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Protective effect of carvedilol versus vitamin E against MSG-induced ataxia model in rats through NRF2 modulation, Antioxidant and Antiapoptotic Effects

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ABSTRACT

Background: Carvedilol (CAR) is an adrenoreceptor antagonist used in cardiovascular disease management, such as congestive heart failure and hypertension. In addition to α and β receptor blockade, carvedilol shows additional antioxidant and anti-apoptotic effects. It has been included in research studies for many neurological conditions, but its utility in cerebellar ataxia has not been explored yet. This study sought to investigate the protective impact of carvedilol on cerebellar ataxia in rats using Monosodium glutamate (MSG). we aimed to evaluate its antiapoptotic and antioxidant properties, and to further compare its effect with vitamin E (Vit E).

Materials and methods: For induction of ataxia, MSG (6g/kg/d) was injected intraperitoneally for 10 days. Twenty-four Sprague Dawley male rats, weight (180–200 g), age (8–10 weeks) were split randomly into four groups: control group, MSG group (6g/kg/day, Ip for 10 days), MSG + Vit E (250 mg/kg/day), orally for ten days, MSG+CAR (2 mg/kg/day), orally for 10 days. At the end of drug administration, behavioral assessment by rotarod was evaluated, and cerebellar tissue samples were collected from the sacrificed animals for histopathological, biochemical, and immunohistochemical studies.

Results: The behavioral tests proved that treatment of rats with vitamin E has improved locomotor behavior in comparison to the MSG group. The rats showed increased latency and a decrease in the number of falls from the rotarod. In addition, biochemical analysis showed improvement in the vitamin E-treated rats, which was confirmed by increased GSH levels, reduction in the total ROS, and increase in NRF2 gene expression. The histopathological assessment with H&E showed a regain of almost normal histopathological features of the cerebellar neurons with a mild loss of Purkinje cells. Immune histochemical staining of cerebellar samples showed reduced positive staining of caspase-3 in most Purkinje cells. Carvedilol caused a significant improvement in the treated rats regarding all these parameters, which was less evident than the Vit E results.

Conclusion: Both Vit E and carvedilol exhibited a protective effect in ataxia induced by MSG via upregulation of the NRF2 expression, exerting antioxidant effects and inhibiting apoptotic pathways.

Keywords: *Cerebellar ataxia; carvedilol; vitamin E; antioxidant; MSG.*

1. INTRODUCTION

Cerebellar ataxia is a neurodegenerative disorder that affects the cerebellum and its associated systems. It is manifested by gradually worsening incoordination that causes problems with balance, gait, and motion, which eventually lead to considerable disability (Buckley et al., 2018). Oxidative stress, mitochondrial dysfunction, neurodegeneration, and apoptotic

cell death have been linked to ataxia, where elevated levels of cytochrome c, reactive oxygen species (ROS), and caspase 3 activity are shown (Y. C. Wang et al., 2011). Nuclear factor erythroid-2-related factor 2 (NRF2) is a regulatory transcription factor cellular resistance and adaptive response to oxidants by induction of the antioxidant enzymes. This results in detoxification and elimination of oxidant radicals. The antioxidant response element (ARE) is located on regulatory regions of the NRF2-regulated genes. It depends primarily on NRF2 stabilization, accumulation, and nuclear translocation (Ngo & Duennwald, 2022). In addition, Nrf2 has been proven to regulate cellular apoptosis through up-regulation of antiapoptotic protein Bcl-2, which can diminish the mitochondrial cytochrome c release, reduce the caspases activity, and decrease DNA fragmentation. The antioxidant and antiapoptotic effects of Nrf2 help reduce the incidence of cell death and promote cell survival (Niture & Jaiswal, 2012).

MSG, the sodium salt of glutamic acid, is used extensively in the food business as a taste enhancer and food additive, producing a savory taste. Extensive consumption of MSG has been connected to the term Chinese restaurant syndrome. The syndrome consists of a complex of symptoms that typically include flushing, headache, facial pressure, chest pain, tingling, numbness, mouth-burning sensations, and generalised weakness (Campbell, 2014). Moreover, several studies have linked MSG to various neurodegenerative diseases, including Alzheimer's disease, Parkinsonism, and ataxia (Martami & Holton, 2023). MSG-induced neurotoxicity is mediated through enhanced lipid peroxidation, oxidative stress, subsequent apoptosis, and neuronal degeneration. MSG elevates glutamate levels and enhances intracellular calcium, which mediates the opening of mitochondrial transition pores (MTP), caspase activation, apoptosis markers, and neurodegeneration. (Sreeganga S et al., 2023).

Carvedilol is a β-adrenoreceptor antagonist with vasodilator, antioxidant, and anti-apoptotic properties. It is used to treat cardiovascular conditions such as congestive heart failure, hypertension, and myocardial infarction (Church et al., 2015). It has been included in research studies for many neurological conditions, focusing on its antioxidant and anti-apoptotic features. It appears to have a neuroprotective effect by scavenging the reactive free radicals implicated in brain cell apoptosis (Yao & Chen, 2022). Vitamin E is a fat soluble vitamin having anti-inflammatory and antioxidant qualities, which can shield cells from the harm that free radicals (Rychter et al., 2022). In an attempt to search for drugs capable of upregulating NRF2 and improving mitochondrial function, vitamin E and carvedilol were evaluated in this study in MSG-induced cerebellar ataxia.

2. Materials and methods:

2.1 Chemicals and drugs:

Mono Sodium Glutamate (MSG), El Nasr Pharm. Chem. Co., Egypt. Carvedilol, (carvipress®, 12.5 mg tablet, Global Napi Pharmaceuticals Egypt). Vitamin E, 400mg, Pharco Pharmaceuticals.

2.2 *Experimental animals*:

Twenty-four male rats, Sprague Dawley, age 8–10 weeks, and weight 180–200g, were obtained from Mansoura Experimental Research Centre (MERC). Before the experiment began, rats were housed in standard conditions (25 °C_12-hour light-dark cycle) for a week to acclimatise. During the trial, rats were provided a typical food pellet diet.

2.3 Grouping of animals and experimental design:

Rats were split into 4 groups, each containing 6 rats: Group 1: Non-treated control normal group: received distilled water orally and IP for 10 days. Group 2: Non-treated MSG group: 10 days IP injection of MSG (6 g/kg/day) (Youssef2 et al., 2015). Group 3: Vitamin E-treated MSG group: Rats received IP MSG (6 g/kg/day) + Vit. E (250 mg/kg/day) for 10 days, orally by gavage (Chaudhary et al., 2003). Group 4: Carvedilol-treated MSG group: Rats received IP MSG (6 g/kg/day) + CAR (2 mg/kg/day) for 10 days by oral gavage (Baraka et al., 2021). Animals were sacrificed 24 hours following the final dose using sodium-pentobarbital anaesthesia (40 mg/kg; IP) (Korayem et al., 2014).

2.4 *Behavioral testing (rotarod)*:

Two days before recording, rats were allowed to walk on the rotarod to familiarize with the apparatus. On the first and 10th days, behavioural testing was conducted on the rotarod for a maximum of 180 seconds for each trial. Rats' number of falls and the latency to fall from the apparatus were noted. The latency was calculated as a percentage by calculating the average of the two longest periods on the revolving rod, divided by 180 seconds. (Prastiwi et al., 2015).

2.5 *Tissue preparation*:

After motor coordination testing, the anesthetized rats were sacrificed, and cerebellar tissue samples were obtained. A part of one cerebellar hemisphere was washed with 0.9% saline, dried on filter paper, and weighed. Samples were homogenised in ice-cold PBS, and centrifugation at 2000-3000 rpm for 20 minutes was done. The supernatant was separated and stored at -80°C until use for biochemical assay. The other part was snap frozen, immersed in liquid nitrogen, and kept at - 80°C for

gene expression analysis. The rest of the cerebellar tissue was trimmed into 4 mm-thick slices and used for histopathological examination.

2.6 *Biochemical assessment*:

2.6.1. Enzyme-linked immunosorbent assay of total reactive oxygen species:

Levels of total ROS were determined in cerebellar tissues by Rat reactive oxygen species, ROS ELISA Kit (MyBioSource, San Diego, USA). Samples and standards containing biotin-conjugated polyclonal antibody preparation tailored for ROS were added to the corresponding microtiter plate wells. Horseradish Peroxidase (HRP) coupled with Avidin was added and incubated. Only ROS-positive wells exhibited a color change after adding sulfuric acid. The colour shift was spectrophotometrically identified at 450 nm ± 2nm. The samples' optical density (O.D.) was then compared to the standard curve to ascertain the ROS content in the samples, and the results were represented as pg/mg tissue.

2.6.2 ***Colorimetric detection of reduced glutathione (GSH)***:

The colorimetric determination kit for reduced glutathione (Biodiagnostic, Giza, Egypt) was employed. The method depends on the creation of the yellow chemical, 5,5_dithiobis (2-nitrobenzoic acid) (DTNB and reduction with glutathione. The absorbance is then measured spectrophotometrically at 405 nm, and mmol/g tissue was used to express the results.

2.7 *Real-time polymerase chain reaction (PCR) quantification of NRF2*:

The relative expression of NRF2 was assessed using quantitative real-time reverse transcription-polymerase chain reaction (qRT-PCR). The mRNA of Nrf-2 was quantified with the Real-time PCR System (Applied Biosystems, Foster City, CA, USA). The total RNA was extracted from the cerebellum following the manufacturer's instructions using the RNeasy Mini Kit (Qiagen, USA). The RNA was reverse-transcribed into complementary DNA (cDNA) via the Arktik Thermal Cycler (Thermo Fisher Scientific Inc., USA) kit. A total of 20 µl was used to set up real-time PCR experiments, which included cDNA 100 ng, 10 µl of SYBR Green Master Mix, 1 µl of primer, and nuclease free water 4 µl. The PCR cycling conditions included a 10-minute reverse transcription cycle at 55°C, an 8-minute enzyme activation cycle at 95o c, 40 denaturation cycles at 95º C for 10 seconds, and an annealing and extension step at 60°C for an additional 60 seconds. The housekeeping gene Gapdh was amplified to guarantee that equal amounts of cDNA were added to the PCR. The 2-ΔΔCT comparative technique was used for the calculation of the relative fold changes in gene expression (Schmittgen & Livak, 2008). All primers were synthesized by Thermo Fisher Scientific (USA). The forward and reverse primer sequences are provided in Table 1

Table 1: Primer sequences used for real-time PCR.

Gene Symbol	Primer sequence from 5′- 3′ F: Forward primer, R: Reverse primer	Gene Bank Association numbers	
Nrf2	F: TCCCAAACAAGATGCCTTGT R: AGAGGCCACACTGACAGAGA	NM_001399173.1	(Eid & Abdel-Naim, 2020).
GAPDH	F: ATGGTGAAGGTCGGTGTGAACG R: TGGTGAAGACGCCAGTAGACTC	XM_017592435.10	(Farhat et al., 2021).

2.8 *Histopathological assessment*:

The cerebellar tissue samples were prepared by submerging them in 4% formaldehyde solution and embedding them in paraffin for 24 hours. Sections that were two to three micrometres thick were stained with haematoxylin and eosin, placed on coated glass slides, and examined under the light microscope (Prastiwi et al.,2015).

2.9 *Immunohistochemical assay of caspase-3*:

Immunohistochemical staining was done on 4-µm cerebellar sections exposed to formalin fixation and paraffin embeding. Caspases-3 antibodies at a 1:50 dilution were used for apoptosis detection (DAKO , Carpinteria, CA). The slides were heated by steam in an EDTA solution (pH 8.0), 1 mmol/L, for 30 minutes in order to perform antigen retrieval. An automated immunostainer (DAKO) was used to inhibit endogenous biotin before staining. A streptavidin-biotin detection system (DAKO) was then used.

2.10 Statistical Analysis:

The Statistical Package for the Social Sciences (SPSS) version 26 was used to code, process, and statistically analyse the collected data. The Shapiro-Wilk test and Levene's test were used to confirm the homogeneity of variances and the assumption of normality in each group, respectively. The mean ± SD (standard deviation) was used to represent continuous variables. To check for significant differences between more than two normally distributed groups, continuous data were

subjected to the post hoc Tukey and Analysis of Variance (ANOVA) tests. The P-value < 0.05 is considered significant.

3. Results:

3.1 *Rotarod test*:

Rotarod assay results showed significant increase (P value < 0.05) in the falls number and a significant reduction in the latency (%) of falls in the non-treated MSG group in comparison to the control group. The rats treated with Vit E and CAR demonstrated improved motor coordination on the rotarod, evidenced by a significant increase in latency to fall from the rotarod and a significant reduction in the number of falls compared to the MSG group. Figures 1&2.

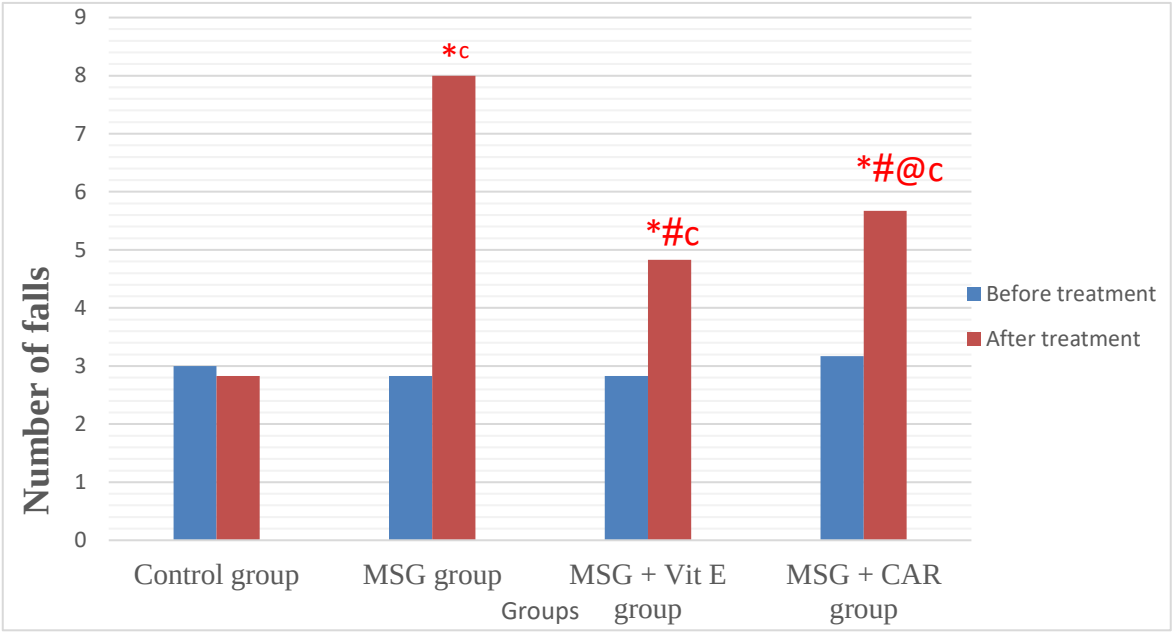


Figure 1: Effects of oral administration of Vit. E and CAR. on the number of falls of rats from the rotarod apparatus.

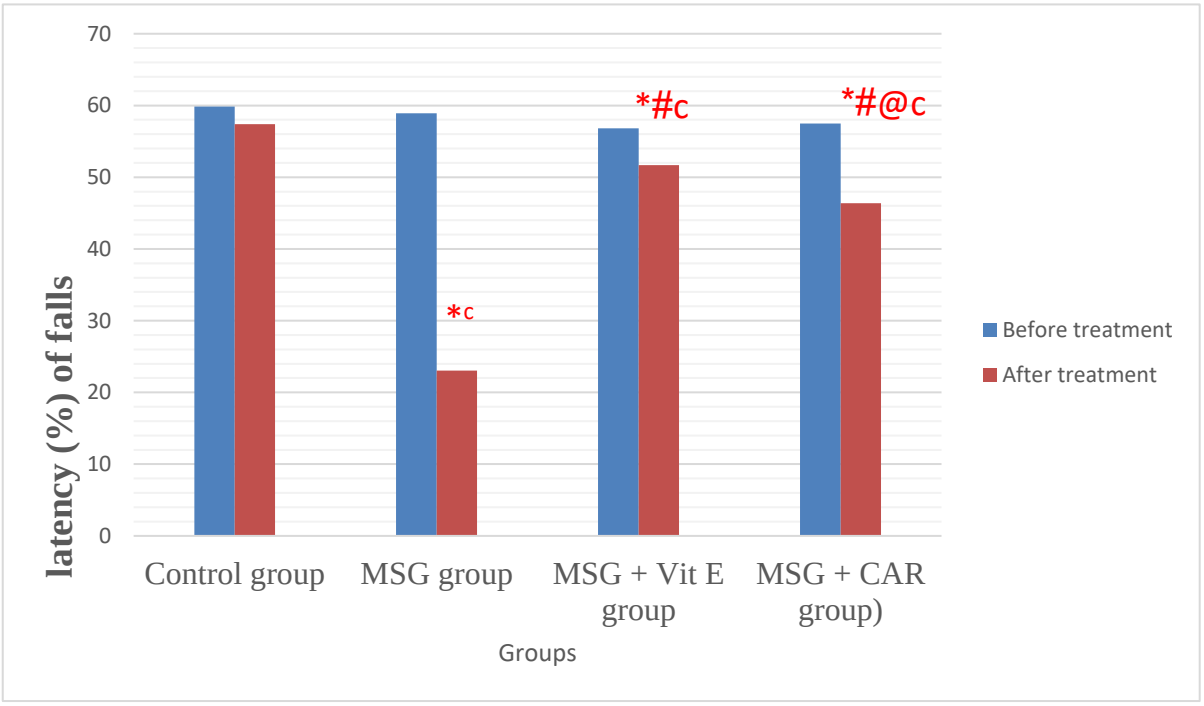


Figure 2: Effects of oral administration of Vit. E and CAR. on latency % of falls from the rotarod apparatus.

Means of six rats ± SD were used to express the data. The groups were compared using a post hoc Tukey test following the one-way ANOVA test; significance was declared at $p < 0.05$. The groups were compared before and after treatment using t-test.

* Significance versus the non-treated control group.

Significance versus non-treated MSG group.

@ Significance versus Vitamin E-treated group.

c significance in the group before and after treatment.

3.2 *Effect of oral vitamin E and carvedilol on total reactive oxygen species and GSH*:

As indicated in Table 2, the administration of MSG has led to a significant elevation in cerebellar total ROS levels and a significant decrease in GSH levels compared to the control group. Furthermore, as seen by the significant decline in total ROS and the significant elevation in GSH levels in cerebellar tissue, vitamin E and carvedilol treatment significantly restored MSG-induced changes in the previously described parameters. In MSG-treated rats, vitamin E resulted in a significant reduction in the cerebellar ROS levels as compared to rats in the CAR-treated group.

Table 2: Effect of oral vitamin E and carvedilol on cerebellar levels of total ROS and GSH.

Groups (n=6)	ROS (pg/ml)	GSH (mmol/g tissue)
Non-treated control group.	23.38 ± 3.37	1.96 ± 0.17
Non-treated MSG group.	90.52 ± 2.62*	0.88 ± 0.18*
Vitamin E-treated group.	29.52 ± 3.36$^{*\#}$	1.71 ± 0.15$^{*\#}$
Carvedilol-treated group.	36.78 ± 3.99$^{*\#@}$	1.48 ± 0.10$^{*\#@}$

Means of six rats ± SD were used to express the data. The groups were compared using a post hoc Tukey test following the one-way ANOVA test; significance was declared at $p < 0.05$.

* Significance versus non-treated control group.

Significance versus non-treated MSG group.

@ Significance versus Vitamin E -E-treated group.

3.3 *Effect of oral Vitamin E and carvedilol on cerebellar NRF2 gene expression*:

The cerebellar NRF2 gene expression was reduced significantly in MSG-treated rats than in the untreated control group. However, compared to rats treated with MSG, therapy with vitamin E and carvedilol resulted in significant increase in the NRF2 gene expression in cerebellar tissue. No statistically significant difference was found between the vitamin E and CAR-treated groups.

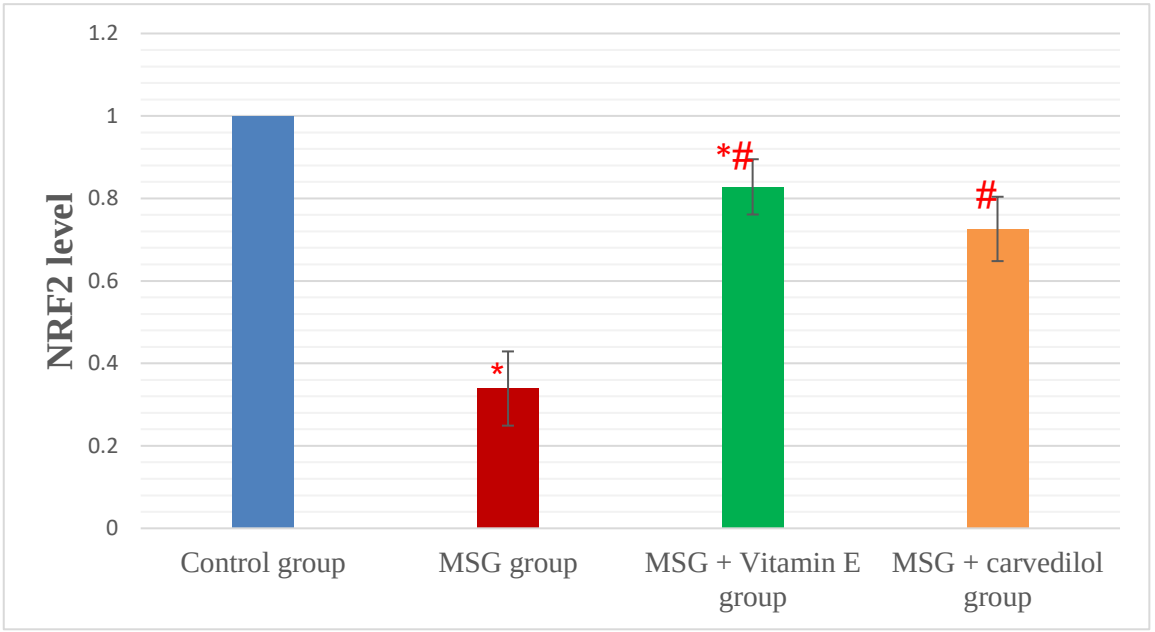


Figure 3: Effects of oral vitamin E and carvedilol on cerebellar NRF2 gene expression.

Means of six rats ± SD were used to express the data. The groups compared using a post hoc Tukey test following the one-way ANOVA test; significance was declared at $p < 0.05$.

* Significance versus non-treated control group.

Significance versus non-treated MSG group.

@ Significance versus Vitamin E-treated MSG-induced ataxia group.

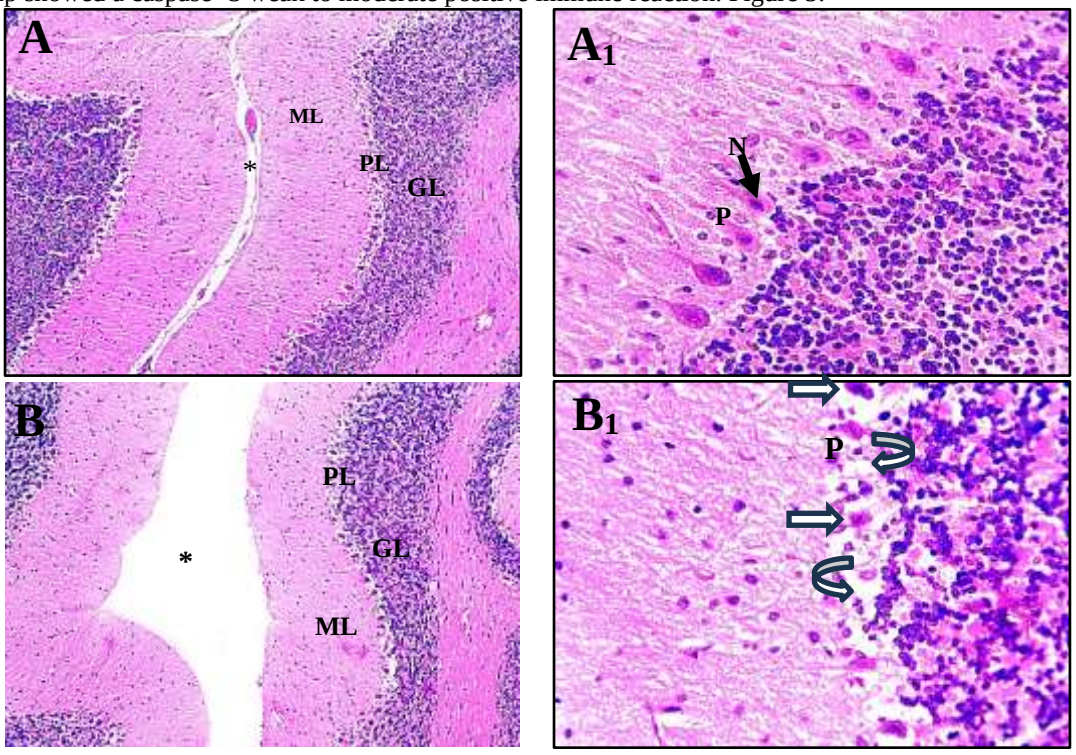
3.4 *Histopathological results*:

H&E-stained microscopic images of cerebellar sections from the non-treated control group showed a narrow distance between cerebellar folia, each folium exhibits normal white matter and grey matter consisting of molecular, Purkinje, and granular layers. The Purkinje layer consists of uniform flask-shaped Purkinje cells with well-defined nuclei and eosinophilic cytoplasm. Cerebellar sections from the non-treated MSG group show a widened distance between cerebellar folia along with marked Purkinje cell degeneration. Distortion of the pyriform shape of Purkinje cells, edematous cytoplasm, and degenerated pyknotic nuclei have also been noted.

Cerebellar sections from the vitamin E-treated group show decreased distance between cerebellar folia, with mild loss of Purkinje cells that have almost regenerated and restored their pyknotic, rounded nuclei. Cerebellar sections from the carvedilol-treated group showed decreased distance between cerebellar folia with moderate loss of Purkinje neurons (Ax100&Bx400). Figure 4

3.5 *Immunohistochemical assay of caspase-3*:

Photomicrographs of cerebellar sections from the control group exhibited a negative immunostaining against the caspase-3 antibody, which is indicated by the absence of brown staining in the cytoplasm of the Purkinje cells. A caspase-3 strong, positive immune reaction was evident in the MSG-treated group. The vitamin E-treated group showed light brown discoloration of the cytoplasm of Purkinje cells, indicating a weak positive caspase-3 immunoreaction.While carvedilol-treated group showed a caspase- 3 weak to moderate positive immune reaction. Figure 5.



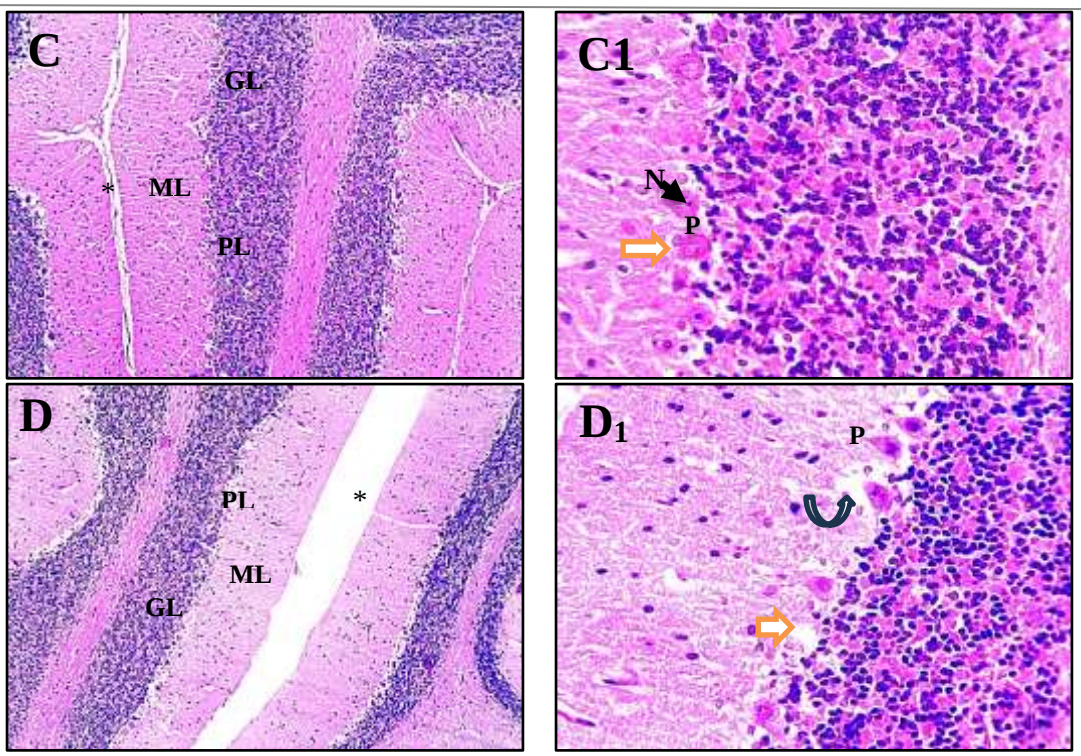


Figure 4: Histopathological findings of Haematoxylin & Eosin-stained sections from different groups:

Non-treated control group: Normal layers of the cerebellar cortex, Purkinje layer (ML), molecular layer(PL), and granular layer (GL) with a narrow distance (*) between cerebellar folia. Pyriform, flask-shaped Purkinje cells (P) with pyknotic vesicular nuclei (N) and eosinophilic cytoplasm. (Ax100 & A1x400). **Non-treated MSG group:** few shrunken Purkinje cells (P), hardly detectable condensed nuclei (white arrows), empty areas with loss of P cells (curved arrows), and a wide distance (*) between cerebellar folia. (Bx100 & B1x400). **Vitamin E-treated MSG group:** restored appearance, close to the control group, reduced distance (*) between cerebellar folia. The Purkinje cells (P) almost restored their uniform flask shape with rounded vesicular nuclei (N). (Cx100 & C1x400). **Carvedilol-treated MSG group:** regeneration of the Purkinje cell layer, some normal Purkinje cells (P) surrounded by halo spaces (curved arrows), and some degenerated, shrunken Purkinje cells appear as an empty area (white arrow). Reduced distance (*) between cerebellar folia. (Dx100 & D1x400).

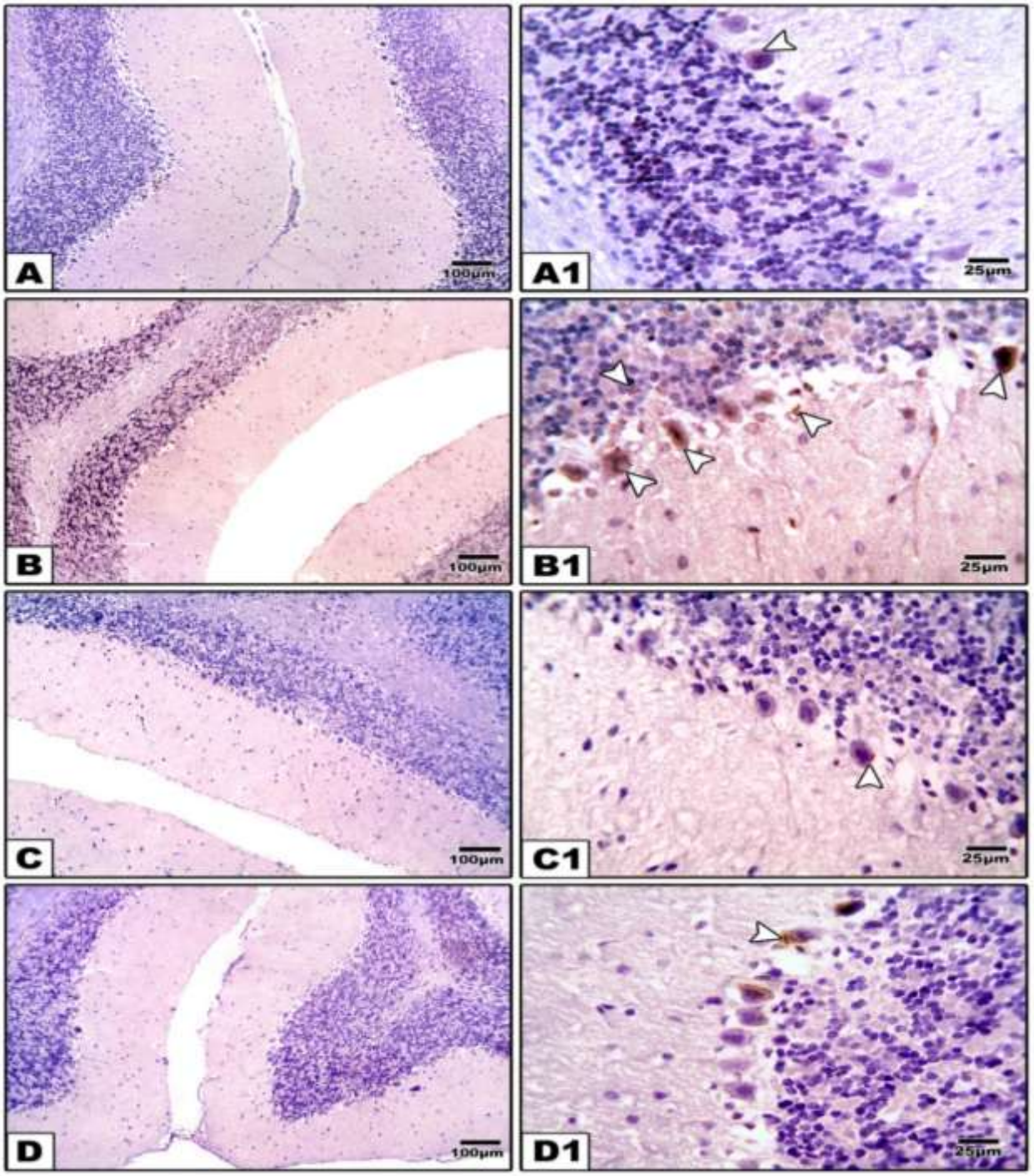


Figure 5: Immunohistochemical images of cerebellar sections immunolabeled with caspase-3 antibody.

Caspase-3 expression is indicated by brown staining. **Non-treated control group:** negative expression of caspase-3 in Purkinje neurons (Ax100 & A1 x400). **Non-treated MSG group:** strong positive staining of remaining Purkinje neurons against caspase (arrows) (Bx100 & B1 x400). **Vitamin E-treated group:** mild negative positive expression in Purkinje neurons against caspase-3 (Cx100 & C1 x400). **Carvedilol-treated group:** mild to moderate positive expression of caspase-3 (Dx100 & D1 x400).

4. Discussion

The current study evaluated the potential antiapoptotic and antioxidant impacts of carvedilol in experimentally induced MSG cerebellar ataxia in rats and compared its effects with vitamin E. Administration of MSG in rats resulted in significant

impairment of motor coordination on the rotarod apparatus compared with control group. These results align with findings in other research, as Aminuddin et al. (2015), who mentioned that MSG-induced ataxia leads to alteration of the rotarod testing results and impaired motor coordination of rats. Moreover, Abogresha et al. (2019) observed that female Wistar rats exposed to IP MSG exhibited decreased motor performance and low latency in all assessment sessions as detected by open field and rotarod tests. In our study, MSG induced an elevation in cerebellar ROS and reduced the GSH levels. Similarly, Kesherwani et al. (2024) found that MSG induces oxidative stress and inflammation that reduced the levels of SOD, CAT, and GSH significantly, and elevated levels of TNF α and MDA. Additionally, Zedan et al. (2024) demonstrated that MSG induced oxidative stress in the brains of rats when used in a model of attention-deficit hyperactivity disorder. MSG-induced oxidative stress is marked by a substantial increase in MDA levels and a marked decrease in NRF2 activity and level. In cerebellar tissue, MSG-induced ataxia additionally resulted in decreased NRF2 gene expression. These findings were parallel to Gao et al. (2018), who mentioned that NRF2 levels appeared to decline in a metabolic syndrome model when obesity was induced using MSG.

Microscopic images stained with H&E and immunohistochemically stained sections from the cerebellum revealed that MSG-induced ataxia resulted in significant degeneration of Purkinje cells. The histopathological changes in these cerebella appeared as a widely distorted Purkinje cell layer with shrunken Purkinje cells, leaving a halo of space around them. Owoeye & Salami et al. (2017) & Ashraf et al. (2017) reported that MSG administration to adult albino rats for fifteen days led to the loss of the Purkinje cell layer and widened intercellular spaces between cells. In addition, Hazzaa et al. (2020) & Mathew & Joy et al. (2020) noticed that caspase-3 exhibited a strong positive nuclear immunoreactivity in the hippocampus of the rats exposed to MSG, suggesting that MSG is a stressor neurotoxin that can trigger caspase-dependent apoptotic signaling cascades.

The neuronal damage induced by MSG could be attributed to stimulation of lipid peroxidation, glutamate excitotoxicity, and apoptotic cell degeneration caused by excessive oxidative stress. Glutamate and calcium overload result in mitochondrial dysfunction that leads to a reduction of the antioxidant mechanism and excessive production of ROS (Moldovan et al., 2023). MSG induces ER stress and excessive mitochondrial calcium accumulation, which triggers MPTP opening and proapoptotic mitochondrial alterations. The release of apoptosis protease activating factor-1 (APAF-1), cytochrome C, and apoptosis inducing factor facilitates procaspases activation to caspases (caspase -3), thereby promoting apoptosis (Onaolapo et al., 2016). MSG-induced oxidative stress and excitotoxicity disrupt the PI3K/Akt pathway and enhance GSK-3β activity, leading to Nrf2 phosphorylation, degradation, reduced nuclear translocation, and increased nuclear export (Sharma et al., 2020).

The current study showed that oral Vit. E (250mg/kg/day) improved the rats' motor coordination on the rotarod apparatus, evidenced by a significant reduction in the number and increased latency to fall from the apparatus. These data align with Abbarin et al. (2023), who mentioned that vitamin E has enhanced the motor coordination of autistic mice exposed to valproate and reduced oxidative stress markers. The improvement in behavioral test results corresponded with a significant decrease in the markers of oxidative stress and a significant elevation of the GSH level and NRF2 gene expression. Our findings were consistent with Bolotta et al. (2020), who found that vitamin E significantly increased the GSH/GSSG ratio—a crucial measure of oxidative redox—in a clinical trial involving patients with Friedrich's ataxia by raising GSH levels and lowering GSSG content. Additionally, Mishra et al. (2019) & He et al. (2019) declared that Vitamin E modulation of NRF2 and KEAP1 functions is a mechanism that explains antioxidant effects via activation of ARE and subsequent expression of antioxidant enzymes.

The histopathological and immunohistochemical assessment of cerebellar sections obtained from rats in our study revealed nearly regenerated Purkinje cells with few positively stained Purkinje neurons against caspase-3, as compared to the MSG group. According to da Cunha Germano et al. (2023) in TTP-deficient mice exhibiting ataxia, vitamin E administration reduced oxidative stress and lipid peroxidation and nearly entirely stopped the onset of neurological symptoms, resulting in the reduction of Purkinje cerebellar cell atrophy. Additionally, Rizvi et al. (2014) revealed that mice given vitamin E supplements significantly improved their rotarod motor performance, significantly decreased oxidative stress markers, degenerative Purkinje cell alterations, and a significant improvement in the integrity of these neurons. Furthermore, Ziamajidi et al. (2023) found that rats pre-treated with vitamin E exhibited a significant decrease in the apoptosis rate, caspases-7 and 3, and gene expression of Bax protein, while the expression of Bcl-2 was elevated.

Vitamin E, a fat-soluble vitamin having neuroprotective properties mediated by the inhibition of lipid peroxidation and oxidative stress, excitotoxicity, and apoptotic cell death (Liao et al., 2022). It can protect cells against apoptotic cell death and oxidative stress through NRF2 activation and its downstream genes and modulating key antioxidant enzymes, which prevent redox homeostasis. According to (M. Wang et al., 2021) the pro apoptotic markers caspase -3 and Bax are decreased by vitamin E, whereas the anti-apoptotic marker BCL2 is elevated. Furthermore, vitamin E-mediated cellular survival and protection against apoptosis are linked to downregulation of GSK3β levels and activity and activation of the PI3K/AKT signalling pathway (Idriss et al., 2020).

The current study detected that oral administration of carvedilol (2 mg/kg/day) in rats showing signs of MSG-induced ataxia for 10 days resulted in significant improvement in motor assessment, rotarod latency, and reduced the number of falls. Our findings concurred with those of Kamal et al. (2022), who assessed the impact of carvedilol in a rat model of Parkinson's disease using rotenone. Rats' performance in the Y-maze and open field tests was enhanced by carvedilol. In our results,

treatment of the diseased rats with carvedilol produced a significant reduction in the levels of oxidative stress markers and an increase in NRF2 gene expression and the GSH levels. These results were in Akindele et al. (2018), who mentioned that carvedilol has a cytoprotective effect against ROS which is mediated through the suppression of free radical generation and an increase in antioxidants including GSH, GPx, SOD, and CAT. The antioxidant action of carvedilol is attributed to the reduction in lipid peroxidation and prevention of the emergence of free radicals. Also, carvedilol shows scavenger action against free oxygen radicals and an increase in GSH, which detoxifies reactive intermediate oxygen products. Moreover, Akintoye et al. (2023) reported that the pathway of NRF2 is induced by carvedilol, which activates the transcription rate of the antioxidant enzymes and raises their levels in the blood, including catalase and superoxide dismutase. Activation of the NRF2 pathway could be mediated by carvedilol, thus stimulating the transcription of many antioxidant enzymes and protecting against oxidative stress (Zhang et al., 2022). Carvedilol treatment improved the histological changes induced by MSG in the cerebellum. our data were in line with Magadmi et al. (2021), who demonstrated that carvedilol exhibits a neuroprotective effect in a diabetic neuropathy model in vitro. Carvedilol significantly increased the viability of dorsal root ganglia and protected them from high glucose-induced morphological changes. It also increased the neuronal survival and neurite length in high glucose media. furthermore, our results showed that carvedilol reduced the immunohistochemical staining with caspase-3 in cerebellar cells. These results were in line with Tolga Kafadar & Ali Gök, et al. (2022), who declared that the use of carvedilol in a liver ischemia reperfusion injury model managed to reduce cell death and apoptosis by decreasing caspase-3 levels and raising Bcl-2 levels.. Also, Zheng et al. (2023) demonstrated that carvedilol reduced the neuronal apoptotic signals after ischemic stroke by decreasing cytochrome c release and reducing caspase -3 expression.

5. Conclusion

In conclusion, the present study demonstrated that carvedilol exerted remarkable antioxidant and antiapoptotic actions in the MSG-induced model of cerebellar ataxia; however, being less significant than results mediated by vitamin E treatment, carvedilol could be recommended in the treatment of cerebellar ataxia.

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