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Assessment of the neurobehavioral and histomorphological effects of quercetin on monosodium glutamate-induced changes in the rat cerebral cortex

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ABSTRACT

Consumption of monosodium glutamate (MSG), a widely used flavour enhancer has been associated with oxidative stress, proinflammation and neurodegeneration. There have also been suggestions that the use of flavonoids like quercetin could exert neuroprotective potentials in MSG-induced neurotoxicity; necessitating this study. This study examined the effects of quercetin supplementation on MSG-induced changes in neurobehaviour and cerebrocortical histomorphology in rats. Sixty male rats (120–150 g) were assigned to six groups of ten each. Group A (control) were fed standard rat chow and administered saline orally (10 ml/kg). Groups B and C were fed quercetin-supplemented diets at 200 and 400 mg/kg respectively, while group D received MSG orally (80 mg/kg body weight). Rats in groups E and F were fed quercetin-supplemented diets and administered MSG orally. Treatment was for a period of 35 days. On day 36, animals were exposed to the behavioural paradigms following which they were euthanised. Blood was taken for biochemical assays while the cerebral cortex was excised and processed for general histology. The results showed significant decrease in body weight and feed intake in the MSG-treated groups and a reversal by quercetin. Horizontal locomotion and rearing decreased with MSG while grooming increased. The administration of quercetin reversed these changes. Result of cerebral histomorphology revealed variable degrees of preservation of the architecture of the cerebral cortex in groups E and F compared to group D. These findings suggest that the use of quercetin offers a promising neuroprotective strategy against monosodium glutamate-induced cerebral cortex toxicity.

KEYWORDS: Antioxidants; Flavonoids; Monosodium glutamate; Neuroprotection

1. Introduction

Monosodium glutamate (MSG), the sodium salt of glutamic acid, is a widely used flavour enhancer found in processed foods, canned soups, snacks, frozen meals, and Asian cuisine. It enhances the savoury umami taste by stimulating specific taste receptors on the tongue [1]. While the human body naturally produces glutamate, essential for metabolism and brain function, excessive dietary intake of MSG is associated with adverse health outcomes [2]. Research links high MSG consumption to oxidative stress, neurotoxicity, obesity, metabolic syndrome and liver injury [3]. These effects stem from the overactivation of neurotransmitter systems, particularly glutamate, an excitatory neurotransmitter critical for cognitive functions like learning and memory [4]. Excessive activation of glutamate receptors in the central nervous system can lead to neuronal damage, contributing to acute and chronic neurological conditions, including hypoxic-ischemic injury, traumatic brain injury, Alzheimer's disease, Parkinson's disease, and Huntington's disease [5]. Glutamate-related neurotoxicity involves the accumulation of MSG in the brain, causing excitotoxicity and subsequent damage to neurocognitive functions including memory, attention, and decision-making. [6]. MSG is commercially synthesized through protein hydrolysis or fermentation and is present in

various flavour-enhancing additives like hydrolysed vegetable proteins and yeast extracts. [7].

Humans are exposed to dietary glutamate through digestion of protein-rich foods or direct consumption of MSG-containing products, with absorption mediated by a specific amino acid transport system in the gut. [8-12]. While the potential toxic potential of MSG has been queried [13, 14], with a few studies demonstrating that mode of intake of MSG could be crucial in the development of MSG induced neurotoxicity [15 16]. There have been suggestions that the consumption of flavonoid rich supplements like quercetin could be protective against the development of MSG-induced toxicities [17].

Quercetin, a dietary flavonoid with strong antioxidant and anti-inflammatory properties, has shown promise in mitigating oxidative damage and neurodegeneration [18]. Studies suggest quercetin can counteract neuronal injury and reduce inflammatory responses, particularly in ischemic and reperfusion-related brain damage. Quercetin's neuroprotective effects may stem from its ability to reduce oxidative stress, modulate inflammatory cytokines, and enhance neuronal resilience, making it a potential therapeutic agent for managing MSG-induced neurotoxicity [19]

This study investigated quercetin's ability to mitigate MSG-induced cognitive and structural brain damage. Specifically, it assesses the effects of quercetin on body weight, food intake, and exploratory behaviour. Additionally, the study examined the effect of quercetin on oxidative stress parameters, inflammatory cytokines and on structural changes induced by MSG. This was with a view to ascertain the possible ameliorative effects of quercetin induced neurotoxicity and quercetin's protective potential.

2. Materials and Methodology

2.1 Chemicals and Drugs

Monosodium glutamate (250g, Sigma-Aldrich) Quercetin (500 mg, MRM Nutrition, USA), Normal saline, Assay kits for lipid peroxidation (malondialdehyde), interleukin-1β, interleukin-6 and Total antioxidant capacity (TAC) (Biovision Inc., Milpitas, CA, USA).

2.2 Animals

The healthy Wistar rats used in this study were obtained from Empire Breeders in Osogbo, Osun State, Nigeria. Rats were housed in hardwood cages measuring 20 x 10 x 12 inches within room temperature (25°C ±2.5°C), with lights on at 7:00 am and off at 7 pm. Rats were granted unrestricted access to feed and water. All procedures were conducted in accordance with the protocols of the Faculty of Basic Medical Sciences, Ladoke Akintola University of Technology, and complied with the European Council Directive (EU2010/63) on the care and use of animals in scientific research.

2.3 Experimental Methods

Sixty male rats weighing 120-150g each were used for this study. Rats were randomly assigned into six groups of ten animals each. Group A, control group, were fed standard rat chow and also administered normal saline orally at 10 ml/kg. Rats in group B and C served as quercetin control, and were fed quercetin incorporated into rodent chow at 200 and 400 mg/kg of feed respectively and also administered saline orally. Rats in group D (MSG control), were fed rodent chow and administered MSG orally at 80mg/kg body weight, while rats in groups E and F were fed quercetin supplemented diet at 200 and 400 mg/kg, and also administered MSG orally. Monosodium glutamate was administered orally via a cannula, with MSG dosages determined according to the prior research of [20]. Quercetin dosages were also determined according to the prior research [21]. After treatment, animals were exposed to the behavioural paradigms including the open field, elevated plus maze, open field, and Y-maze. Twenty-four hours post-testing, rats were sacrificed by cervical dislocation, and blood was drawn for analysis of lipid peroxidation measured by malondialdehyde levels, total antioxidant capacity and interleukins (IL-6 and IL-1β). Rat brains were excised, fixed in 10% formol-calcium, and the cerebral cortex sections were processed, embedded in paraffin, and stained with haematoxylin and eosin and cresyl fast volet or general histological evaluation.

2.4 Determination of Feed intake and Body weight

Feed intake and body weight were assessed respectively using a Mettler Toledo weighing balance (Type BD6000, Greifensee, Switzerland) following previously described protocols [22]. Relative change in feed intake and body weight was calculated for individual rats using the equation shown below.

$$\frac{\text{Final body weight (or feed intake)} - \text{Initial body weight (or feed intake)}}{\text{Initial body weight (or feed intake)}}\ g$$

2.5 Behavioural Testing

2.5.1 Open field Behaviours

Open-field responses in rats illustrate arousal, inhibitory, and inspective exploration behaviours, as well as anxiety behaviours. Stereotypic behaviours, have also been exemplified by this paradigm. These behaviours are typically considered fundamental and signify a rodent's capacity for exploration. Ten minutes of behaviours in an open field, including grooming, rearing, and horizontal movement were observed and recorded

in the open field apparatus. The open-field paradigm consists of a square enclosure with a rigid floor, measuring 36 x 36 x 26 cm. The wood was painted white, and the floor was segmented by permanent blue markings into 16 equal squares. Each rat was positioned near the centre of the field as previously described [17]. Total horizontal locomotion (number of floor units traversed by all paws), rearing frequency (number of instances the rat stood on its hind legs, either with its forelimbs against the walls of the observation cage or freely in the air), and grooming frequency (number of body-cleaning actions involving paws, licking of the body and pubis with the mouth.

2.5 Biochemical Test

2.5.1 Lipid Peroxidation

Lipid peroxidation levels were measured by quantifying the malondialdehyde content within test samples following previously described protocols [23].

2.5.2. Interleukin (IL) -1β and Interleukin-6

Interleukin (IL)- 1β and Interleukin-6 levels were measured using the enzyme-linked immunosorbent assay methods following the direction of the manufacturer.

2.5.3 Antioxidant Status

Total antioxidant capacity was measured using the Trolox Equivalent Antioxidant Capacity Assay principle which is based on the ability of antioxidants within a sample to react with oxidized products. Total antioxidant capacity for each sample was determined as previously described [24].

2.6 Tissue Histology

Rat brains were dissected, sectioned and fixed in neutral-buffered formol-calcium. The cerebral cortex was processed for paraffin-embedding, cut at 5 µm and stained with haematoxylin and eosin and cresyl fast violet histological analysis.

2.7 Photomicrography

Cerebral cortex slides were examined under an Sellon-Olympus trinocular light microscope with a digital camera attached.

2.8 Statistical Analysis

Data was analysed using Chris Rorden's ANOVA. One-way analysis of variance (ANOVA) was used for analysis, Tukey HSD test was used for comparisons. Results were expressed as mean ± S.E.M. and $p < 0.05$ was taken as the level of significant difference from control.

3. Results

3.1 Effect of quercetin on body weight

Figure 1 shows the effect of quercetin on relative change in body weight in MSG-treated rats. There was a significant ($p < 0.05$) increase in body weight with quercetin (Q) at 200 and a decrease with Q400, MSG, MSG+Q200 and MSG+Q400 compared to control. Compared to MSG, body weight increased with MSG+Q200 and decreased with MSG+ Q400.

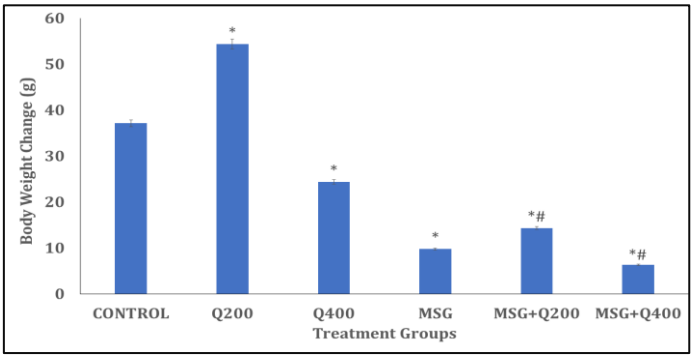

Figure 1: Effect of Quercetin on Relative change in body weight. Each bar represents Mean ± S.E.M, *p<0.05 significant difference from control. #p<0.05 significant difference from MSG Number of rats per treatment group =10. MSG: Monosodium glutamate Q: Quercetin.

3.2 Effect of quercetin on feed intake

Figure 2 shows the effect of quercetin on feed intake in MSG-treated rats. Feed intake increased significantly ($p < 0.05$) with Q)200, Q400, MSG+Q200 and MSG+Q400 and decreased with MSG compared to control. Compared to MSG, Feed intake increased with MSG+Q200 and MSG+ Q400.

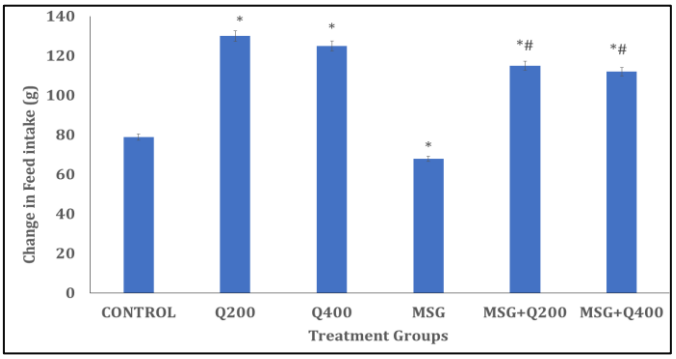

Figure 2: Effect of Quercetin feed intake in MSG-treated rats Each bar represents Mean ± S.E.M, *p<0.05 significant difference from control. #p<0.05 significant difference from MSG. Number of rats per treatment group =10. MSG: Monosodium glutamate Q: Quercetin.

3.3 Effect of quercetin locomotor activity

Figure 3 shows the effect of quercetin on locomotor activity measured as number of line crossings /10 minutes in MSG-treated rats. There was a significant ($p < 0.05$) decrease in line crossing with Q400, MSG, and MSG+Q200 compared to

control. Compared to MSG, line crossing increased significantly with MSG+Q200 and MSG+Q400.

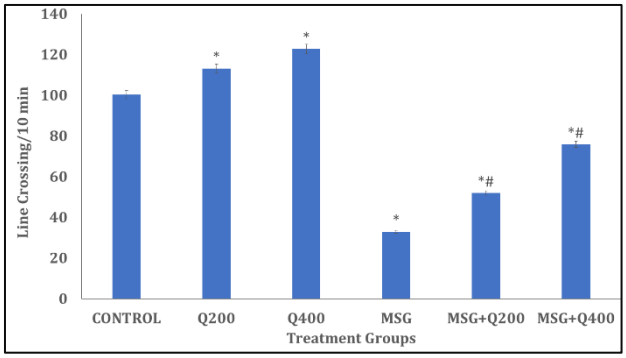

Figure 3: Effect of Quercetin on locomotor activity. Each bar represents Mean ± S.E.M, *p<0.05 significant difference from control. #p<0.05 significant difference from MSG. Number of rats per treatment group =10. MSG: Monosodium glutamate Q: Quercetin.

3.4 Effect of quercetin on rearing activity

Figure 4 shows the effect of quercetin on rearing in MSG-treated rats. There was a significant ($p < 0.05$) increase in rearing with Q200 and a decrease with Q400, MSG, MSG+Q200 and MSG+Q400 compared to control. Compared to MSG, rearing increased significantly with MSG+Q200 and MSG+Q400.

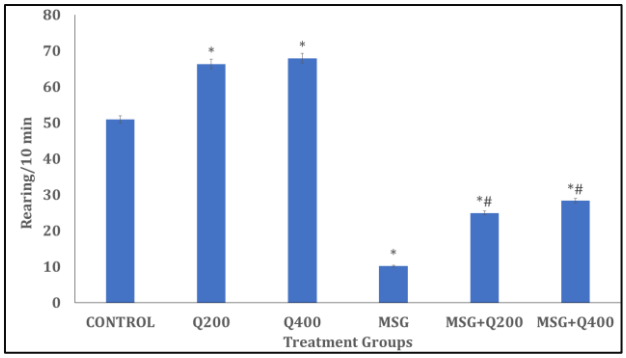

Figure 4: Effect of Quercetin on rearing activity. Each bar represents Mean ± S.E.M, *p<0.05 significant difference from control. #p<0.05 significant difference from MSG. Number of rats per treatment group =10. MSG: Monosodium glutamate Q: Quercetin.

3.5 Effect of quercetin on self-grooming behaviour

Figure 5 shows the effect of quercetin on self-grooming behaviours in MSG-treated rats. There was a significant ($p < 0.05$) increase in self-grooming with MSG, compared to control. Compared to MSG, self-grooming decreased significantly with MSG+Q200 and MSG+Q400.

3.6 Effect of Quercetin on oxidative stress and inflammatory markers

Tables show the effect of quercetin on oxidative stress markers (Table 1) including lipid peroxidation levels measured as malondialdehyde (MDA) content and Total antioxidant capacity (TAC) and inflammatory cytokines (Table 2) including interleukin-1β, and interleukin-6. Lipid peroxidation measured as MDA levels decreased with Q200 and Q400 and increased with MSG, MSG+Q200 and MSG+Q400 compared to control. Compared to MSG, MDA levels decreased with MSG+Q200 and MSG+Q400.

Total antioxidant capacity (TAC) increased significantly with Q400, MSG+Q200 and MSG+Q400 compared to control. Compared to MSG, TAC levels increased with MSG+Q200 and MSG+Q400. Malondialdehyde increased significantly in MSG compared with the control group. Compared to the MSG, MDA decreased MSG+Q200 and MSG+Q400.

Interleukin-1β (IL-1β) increased significantly with MSG compared to control and decreased significantly with MSG+Q200 and MSG+Q400 compared to MSG. Interleukin 6 (IL-6) levels increased significantly with MSG and decreased with MSG+Q200 and MSG+Q400 compared to control. Compared to MSG IL-6 decreased with MSG+Q200 and MSG+Q400.

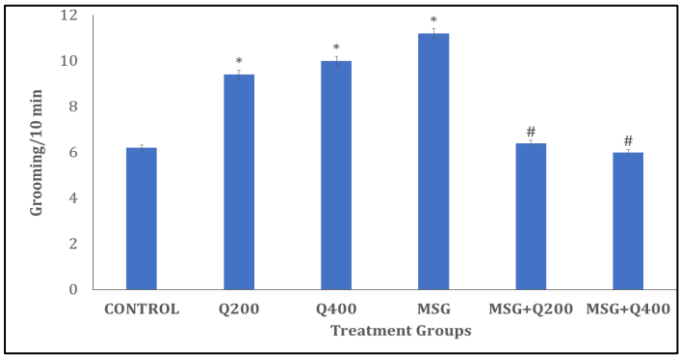

Figure 5: Effect of Quercetin on self-grooming. Each bar represents Mean ± S.E.M, *p<0.05 significant difference from control. #p<0.05 significant difference from MSG. Number of rats per treatment group =10. MSG: Monosodium glutamate Q: Quercetin.

Table 1: Effect of quercetin on oxidative stress parameter

Groups	TAC (Trolox Equivalence)	MDA (Um)
CONTROL	10.08 ± 0.23	0.6 ± 0.05
Q200)	10.81 ± 0.87	0.94 ± 0.07*
Q400	13.66 ± 0.15*	0.82 ± 0.01*
MSG	5.63 ± 0.24*	2.75 ± 1.09*
MSG+Q200)	13.5 ± 0.98*#	0.72 ± 0.04#
MSG+Q400	13.89 ± 2.03*#	0.76 ± 0.05#

Mean ± S.E.M, *p<0.05 significant difference from control. #p<0.05 significant difference from MSG. Number of rats per treatment group =10. MSG: Monosodium glutamate Q: Quercetin.

Table 2: Effect of quercetin on proinflammatory cytokines

GROUPS	IL-1 (pg/ml)	IL-6 (pg/ml)
A (CONTROL)	42.33±1.7	**6.19±0.14**
B (Q200)	46.98±12.09	**7.1±1.16**
C (Q400)	48.89±8.41	**6.84±1.08**
D (MSG)	66.59±5.1*	**13.91±0.27***
E (MSG+Q200)	43.39±1.28#	**4.25±0.02*#**
F(MSG+Q400)	44.39 ±1.28#	**4.25±0.02*#**

Mean ± S.E.M, *p<0.05 significant difference from control. #p<0.05 significant difference from MSG. Number of rats per treatment group =10. MSG: Monosodium glutamate Q: Quercetin.

3.6 Effect of quercetin on cerebral cortex histomorphology

Plate 1 shows the effect of quercetin administration on the histomorphology of the cerebral cortex The haematoxylin and eosin-stained slides revealed distinct layers of the cerebral cortex with presence of numerous granule cells, pyramidal cells and neuroglial cells with control (Plate 1a) and the quercetin groups (1B, 1C) respectively. Multipolar shaped pyramidal cells with large, rounded, vesicular nucleus is seen scattered throughout the neuropil; granular neurons with large open-faced nuclei prominent nucleoli and scant cytoplasm are also observed; features which are in keeping with normal cerebral cortex histomorphology. In the MSG group (Plate 1D) numerous neuroglial cells and degenerating pyramidal and granule neurons were observed, features are suggestive of neuronal degeneration. In groups administered MSG with quercetin (1E, 1F) features in keeping with protection against neuronal injury was observed**.** Photomicrograph of cresyl fast violet (Plate2 A-F) stained cerebral cortex sections revealed the characteristic layered arrangement of the cerebral cortex with well-delineated multipolar pyramidal cells, deeply stained granule cells, neuroglia (NG), and prominent Nissl bodies with control and quercetin groups respectively (2A-C). However, degenerating pyramidal cells with pale-staining nuclei and reduced Nissl substance were observed in the MSG group (Plate 2D), while protection against neuronal injury, with better preservation of Nissl bodies, was evident in the MSG+ Q groups (Plate 2E & 2F).

4. Discussion

The cerebral cortex plays a key role in memory, thinking, learning, reasoning, problem solving, emotions, conscience and functions related to sense. This study investigated the possible protective effects of quercetin on changes in the brain behaviour, biochemical (inflammation markers) and histomorphological, in healthy rats administered monosodium glutamate. The results showed that quercetin protects against monosodium glutamate-induced changes in body weight, feed intake, behavioural parameters (open field) inflammatory markers and histomorphology.

In this study, relative body weight increased in the control group and decreased significantly in the groups administered monosodium glutamate. On the other hand, treatment with quercetin at 200 mg/kg mitigated MSG-induced weight loss. The effects on body weight and food intake observed with Monosodium glutamate (MSG) in this study are consistent with the results of a number of other studies that had also reported that the administration of MSG causes significant weight loss and loss of appetite [25].

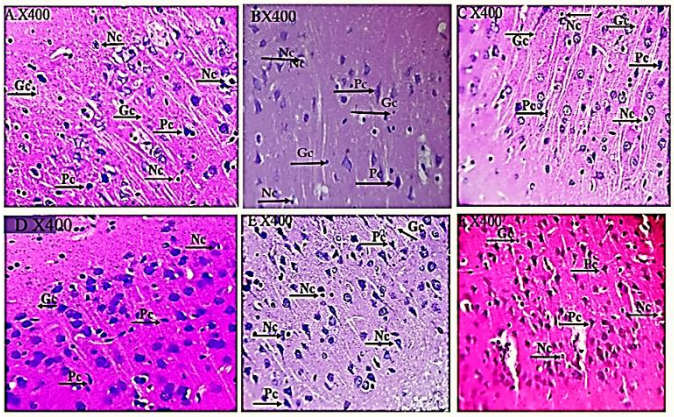

Plate 1: Representative photomicrograph of haematoxylin and Eosin-stained sections of the rat cerebral cortex. revealed distinct layers of the cerebral cortex with presence of numerous granular cells (GC), pyramidal cells (PC) and neuroglia (NC). X100

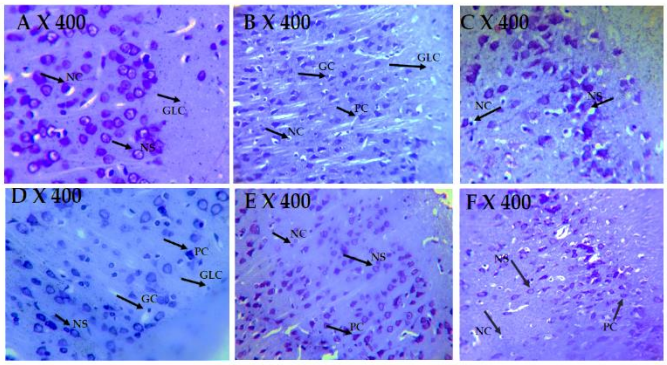

Plate 2: Photomicrograph of cresyl violet stained sections of the rat cerebral cortex revealed characteristic layered arrangement of the cerebral cortex with well-delineated pyramidal cells (PC), granule cells (GC) and neuroglia cell (NC)

In this study, relative body weight increased in the control group and decreased significantly in the groups administered monosodium glutamate. On the other hand,

treatment with quercetin at 200mg/kg mitigated MSG-induced weight loss. The effects on body weight and food intake observed with Monosodium glutamate (MSG) in this study are consistent with the results of a number of other studies that had also reported that the administration of MSG causes significant weight loss and loss of appetite [25].

Quercetin is a biologically active flavonoid that has been studied extensively for its effect on body weight [26]. Results of these studies have varied significantly, with a few reporting quercetin's ability to mitigate weight gain others observed no effect on body weight in normal sized animals [27] in some other instances. In this study, groups administered quercetin at 200 mg/kg showed significant increase in body weight from control with no observable difference in quercetin at 400 mg/kg supporting studies that had reported such effects. [28]. This would suggest that quercetin's effect on weight only came into effect in situations of body weight abnormalities like disease related weight loss or conditions of obesity. In groups administered quercetin at 200 mg/kg there was significant increased observed, supporting earlier observations that quercetin at 200 mg/kg effect on the body was to restore normalcy. [29] A few studies have also reported that quercetin did not increase energy consumption. [30] Quercetin at 200mg/kg supplemented diet reversed MSG induced decrease in food intake, consistent with the results of other studies that had observed quercetin's ability to reverse food intake in a disease model [31]. Quercetin's effects on body weight and food intake can also be attributed to its ability to influence central processes that regulate energy. Studies have continued to report the benefits of quercetin in modulating inflammatory activity and in protecting against brain injury [32]. Neurobehavioural paradigms are non-invasive models that are employed for the assessment of normal central nervous system function or to investigate the effects of drug and or drug candidates on the functioning of the central nervous system in health or disease [33]. Several studies have demonstrated. Recent research has focused on the potential neurological effects of MSG, particularly its excitotoxic properties in high concentrations. Animal studies have demonstrated that excessive glutamate intake, as from MSG, can lead to neurotoxicity and neuronal damage in the brain. [34]. Rearing is lesser in MSG control group compared with the co-administration of quercetin and monosodium glutamate. Also, in this study, line crossing significance increase with MSG+Q200 and MSG+Q400 compared to the MSG group supporting studies that had reported such effects, self-grooming significantly increased in MSG treated group compared to control group. Compared to MSG group, grooming significantly decreased with MSG+Q200 and MSG+Q400. Rats treated with monosodium glutamate 80mg/kg exhibited significantly reduces line crossing compared to the control group, supporting studies that had reported such effects. [35]. Negative impact of MSG exposure may be due to disruption in neurotransmitter system, particularly dopamine and acetylcholine level. Most studies have examined quercetin benefits in Alzheimer's disease, In this study, it was observed that quercetin reversed MSG induced changes in behaviour and brain injury through its ability to modulate neurotransmitter levels and glia fibrillary acidic protein immunoreactivity in the cerebral cortex. Quercetin's inflammatory effects have also been postulated as a potential mechanism for its effects on the brain. Studies examining the mechanisms responsible for quercetin's effect on the brain have also listed quercetin's ability to rescue apoptotic pathways and increase neurogenesis as potential mechanisms. In this study, H&E staining highlighted neuronal degeneration in MSG control group, quercetin treated groups showed protection against neuronal injury in cells morphology, suggesting synergistic protection. Cresyl fast violet staining further supported the neuroprotection. Showing partial to near-complete recovery of Nissl bodies in treatment groups.

Conclusion

This study increased our knowledge of the neuroprotective effect of quercetin**,** The information would assist in regulation of bodies in making objective appraisals of the effect of quercetin on the effects caused by monosodium glutamate neurotoxicity.

Enhancements in open-field behaviours, including heightened locomotion and diminished anxiety, coupled with the maintenance of cerebral cortex integrity, underscore the potential of the treatment. Quercetin approach targets oxidative stress and cholinergic dysfunction, providing a comprehensive strategy for addressing neurodegenerative conditions associated with these mechanisms. The findings of this study suggest that quercetin may be used as neuroprotective agent, particularly to lessen the side effects cause by monosodium glutamate. But its

potential direct interaction with neurotoxicity is one area that needs more findings.

Funding.
None

Availability of data and materials
Data are available from the corresponding author on request.

Declarations Ethics approval
Ethical approval for the research was granted by the ethical committee of the faculty of Basic Medical Sciences with Identification code (ERC/FBMS/029/2024)

Competing interests
None

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