018).

Neuronal dysfunction and death is a complex phenomenon that involves failure of metabolic processes, protein mitochondrial dysfunction, increased oxidative stress, defective proteasome system, protein aggregation, changes in iron metabolism, and excitotoxicity and inflammation (Dajas *et al*., 2013). The process of MSG triggering excitotoxicity plays a major role in the initiation, as well as the progression of neurocognitive and locomotor disorders (Ahmed *et al*., 2015; Renaud *et al*., 2015). Therefore, it is imperative to stop the progression of MSG insult in the brain.

Consumption of polyphenolic rich diets helps reduce the risk of chronic human diseases. Phenolic groups in polyphenols have the ability to accept an electron to form relatively stable phenoxyl radicals, phenoxyl radical in turn disrupts chain oxidation reactions in cellular components (Pandey and Rizvi, 2009). Polyphenols can be classified

into flavonoid and non-flavonoid polyphenolic compounds. Luteolin is a form of flavonoid while caffeic acid is a form of non-flavonoid polyphenolic compouind. *Phoenix dactylifera* is said to be packed with lots of polyphenolic compound. Luteolin, caffeic acid and *P. dactyliferaa* have been used in this study against neurotoxicity. Furthermore, it has been reported that polyphenol-rich foods and beverages may increase plasma antioxidant capacity (Tsao 2010). Also, Polyphenols has been suggested to protect cell constituents against oxidative damage, thereby limiting the risk of various degenerative diseases associated with oxidative stress (Luqman and Rizvi, 2006; Pandey *et al*., 2009; Pandey and Rizvi, 2009). *Phoenix dactylifera* (*P. dactyliferaa*) which belongs to the family Arecaecae (Sami *et al*., 2017) is referred to as date palm fruit in English, 'dabino' by the Hausas while the Yorubas call it 'labidun' (Mustafa *et al*., 1986; Biglari *et al*., 2008). The extensive nutraceutical values of *P. dactyliferaa* have been documented to include anticancer, antimutagenic, antioxidant and anti-inflammatory effects among others (Vyawahare *et al*., 2009; Pujari *et al*., 2014). *Phoenix dactylifera* fruit extract contains various phenolic compounds such as caffeic acid (dactyliferic acid), ferulic acid, luteolin, and quercetin. (Allaith, 2005) implicated for the nutraceutic activities above, but the antioxidant activity of *P. dactyliferaa* is majorly related to the total phenolic contents (Biglari *et al*., 2008). Caffeic acid (3, 4-dihydroxycinnamic acid), an important constituent of *P. dactyliferaa* , is a non-flavanoid catecholic compound present in other plants (Clifford, 1999), with a broad spectrum of pharmacological activities, including anti-inflammatory, antioxidant and immunomodulatory effects (Chan and Ho, 1997; Gulcin, 2006). It has been established that phenolic acids bearing a carbonyl group separated from the aromatic ring (e. g. cinnamic acid, caffeic acid) are able to exhibit more potent pharmacological properties than their counterparts where the carbonyl is directly linked to the aromatic ring (Luc *et al*., 2012). Luteolin (3, 4, 5, 7-tetrahydroxy flavone), another important flavanoid in *P. dactyliferaa* , is naturally found in several other plant species (Kim *et al*.,2000; Lopez-Lazaro, 2009), also has antioxidant, anticancer, anti-inflammatory, and neuroprotective properties (Chen *et al*., 2008). Presence of four hydroxyl moieties, oxygen molecules, and carbon-carbon double bonds in luteolin is advantageous to the various pharmacological properties its able to exhibit (Kim *et al*., 2000; Nabavi *et al*., 2009).

Numerous studies have asserted that MSG causes neurotoxicity, oxidative stress, inflammation and predisposition and worsening of the neurological disorders. However, there is persistent increase in MSG consumptions, thus contributing to the growing population of persons living with neurodegenerative diseases (Eweka, 2007; Hughes, 2009). Although there are potent glutamate-releasing inhibitors (glutamatergic drugs), but with several side effects, thus the need for novel natural agents with possible therapeutic effects in MSG neurotoxicity, which *P. dactyliferaa*, caffeic acid and luteolin are potential candidates.

Hence, the study aimed at investigating the ameliorative effect of luteolin, caffeic acid as well as *P. dactyliferaa* on MSG-induced neurotoxicity in the dentate gyrus of Wistar rats. Therefore, it is imperative to find affordable means of combating MSG toxicity.

MATERIALS AND METHODS

Chemicals: Luteolin (CAS No 491-70-3) and caffeic acid (CAS No 331-39-5) were obtained from Henan Kaixiang Biological Technology Ltd. China. Dried fruits of *Phoenix dactylifera* were obtained at Sango area of Ilorin, Kwara State and were certified at the Department of Plant Biology at the University of Ilorin, with voucher number UILH/001/1205. Analytical grade of methanol (CAS 67-56-1) was procured from Central Research Laboratory, Tanke, Ilorin for the methanolic crude extract of *Phoenix dactylifera* fruits.

Experimental Animals: Forty-eight male Wistar rats (120-150 g) were used for this study. These animals were accommodated in the animal holdings of the Faculty of Basic Medical Sciences, College of Health Sciences, University of Ilorin, where they had free access to food and water in accordance to the Guide for the Care and Use of Laboratory Animals of University of Ilorin, Ilorin Kwara State. Ethical approval was obtained from the Ethical Committee of the University of Ilorin through the Faculty of Basic Medical Sciences, University of Ilorin (UERC\ASN\2018\1258).

Experimental Design: The animals were grouped into eight, with six animals in each group (n=6). Groups 1-8 received the following treatment respectively; oral administration of 1.6mL/kg normal saline; 4000mg\kg monosodium glutamate (Faronmbi and Onyema, 2006) for 7 days; 4000mg\kg monosodium glutamate for 7 days and 100 mg\kg caffeic acid (Anwar *et al*., 2012) for 14 days concurrently; 4000mg\kg monosodium glutamate for 7 days and 500 mg\kg *Phoenix dactylifera* (Dibal *et al*., 2016) for 14 days concurrently; 4000mg\kg monosodium glutamate for 7 days and 100 mg\kg luteolin (Lu *et al*., 2015) for 14 days concurrently; 100 mg\kg.caffeic acid for 14 days followed by 4000mg\kg monosodium glutamate for 7 days; 500 mg\kg *Phoenix dactylifera* for 14 days followed by 4000mg\kg monosodium glutamate for 7 days; and 100 mg\kg luteolin for 14 days followed by 4000mg\kg monosodium glutamate for 7 days respectively.

Behavioural Analysis: The memory index of the animals was assessed with the Y maze test. The Y maze test was majorly used to assess spatial working memory in experimental rats. The test was conducted on day 21 of administration in a Y-shaped maze with opaque wooden arms. The three arms were of equal length (30 cm), width (10 cm) and height (15 cm). The arms were interconnected at a 120° angle from each other. The experimental animals were placed in the centre of the maze, (i.e. the junction that connects the 3 arms) one after the other. The animals were allowed to explore the three arms freely for 5 minutes. The number of arm entries and the number of triads was recorded; this was used to calculate the percentage alternation. It is important to note that an entry was being recorded when all four paws of the experimental animals were within the arm. The maze was cleaned with 95% ethanol in between two trials. This was to ensure that they

did not trace the odour of the previous animal, which could cause bias in their trend of movement. However, the percentage alternation was calculated using the formula stated below.

Percentage alternation=

$$\frac{number\ of\ complete\ triad\ enteries}{number\ of\ arm\ enteries - 2} x\ 100$$

(Hughes, 2004; Oriel and Kofman, 2015).

Animal Euthanization: After completion of administration, the rats were euthanized using ketamine on day 22. Two animals were perfused through the heart with 4% paraformaldehyde and their brain tissues excised. To obtain a coronal section of the hippocampus, the whole brain was cut coronally into two halves at the highest point and sections were taken 2mm away from the both halves. The tissue block produced was sectioned with the aid of a rotary microtome. The tissue sections were at 5 microns thick while the knife was placed at 45° to the block of wax containing the tissue. The other animals were not perfused and their brain tissues were homogenized for biochemical assays.

Histological Analysis: The haematoxylin and eosin (H and E) (Sheehan and Hrapchak 1987) staining technique was used to demonstrate the general histo-architecture of the cells; to show location of normal or abnormal nucleus of the granule cells in the granule layer of the dentate gyrus.

Determination of Biochemical Parameters: The 0.1g of the hippocampus was homogenized in 0.4 ml of 5% sucrose solution and taken to the centrifuge. The homogenate was spun for 10 minutes at 5000 revolutions per minute and the supernatants were placed in plain bottles and taken for analysis of superoxide dismutase, glutathione peroxidase and malondialdehyde. The estimation of superoxide dismutase was carried out using the methods of Sun and Zigma (1978), malondialdehyde was estimated using the methods of Buege and Aust (1978) and glutathione peroxidase was estimated using the methods of Reddy *et al*. (1995).

Statistical Analysis: Values were reported as means ± standard error of mean (SEM), comparison amongst groups was carried out using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test for multiple comparison and considered significant at $p < 0.05$. Graph pad prism version 7.0 was used for the statistical analysis.

RESULTS

Spontaneous Alternation Test: The percentage spontaneous alternation in the Y maze by the Wistar rats after exposure to normal saline, MSG, caffeic acid, luteolin and *Phoenix dactylifera* fruit is shown in Table 1. There was a marked ($p<0.05$) reduction in the percentage alternation in rats exposed to MSG alone compared with the saline-treated rats and other groups. The Co and pre-treatment with caffeic acid, luteolin and *P. dactyliferaa* then MSG caused significantly ($p<0.05$) increase in % alternation as compared to groups given MSG only.

Table 1:
The Mean and standard error of mean (SEM) of percentage alternation of Y maze

Experimental Groups	Percentage alternation
Control	90±2.2
MSG	45±1.3[a]
MSG+CAF	71±4.0[b]
MSG+LUT	68±3.3[b]
MSG+PD	72±4.7[b]
CAF--MSG	80±7.4[b]
LUT--MSG	85±4.7[b]
PD--MSG	82±3.0[b]

[a, b] signifies statistically significantly different as compared to control and MSG groups respectively

Cytoarchitecture of the Dentate Gyrus: The rats that were given normal saline, co treatment and pretreatment with luteolin, pretreatment with caffeic acid and *P. dactyliferaa* and MSG were dominated with intact granule cells (the nucleolus are centrally placed and cells are spherical in shape) while rats co-treated with caffeic acid and *P. dactyliferaa* with MSG were dominated with non-intact granule cells (the nucleolus cannot be visibly seen and the cell shape has lost is sphericity) and scanty intact granule cells. The MSG only group had predominantly non-intact granule cells as seen in Plate 1.

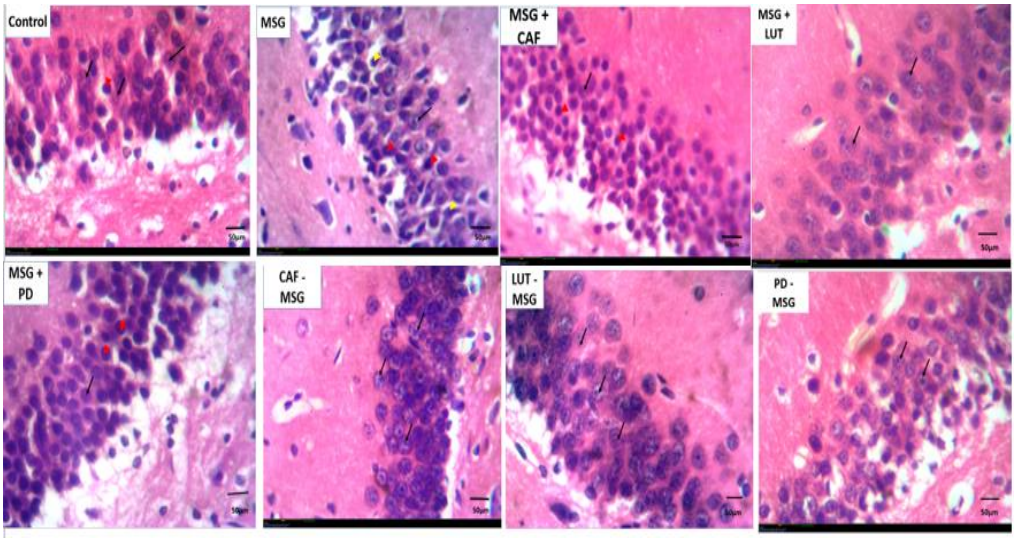

Plate 1:
Representative photomicrographs of the dentate gyrus of adult male Wistar rats showing the cytoarchitectural layer of its dentate gyrus with Hematoxylin and Eosin stain
Scale bars = 50µm. Magnification: x 400. Control, MSG = monosodium glutamate, LUT + MSG = Luteolin and MSG concurrently, MSG + PD = *Phoenix dactylifera* and MSG concurrently, MSG + CAF = caffeic acid and MSG concurrently, LUT – MSG = pre luteolin then MSG, PD – MSG = pre *Phoenix dactylifera* then MSG, CAF –MSG = pre caffeic acid then MSG. The black arrow indicates normal mature granule cells and red arrow head indicates immature granule cells.

Table 2:
The Mean and standard error of mean (SEM) of Hippocampal Malondialdehyde (MDA)Concentrations, Superoxide dismutase (SOD) and Glutathione Peroxidase (GPx) activities

Experimental groups	Malondialdehyde (U\ mg protein)	Superoxide Dismutase activities(U\mgprotein)	Glutathione Peroxidase(U\mg Protein)
Control	0.098±0.02	542±20	164±11
MSG	0.97±0.03[a]	50±9.6[a]	50±13[a]
MSG+CAF	0.81±0.07[a]	294±23[ab]	63±7[a]
MSG+LUT	0.33±0.05[ab]	164±4.7[ab]	101±8.7
MSG+PD	0.64±0.07[ab]	172±14[ab]	100±11
CAF--MSG	0.071±0.03[b]	458±24[b]	152±8.7[b]
LUT—MSG	0.16±0.01[b]	481±18[b]	138±5.1[b]
PD--MSG	0.32±0.03[ab]	450±9.6[b]	125±11

[a, b] signifies statistically significantly different as compared to control and MSG groups respectively.

Oxidative Stress Markers: The hippocampus of the experimental animals were isolated and homogenized in 5% sucrose. The concentration of malondialdehyde in the hippocampus of male Wistar rats after exposure to normal saline, monosodium glutamate, caffeic acid, luteolin, and *Phoenix dactylifera* fruit is shown (Table 2). There was a statistically significant ($p<0.05$) increment in the concentration of malondialdehyde in the hippocampus of rats exposed to MSG alone when compared with the saline-treated rats and other groups except the groups given concurrent treatment of caffeic acid and MSG. The administrations of caffeic acid, luteolin, and *P. dactyliferaa* before and/or concurrently exposed to MSG caused statistical significant decrease ($p<0.05$) in the concentration of malondialdehyde as compared to MSG only exposed rats. The activities of superoxide dismutase in the hippocampus of male Wistar rats after exposure to normal saline, monosodium glutamate, caffeic acid, luteolin and *Phoenix dactylifera* fruit is shown in Table 2. There was a significant ($p<0.05$) reduction in the activities of superoxide dismutase of rats exposed to MSG alone when compared with the saline-treated rats and other groups. The administrations of caffeic acid, luteolin, and *P. dactyliferaa* before and/or concurrently exposed to MSG caused significant increase ($p<0.05$) in the activities of superoxide dismutase as compared to the hippocampus of groups of rats exposed to MSG only.

The activities of glutathione peroxidase (GPx) in the hippocampus of male Wistar rats after exposure to normal saline, monosodium glutamate, caffeic acid, luteolin and *Phoenix dactylifera* fruit is shown in Table 2. There was a significant ($p<0.05$) reduction in the activities of GPx in rats exposed to MSG alone when compared with the saline treated rats, and other groups except the groups given concurrent treatment of caffeic acid and MSG. The administrations of caffeic acid, luteolin and *P. dactyliferaa* before and/or concurrently exposed to MSG caused significant increase ($p<0.05$) in the activities of glutathione peroxidase as compared to MSG only exposed rats.

DISCUSSION

Spatial memory was measured using percentage of spontaneous alternation. Deficit in spatial memory was indicated by significant reduction in percentage alternation in the MSG treated groups as compared to control. It has been reported that MSG reduces performance in spatial memory as well as the ability for learning task. This is as a result of over-excitation of the N-methyl-D- aspartate (NMDA) receptor (Swamy *et al*., 2013), thereby disrupting the normal course of long-term potentiation (Onaolapo *et al*. 2012).

However, significant increase in spatial memory was obtained in rats given caffeic acid, luteolin, and *P. dactyliferaa* before and/or concurrently exposed to MSG as compared to MSG only exposed rats. It has been reported that caffeic acid, luteolin, and *P. dactyliferaa* improves memory and learning due to their ability to enhance proliferation of granule cells in the hippocampal dentate gyrus. Their ability to exhibit neuroprotective and antioxidant effects are also contributory (Subash *et al*., 2015; Wang *et al*., 2016; Chang *et al*., 2019 and Zhou *et al*. 2019).

Neurogenesis occurs in the dentate gyrus even in adulthood (Hashem *et al*., 2010). It was observed that there was more immature granule cells in the MSG only as compared to control. It was reported that neuronal death within the hippocampus provide stimulus for increased dentate neurogenesis and it was established that dentate neurogenesis was reported in neurodegenerative diseases patients (Hashem *et al*., 2010). This may help compensate for the apoptotic cells during injury. However, pretreatment with caffeic acid, luteolin and *P. dactyliferaa* before MSG had dominant mature granule cells. The treatment exhibited protective effect on the granule cells.

The intensity of lipid peroxidation was accessed by measuring the level of MDA. Significant increase in level of lipid peroxidation in the rats given MSG was due to generation of reactive oxygen species (ROS). Malondialdehyde is a secondary resultant product of lipid peroxidation due to alteration in the membrane intergrity caused by tremendous increase in lipid peroxidation in the membrane which is dominated by polysaturated fatty acid (Fasakin *et al*., 2017; Arise *et al*., 2019). Its increase has been previously reported as a result of excitotoxicity (Arise *et al*., 2019). However, significant decrease in the extent of lipid peroxidation was apparent in rats given caffeic acid, luteolin, and *P. dactyliferaa* before and/or concurrently exposed to MSG as compared to MSG only exposed rats. These were ascertained by significant decrease in the level of MDA. It has been reported that caffeic acid and luteolin have stable chemical structure that aids its scavenging of ROS and is also effective in the scavenging of peroxyl radical involved in lipid peroxidation (Yucel *et al*., 2012; Agunloye and Oboh 2017 and Siddique *et al*., 2018)

Superoxide dismutase (SOD) and glutathione peroxidase (GPx) enzymes are vital protective mechanisms against generated free radicals resulting from tissue damage. The SOD converts superoxide ion to less reactive hydrogen peroxide while GPx reduces lipid peroxide and hydrogen peroxides to lipid alcohols and water respectively. Reduction in the activities of the two enzymes could further help explain the increased lipid peroxidation in the MSG only group. Reduction in the activities of the two has been reported as a leading factor in oxidative stress, excitotoxicity and pathophysiology of neurodegenerative diseases (Onaolapo *et al*., 2016; Arise *et al*., 2019). However, significant decrease in the extent of oxidative stress was apparent in rats given caffeic acid, luteolin, and *P. dactyliferaa* before and/or concurrently exposed to MSG except the group given concurrent treatment of caffeic acid and MSG as compared to MSG only exposed rats. These were ascertained by significant increase in the level of SOD and GPX as compared to MSG only groups. It has been reported that caffeic acid, *Phoenix dactylifera* and luteolin help increase antioxidant capacity by upregulating the activities of SOD and GPx and scavenge or inhibit free radicals (Pujari *et al*., 2014; Alkis *et al*., 2015 and Akinrinde and Adebiyi, 2019). These results in the eventual protective effect being exhibited by caffeic acid, luteolin and Phoenix dactylifera.

In conclusion, this study demonstrated the potentials of luteolin, caffeic acid and *Phoenix dactylifera* on MSG-toxicity on the dentate gyrus. Luteolin, caffeic acid and *Phoenix dactylifera* had mitigating effects on the dentate gyrus cytoarchitecture, oxidative stress and working memory following the deleterious effect caused by MSG, with luteolin being the most effective treatment amongst the three. Pre-treatment with luteolin, caffeic acid and *Phoenix dactylifera* was more effective than cotreatment.

Conflict of Interest

There was no conflict of interest.

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