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Original Research Article

Protective effects of Shilajit on neurotransmitter levels, oxidative stress, and histopathological alterations in monosodium glutamate-induced neurotoxicity in male mice

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Abstract

Purpose: *To investigate the role of Shilajit in ameliorating the effects of monosodium glutamate (MSG) on neurotransmitters, oxidative stress parameters, and brain tissue damage.*
Methods: *Fifty mice were divided into 5 groups of 10 mice each. G-1 received distilled water as control. G-2 received 2 g/kg of MSG, G-3 was given 2 g/kg of MSG with 100 mg/kg of Shilajit (Shi), G-4 was given 4 g/kg of MSG, and G-5 was given 4 g/kg of MSG with 200 mg/kg of Shilajit, by oral route once daily for 14 consecutive days.*
Results: *The 2 and 4 g/kg doses of MSG caused an increase ($p < 0.05$) in brain weights, compared to the control group. Neurotransmitter parameters, including glutamine and acetylcholinesterase, in all treated groups were significantly decreased ($p < 0.05$), except for G-5, which was normal. Epinephrine level showed a significant increase in all treated groups in comparison with G-1, while G-5 was normal. In addition, the serotonin levels were significantly decreased $p < 0.05$ in all treated groups compared to G-1. Oxidative stress parameters showed a significant decrease in glutathione and catalase levels in MSG-only treated groups, while shilajit improved the levels of glutathione and catalase ($p < 0.05$). Histological investigation of brain tissues in G-2, G-3 and G-5 showed normal histological features, while G-4 had histological alterations.*
Conclusion: *Shilajit ameliorates the detrimental effects of MSG-induced toxicity in cortical brain cells in mice, and this can be attributed to its potent anti-inflammatory and antioxidant properties.*

Keywords: *Antioxidant, Glutamate, Inflammation, Serotonin, Shilajit*

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INTRODUCTION

Shilajit is a naturally occurring substance that contains magnesium, potassium, and humic compounds. In addition, it includes proteins, fatty acids, amino acids, particularly glycine, and bioactive substances like gallic and caffeic acids [1]. Shilajit is a common natural, physiologically active, sticky, brown organic substance that is released from rocks in many of the world's mountain ranges [2]. Shilajit is utilized to boost metabolism and has anti-inflammatory and antioxidant effects. Furthermore, it is used to treat allergies and promote immunity [3]. Monosodium glutamate (MSG) is a water-soluble glutamate salt that is frequently found in foods high in protein and is typically produced by the body. Because of its ability to enhance flavor and taste, MSG is used all over the world [4]. High concentrations of food additives can cause neurotoxic injury, brain damage, and lipid peroxidation [5,6].

The consumption of MSG can cause oxidative stress in the brain [7]. MSG usage caused hyperalgesia and elevation of brain nitric oxide levels [8]. The consumption of MSG causes Alzheimer's disease-like pathology, such as amyloid-β accumulation, to manifest earlier, and memory problems [9]. Other disorders include decreased red blood cells (RBC), white blood cells (WBC), and platelet count during MSG consumption. Furthermore, acetylcholinesterase activity is also diminished following MSG use [10]. Obesity and memory impairments were brought on by MSG treatment [11]. Monosodium glutamate can also cause testicular toxicity and apoptosis by destroying gonadotropin-releasing hormone (GnRH) neurons [12].

Human dietary use of MSG has been linked in studies to behavioral abnormalities, inflammation, metabolic disturbance, neurotoxicity, hepatotoxicity, cardiotoxicity, and premalignant variations [13]. Other studies have mentioned that hypertension and impaired neurological and endocrine system function are physiological incidents linked to MSG toxicity [14]. Neurotransmitter levels, including glutamate, serotonin, and norepinephrine, were disrupted by MSG, which clearly shows neurodegeneration [15]. Monosodium glutamate dietary use has resulted in increased atherogenic threat, neurobehavioral impairments, an elevated inflammatory reaction, and oxidative distress in the brain [16]. Additionally, the use of MSG resulted in oxidative stress since it increased lipid peroxidation and decreased glutathione (GSH) and catalase, which may be a symptom of a major redox change [17,18].

Shilajit with chromium and Phyllanthus emblica may improve some diet-induced alterations in blood lipids, insulin efficacy, platelet aggregation, endothelial integrity, and body status [19]. Shilajit is commonly used as an antioxidant and to treat inflammatory disorders. Also, it is used to boost energy and metabolism as well as general health [20]. Shilajit is a helpful treatment for secondary brain injury and has a neuroprotective impact against amyloid β [21]. This work aims to study the role of Shilajit in ameliorating the effects of monosodium glutamate on neurotransmitters, oxidative stress parameters, disorders, and brain tissue damage.

EXPERIMENTAL

Animals

Fifty adult male mice obtained from the National Center for Drug Control and Research (10 for each group), weighing between 20 and 25 g, were used. They were kept in a laboratory with normal conditions at 22 ± 1 ˚C, with access to water and food [22].

Ethical approval

The College of Dentistry at Al-Iraqia University's scientific authority approved the animal experiment and evaluations by the NIH Guide for the Care and Use of Laboratory Animals (code: ES and HER 9-7-2025).

Shilajit and monosodium glutamate preparation

To get 100 and 200 mg/kg of purified Shilajit (Shi; 200 mg; Sayan, China), it was mixed with 20 mL of distilled water as earlier described [23]. The 2 and 4 g/kg solutions of monosodium glutamate (Fufeng Group, China) were made by mixing the powder with 20 mL of distilled water [24]. The concentration of monosodium glutamate and shilajit was chosen based on earlier scientific research [25]. The chemical composition of shilajit by weight was 80 % humic substances. Furthermore, it contains 20 % of potassium, calcium, and magnesium. Also, it contains proteins and amino acids [1].

Design

The animals were divided into five groups (10 animals per group). G-1, control, was treated with distilled water. G-2 was given 2 g/kg of MSG. G-3 was administered 2 g/kg of MSG and 100 mg/kg of Shilajit. G-4 was administered 4 g/kg of MSG. G-5 was administered 4 g/kg of MSG and 200 mg/kg of Shilajit, orally once daily for 14 days.

ketamine 80 mg/kg and xylazine 8 mg/kg intraperitoneally were used to anesthetize the mice at the end of 14 days [26]. Blood was collected by heart puncture (2 mL) for serum neurotransmitter (glutamine, acetylcholinesterase, epinephrine and serotonin) and oxidative stress (glutathione and catalase) parameter analysis by enzyme-linked immunosorbent assay (ELISA), Abnova, KA 1909, Elabscience Co. E-EL-R0355, E-EL-0045, E-EL-0033, E-EL-R2491, E-AB-11036. The brains were removed, weighed, and fixed with formalin 10 %.

Histological examination

The fixed brain was dehydrated by serial ascending concentrations of ethyl alcohol [27]. Furthermore, the tissues were cleared and tissue blocks created via paraffin wax. The blocks were sectioned at 5 µm thickness [28]. The tissues were stained with hematoxylin and eosin solution (H&E). Under light microscopy, the stained specimens were examined and graded. The anomalies in the tissue sections were evaluated from 0 (normal architecture) to 3 (severe histological alterations) for a quantitative histological assessment of the structural variations.

Statistical analysis

Data were evaluated using IBM SPSS Statistics version 22, USA. The outcomes were assessed using the least significant difference (LSD) and the one-way analysis of variance (ANOVA). Values with probability ($P < 0.05$) were considered to be statistically significant. The data were displayed using mean ± standard error of the mean (SEM).

RESULTS

The findings showed that G-2, which received MSG at 2 g/kg, exhibited a significant ($P \leq 0.05$) increase in brain weight (0.65 ± 0.02 g) when compared to the control group (0.61 ± 0.01 g). Additionally, G-3, given 2 g/kg of MSG with 100 mg/kg of shilajit, showed a decrease at $p < 0.05$ in brain weight (0.60 ± 0.02 g). The brain weight (0.66 ± 0.02 g) increased significantly at $p < 0.05$ in G-4 that received 4 g/kg of MSG. However, with the addition of 200 mg/kg of Shi to 4 g/kg of MSG, as seen in G-5, brain weight (0.61 ± 0.03 g) normalized (Figure 1).

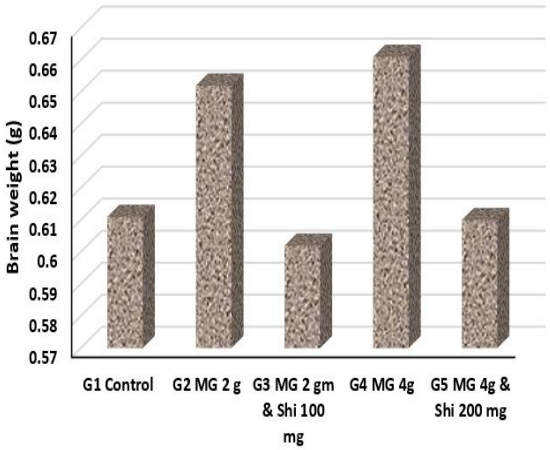


Figure 1: Effect of MSG and Shilajit on the brain weight

The results in Table 1 showed that the serum neurotransmitter parameters, including glutamine and acetylcholinesterase, in all treated groups (G-2 - G-4) were significantly decreased at $p < 0.05$ in comparison with G-1, except that of G-5, which was normal, like the control group. Epinephrine level showed a significant increase at $p < 0.05$ in treated groups (G-2 to G-4), while G-5 was normal, like the control. In addition, the serotonin levels decreased significantly in all treated groups (G-2 to G-5) in comparison with G-1.

Table 1: Impact of MSG and Shilajit on the neurotransmitter levels (n=10)

Group	Glutamine (ng/mL)	Acetylcholinesterase (mU/mL)	Epinephrine (ng/mL)	Serotonin (pg/mL)
G-1 control	51.85 ± 1.01^a	20.68 ± 1.00^a	207 ± 7.65^a	311.84 ± 24.18^a
G-2 (2 g/kg) MSG	41.96 ± 1.02^b	14.97 ± 1.34^b	364.66 ± 39.66^b	177.32 ± 3.96^b
G-3 (2 g/kg) MSG 100 mg/kg Shi	31.46 ± 0.93^c	13.42 ± 0.67^b	392.56 ± 34.38^b	121.31 ± 5.62^c
G-4 (4 g/kg) MSG	27.65 ± 0.45^d	7.21 ± 0.56^c	477.69 ± 28.74^c	90.23 ± 4.53^c
G-5 (4 g/kg) MSG 200 mg/kg Shi	50.83 ± 2.38^a	20.90 ± 1.77^a	208.10 ± 12.01^a	254.51 ± 14.17^d
LSD	3.773	3.291	78.352	37.548

Note: Different letters mean there are significant changes, mean ± SEM, $P < 0.05$

When compared to the control group (1.19 ± 0.23 nmol/mL), group 2, which received MSG at 2 g/kg, showed no significant changes (1.14 ± 0.01 nmol/mL) glutathione level at $p \leq 0.05$. In addition, group 3 demonstrated a normal (1.20 ± 0.08 nmol/mL) glutathione level after receiving 2 g/kg

of MSG together with 100 mg/kg of shilajit. Furthermore, group 4, after receiving 4 g/kg of

MSG, showed a significantly decreased glutathione level (1.13 ± 0.02 nmol/mL). However, group 5 showed that shilajit improved the glutathione level (1.20 ± 0.03 nmol/mL; Figure 2).

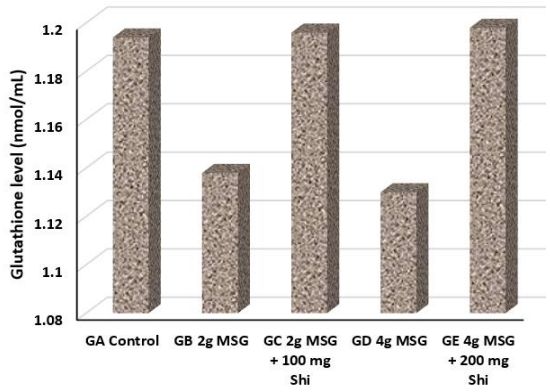


Figure 2: Effect of MSG and Shilajit on the glutathione level

The results showed that the catalase level decreased significantly at $p < 0.05$ in group 2 (12.80 ± 0.52 pg/mL) and group 4 (12.68 ± 0.44 pg/mL) when animals were treated with low and high doses of MSG, respectively. However, shilajit improved at $p < 0.05$ the catalase levels in group 3 to (14.14 ± 0.63 pg/mL) and group 5 to (13.34 ± 1.68 pg/mL) at $p < 0.05$ (Figure 3).

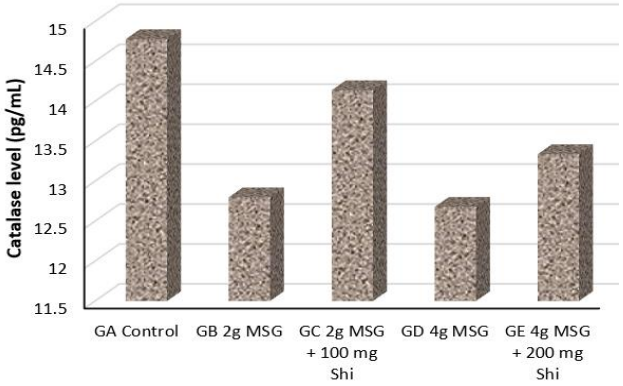


Figure 3: Effect of MSG and Shilajit on the catalase level

The histological effects are presented in Table 2, showing the effect on animals treated with different doses of MSG and Shilajit compared with the control group.

Table 2: Histological alterations in the cerebrum and cerebellum of control and treated groups (n=10)

Histological changes	G-1 Control			G-2 (2 g/kg MSG)			G-3 (2 g/kg MSG & 100 mg/kg Shi)			G-4 (4 g/kg MSG)			G-5 (4 g/kg MSG & 200 mg/kg Shi)		
	N	%	Area (µm)	N	%	Area (µm)	N	%	Area (µm)	N	%	Area (µm)	N	%	Area (µm)
Disarrangement of cortical molecular layer	0	0	0	0	0	0	0	0	0	6	60	229.6±8.29	3	30	2.4±3.95
Degeneration of cortical nerve cells	0	0	0	0	0	0	0	0	0	7	70	167.5±6.42	2	20	2.2±4.66
Cellular necrosis	0	0	0	0	0	0	0	0	0	4	40	114.8±2.86	0	0	0
Pyknosis of nucleus	0	0	0	0	0	0	0	0	0	6	60	60.3±4.57	1	10	1.5±4.74
Cerebellum identified disarrangement of molecular layer with vacuolated spaces	0	0	0	0	0	0	0	0	0	7	70	224.4±4.48	2	20	2±4.24
Gliosis	0	0	0	0	0	0	0	0	0	8	80	247.4±8.96	1	10	1.2±3.79

Histoarchitectural evaluation of brain tissues showed that the control group had normal histological features, including a normal frontal cerebral cortex made up of pyramidal and circular neurons surrounded by eosinophilic glial filaments, and a normal structuring of neuronal layers and fibers (Figure 4). The cerebellum in the control group contains the molecular layer (M), granular layer (Gr), and Purkinje cells (Figure 5).

Histological investigation of the brain tissues in G-2 treated with a low dose (2 g/kg) of MSG showed

normal histological features. These included a normal cerebral cortex made up of pyramidal and circular neurons surrounded by eosinophilic glial filaments, and a normal structuring of neuronal layers and fibers (Figure 6). Furthermore, the cerebellum contains a normal molecular layer, granular layer, and Purkinje cells (Figure 7).

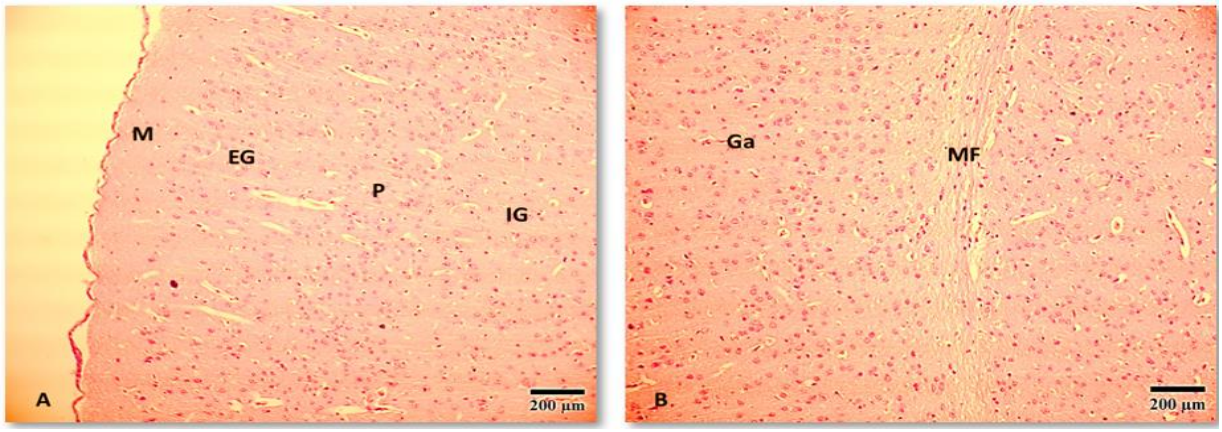


Figure 4: Photomicrograph of cerebral cortex in control group showing: A: molecular layer (M), external granular layer (EG), pyramidal layer (P), inner granular layer (IG), B: ganglionic layer (Ga), multiform layer (MF; H&E) 100x

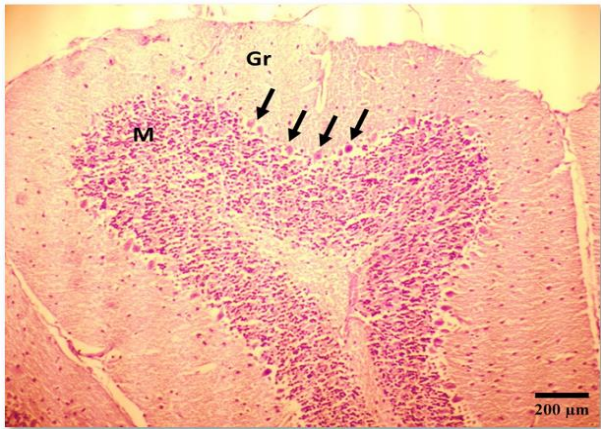


Figure 5: Photomicrograph of cerebellum in control group showing: molecular layer (M), granular layer (Gr), Purkinje cells (arrows; H&E)

Histological evaluation of the frontal brain tissues in G-4 treated with a high dose (4 g/kg) of MSG showed histological alterations, including disarrangement of the cortical molecular layer, degeneration of cortical nerve cells, cellular necrosis, and expanding cortical gliosis in the multiform layer and pyknosis of nerve cells (Figure 10). However, the cerebellum showed disarrangement of the molecular layer with vacuolated spaces, congestion of blood vessels, degeneration of Purkinje cells, and formation of cellular masses (Figure 11).

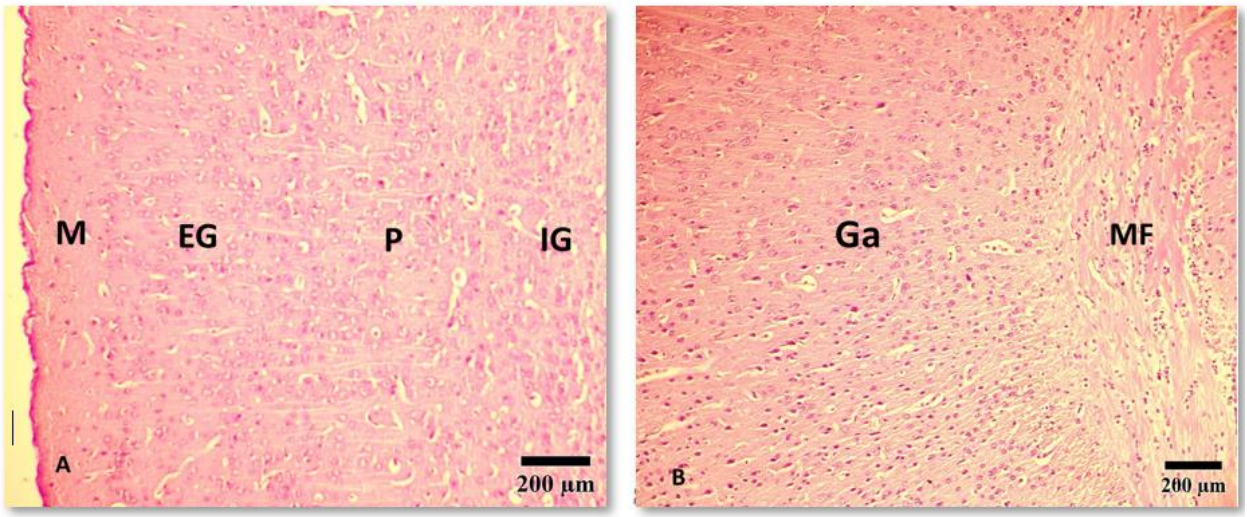


Figure 6: Photomicrograph of cerebral cortex in G-2 showing: A: normal molecular layer (M), external granular layer (EG), pyramidal layer (P), inner granular layer (IG); B: ganglionic layer (Ga), multiform layer (MF; H&E)

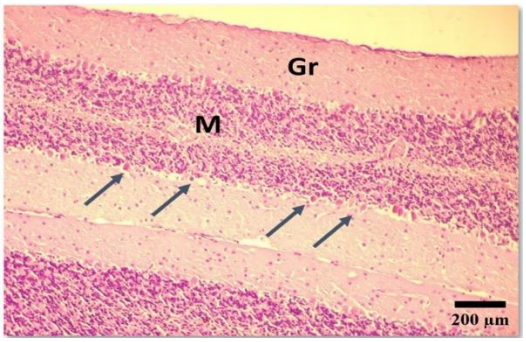


Figure 7: Photomicrograph of the cerebellum in G-2 showing: normal molecular layer (M), granular layer (Gr), Purkinje cells (arrows; H&E).

Histological assessment of the brain tissues in G-3 treated with a low dose (2 g/kg) of MSG with (100 mg/kg) of Shi showed normal histological features, including a normal cerebral cortex made up of pyramidal and circular neurons surrounded by eosinophilic glial filaments, and a normal structuring of neuronal layers and fibers (Figure 8). In addition, the cerebellum contains the molecular layer, granular layer, and Purkinje cells (Figure 9).

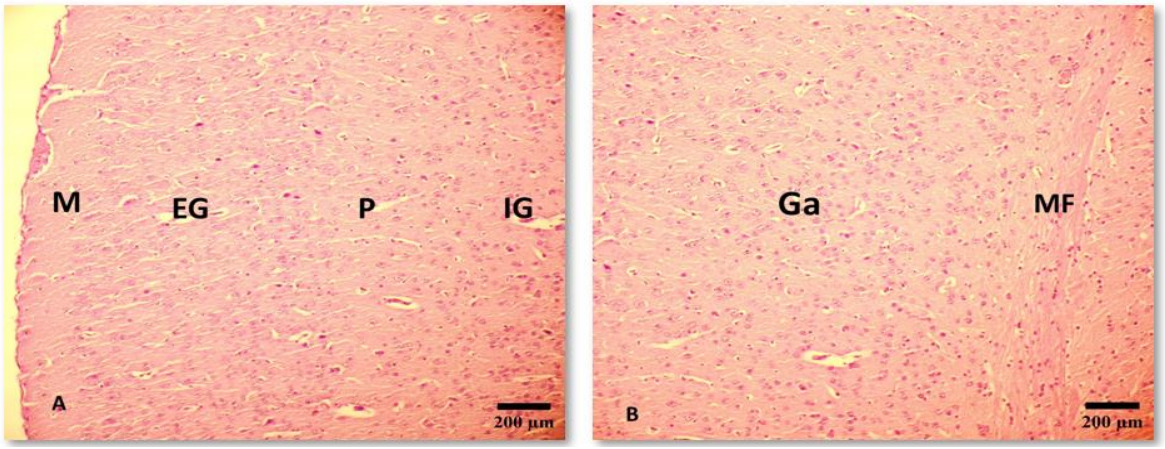


Figure 8: Photomicrograph of cerebral cortex in G-3 showing: A: normal molecular layer (M), external granular layer (EG), pyramidal layer (P), inner granular layer (IG); B: ganglionic layer (Ga), multiform layer (MF; H&E)



Figure 9: Photomicrograph of cerebellum in G-3 showing: normal molecular layer (M), granular layer (Gr), Purkinje cells (arrows; H&E)

Histoarchitectural structures investigation of brain tissues in G-5 treated with a high dose (4 g/kg) of MSG with (200 mg/kg) of Shi had normal histological features, including a normal cerebral cortex made up of pyramidal and circular neurons surrounded by eosinophilic glial filaments, and a normal structuring of neuronal layers and fibers (Figure 12). In addition, the cerebellum contains the molecular layer, granular layer, and Purkinje cells (Figure 13). Concerning the neurotransmitter levels, the results revealed that Shilajit enhanced the activity of glutamine and acetylcholinesterase by augmenting the neuronal cells of the cortex and repairing the damage.

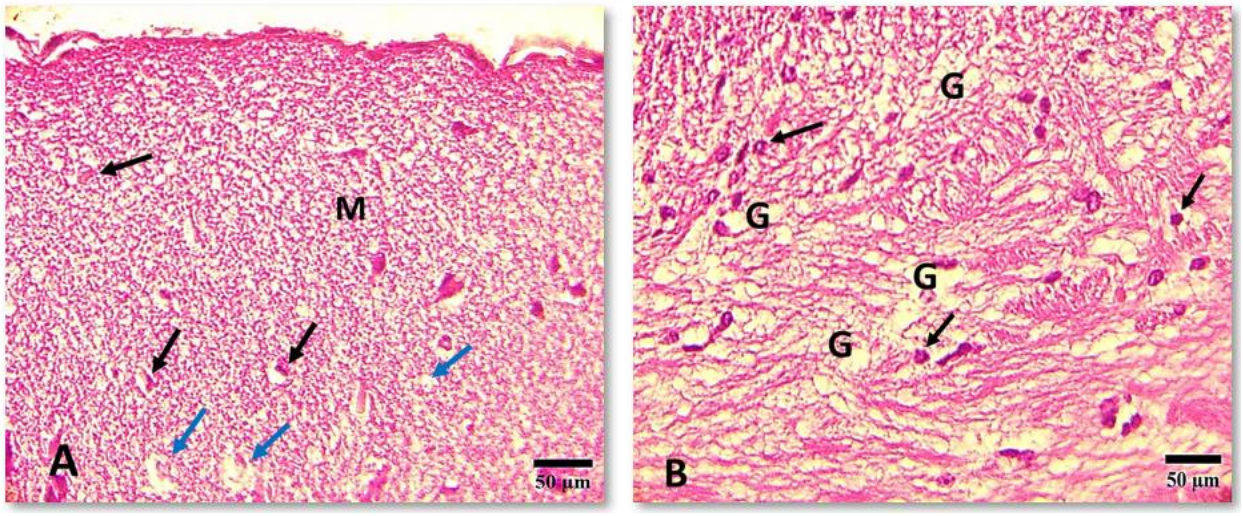


Figure 10: Photomicrograph of cerebral cortex in the group G-4 showing: A: Disarrangement of cortical molecular layer (M), degeneration of cortical nerve cells (black arrows), cellular necrosis (blue arrows). B: expanding cortical gliosis (G) in the multiform layer, pyknosis of nerve cells (arrows; H&E)

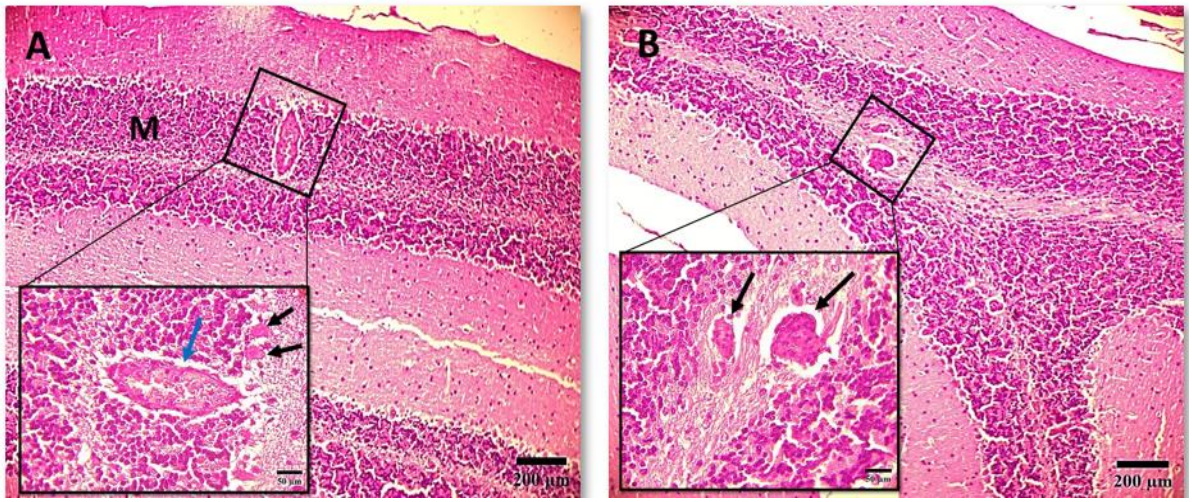


Figure 11: Photomicrograph of cerebellum in G-4 showing: A: Disarrangement of molecular layer (M) with more spaces, congestion of blood vessels (blue arrow), and degeneration of Purkinje cells (black arrows), B: formation of cellular masses (arrows; H&E)

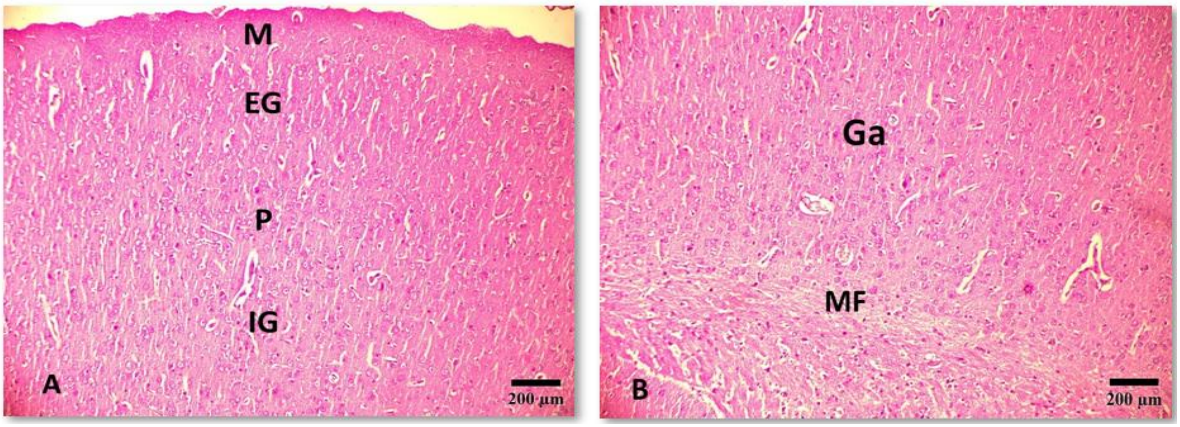


Figure 12: Photomicrograph of cerebral cortex in G-5 showing: A: normal molecular layer (M), external granular layer (EG), pyramidal layer (P), inner granular layer (IG), B: ganglionic layer (Ga), multiform layer (MF; H&E)

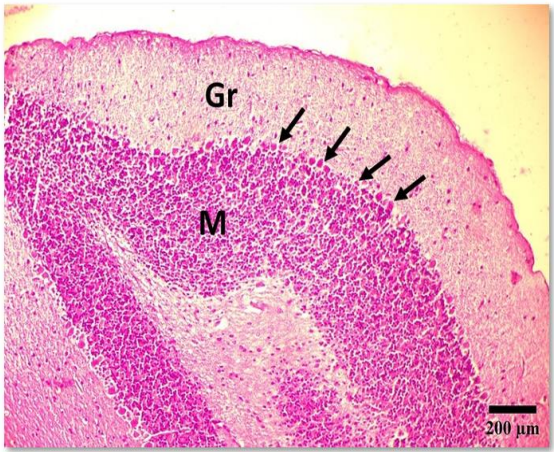


Figure 13: Photomicrograph of cerebellum in G-5 showing: normal molecular layer (M), granular layer (Gr), Purkinje cells (arrows; H&E)

DISCUSSION

Over time and with repeated consumption of foods preserved with MSG, neurotoxic injury and brain damage result. Different concentrations of MSG will cause variable changes in brain weights due to increased levels of oxidative stress, which leads to tissue damage [29]. The outcomes of another study showed that MSG caused alterations in the neural cells of brain tissue, elevated oxidative stress, and adverse effects on weight, function, and cognitive ability [30]. Intake of MSG leads to a decrease in neurotransmitter levels, which is due to an increase in oxidative stress, and this results in neuronal damage and physiological disorders, as noted by Essawy et al [31]. The findings of another study demonstrated that a low dose of MSG had no significant impact on metabolic function, and inflammatory interleukins provoked cellular environment regulation [32].

Shilajit is used to rejuvenate and promote reduced oxidative stress markers following brain injury [33]. Additionally, shilajit, which has antioxidant function, can help eliminate oxidative stress and reduce it. Similar to the protection reported for the antioxidant betanin against MSG, as shown in a study by Baytar et al [17] after using betanin against MSG. The data indicated that a low dose of MSG did not cause brain alterations; on the other hand, Shilajit had antioxidant action and protective effects. The results are consistent with Badiana et al [34], who revealed that the herbal supplement has neuroprotective characteristics in mice that may involve antioxidant defense mechanisms. Damage from the high dose of MSG in the animals of group 4 showed essential features of neurodegeneration, including disorganization of the cortical molecular layer, degeneration of cortical nerve cells, cellular necrosis, expanding cortical gliosis in the multiform layer, and pyknosis of nerve cells. These are attributed to anomalies in neurotransmitter levels as revealed by Essawy et al [31]. The results, which demonstrate a broad antioxidant marker response, were significantly impacted by Shilajit administration; this improvement was observed at the glutathione and catalase levels. This effect agrees with Albrakati [35], who documented that apigenin flavonoids augment neurotransmitter activity through lowering of inflammatory mediators and oxidative stress, and repair of the brain cortex's tissue architecture and improvement of the metabolic conditions.

CONCLUSION

This study reveals Shilajit's ameliorative activity against the detrimental effects of MSG-induced toxicity in the cortical brain cells in mice, which can be attributed to its potent anti-inflammatory and antioxidant properties and improvement of the physiological conditions. Shilajit serves as a defense against brain damage caused by food additives. Long-term effects, the optimal dosage for therapeutic purposes, and the biological mechanisms of action of Shilajit require further study.

DECLARATIONS

Acknowledgement/Funding

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Ethical approval

The College of Dentistry at Al-Iraqia University's scientific authority approved the animal experiment (no. ES and HER 9-7-2025).

Use of Artificial intelligence/Large language models

The authors confirm that AI-based tools were used solely for language editing and manuscript polishing purposes (e.g., grammar, phrasing, and clarity). No AI tools were used to generate content, interpret data, or influence study design, results, or conclusions. All intellectual contributions, study analyses, and interpretations reported in the manuscript are the original work of the authors.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the author(s) named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

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