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ORIGINAL RESEARCH

Morin Mitigates Methamphetamine-Induced Neurotoxicity: Effects on Motor and Cognitive Function

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Introduction: Neurodegenerative diseases are a major public health concern, often associated with motor and cognitive deficits. Methamphetamine (METH) exposure induces lasting neurological impairment and neuronal loss. This study evaluated Morin's potential to reverse these effects, focusing on motor and cognitive dysfunction in METH-induced neurotoxicity.

Methods: Adult rats were randomly assigned into seven groups, including control, Morin-only, METH-only, METH plus fluoxetine, and three groups receiving METH followed by varying doses of Morin. Following METH induction, Morin, a natural flavonoid with antioxidant properties, was administered to rats. Neurobehavioral tests evaluated motor and cognitive function; serum levels of oxidative stress markers, inflammatory cytokines, dopamine, and acetylcholine were measured. Histological and immunohistochemical analyses of the basal ganglia were performed to evaluate neuronal integrity.

Results: METH exposure significantly elevated oxidative stress and inflammatory markers, altered neurotransmitter levels, and impaired both motor and cognitive performance, coinciding with neuronal loss in the basal ganglia. Treatment with Morin ameliorated these effects in a dose-dependent manner. Neuronal degenerative features noted in the METH-only group were significantly ameliorated in the Morin-treated groups.

Conclusion: These findings indicate that Morin mitigates METH-induced neurotoxicity by reducing oxidative stress, and suppressing inflammation. This study demonstrates Morin's potential as a treatment option for the neurological effects of methamphetamine misuse.

Keywords: Morin, methamphetamine, neurotoxicity, motor function, cognitive function, dopamine, acetylcholine, neurodegeneration

Introduction

The use of methamphetamine (METH) presents a significant concern within global society due to its severe neurotoxic effects on the dopaminergic system.[1–5] METH abuse is linked with a range of detrimental neuropsychiatric outcomes, including motor disturbances, cognitive deficits, and neurotoxic changes in the brain.[6–12] It causes oxidative stress, neuroinflammation, and imbalance of neurotransmitter systems, which results in damage to dopaminergic neurons, especially in the basal ganglia.[13–19] This highlights the need for therapeutic agents that can mitigate such adverse effects.

The neurotoxicity of METH is mainly attributed to the ability of METH to enhance the release of dopamine and to inhibit its reuptake which results in high levels of dopamine in the synaptic cleft. This leads to increased dopamine activity which in turn causes oxidative stress and neuroinflammation, both of which are factors that lead to dopaminergic neuronal death.[3,18] It has been established that METH-induced neurotoxicity is associated with increased generation of Reactive oxygen species (ROS), microglial activation, and the release of pro-inflammatory cytokines, which, in turn, amplify neuronal damage.[1,16]

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Morin is a natural flavonoid derived from various plants, including members of the Moraceae family, such as guava (Psidium guajava) and Osage orange (Maclura pomifera).[20] Diverse biological activities of flavonoids, including anti-oxidative, anti-inflammatory and neuroprotective, are due to flavonoids being polyphenolic compounds.[21–23] The main mechanism of action of Morin is its antioxidant effect; scavenging ROS and decreasing oxidative stress.[24] Morin has also been demonstrated to interact with cellular pathways, including the regulation of nuclear factor erythroid 2 related factor 2 (Nrf2) and the inhibition of pro inflammatory cytokines (ie interleukin-6 and tumor necrosis factor alpha).[25]

Morin has been investigated for its numerous pharmacological activities such as antioxidant, anti-inflammatory and neuroprotective activities.[20,24,26–28] Earlier studies have shown that Morin has the potential to forestall neurodegeneration in models of Parkinson's disease, Alzheimer's disease and cerebral ischemia.[15,20,27,28] Zhang et al[29] also showed that Morin has neuroprotective potential in a rodent model of Parkinson's disease. Recent studies have further emphasized both the need and the roles of natural products in combating neurodegenerative diseases such as Alzheimer's.[30–32]

Besides its antioxidant action, Morin has been reported to influence neurotransmitter systems, including the dopaminergic system.[29,33] Zhang et al[29] observed a significant reduction in dopaminergic neuronal death, behavioral deficits, and striatal dopamine depletion in mouse models subjected to neurotoxicity after Morin administration. Investigating the mechanisms by which Morin may mitigate METH-induced neurotoxicity, especially its effects on the dopaminergic system, is crucial.

This study aims to evaluate the efficacy of Morin in the reversal of METH-elicited motor and cognitive deficits as well as the prevention of dopaminergic neuronal degeneration and also to compare these properties with those of fluoxetine, a known selective serotonin reuptake inhibitor (SSRI).

This study aims to evaluate the efficacy of Morin in the reversal of METH-elicited motor and cognitive deficits as well as the prevention of dopaminergic neuronal degeneration and also to compare these properties with those of fluoxetine, a known selective serotonin reuptake inhibitor (SSRI). Fluoxetine is acknowledged for its capacity to reduce oxidative stress and neuroinflammation, both of which are linked to Morin. This comparison allows for the assessment of Morin's potential to offer similar or supplementary neuroprotective effects, especially in METH neurotoxic conditions usually characterized by significant oxidative stress and neurotransmitter dysregulation. It will further enhance our understanding of the neuroprotective properties of Morin and its possible application in the management of neurological impairment caused by METH usage.

Materials and Methods

Animal Grouping and Treatment

Twenty-eight adult male Wistar rats weighing between 180 and 200 g were purchased from the University of Nigeria, Nsukka Veterinary Department. All rats were housed in standard cages under standard conditions (natural light and dark cycles, temperature (27–30 °C)) at the animal house of the Anatomy Department, University of Nigeria Enugu, Campus, Enugu State, Nigeria, and left for two weeks to acclimatize. The rats were randomly assigned into seven groups, each consisting of four rats, and provided with food and water in a conventional laboratory setting. The sequence of the experimental procedure has been summarized in Figure 1D. The various groups received either 8 mg/kg of METH alone, 10 mg/kg of Morin alone, 8 mg/kg METH plus 5 mg/kg, 10 mg/kg, or 20 mg/kg of Morin, 8 mg/kg METH, and 10 mg/kg fluoxetine; however, one of the control groups received an equivalent volume of distilled water. All administration was done intraperitoneally. We administered METH for 21 days following the basal neurobehavioral study. We then administered Morin for 14 days after the post-METH induction neurobehavioral study and then conducted the post-Morin treatment neurobehavioral study. This study adopted the METH dose from a previous studies on METH-induced toxicity, with minimal modifications.[26,34] The dose chosen for Morin administration was based on previous studies on Morin's therapeutic properties.[25]

Neurobehavioral Studies

We housed all rats overnight in the behavioral testing room to allow for appropriate climatization. All behavioral tests were administered in a quiet room between 7 a.m. and 1 p.m. We cleaned all apparatus with an ethanol solution after each

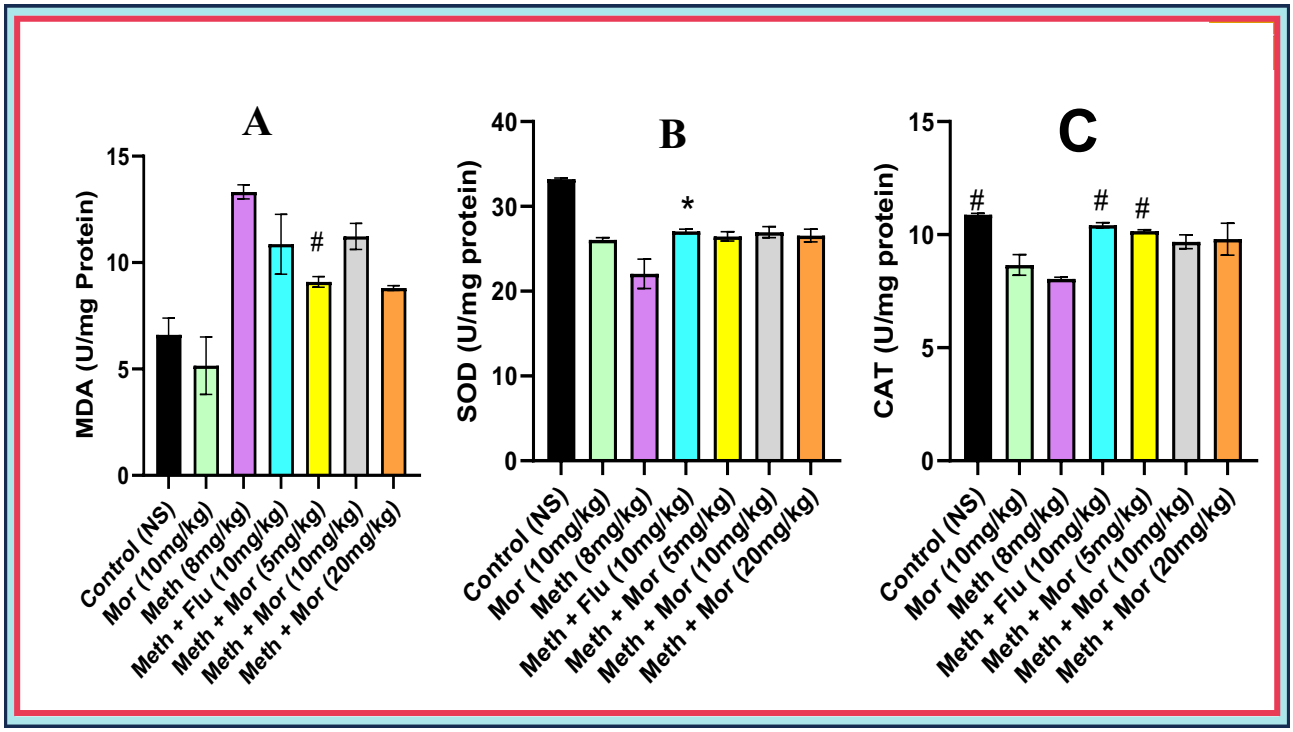

Figure 1 Effect of Morin on (**A**). MDA (**B**). SOD and (**C**). CAT in methamphetamine induced neurotoxicity. Values are expressed as mean ± SEM; *Indicates significant difference from control ($p<0.05$), #Indicated significant difference from Meth-only group ($p < 0.05$). One way ANOVA followed by Tukey post Hoc test.

trial to eliminate any bias from the odor of previous animals. All tests were recorded with a digital camera, and trained blind observers scored the behaviors. All neurobehavioral studies were done three times in the course of this experiment: pre-METH induction (basal), post-METH induction, and post-Morin treatment.

Motor Coordination Test

Walking Beam Test

We carried out a walking beam test for fine motor coordination and balance using the time taken by the rats to traverse the test beam and the number of paw slips as scales of measurement.[35] This was to assess the rats' ability to walk upright across the narrow, elevated beam. The beam was 100 cm long, 3 cm wide, and 25 cm above ground. We gave all experimental rats 5 minutes to complete a trial in a well-illuminated, noise-free room.

Tests for Memory and Cognitive Performance

Y-Maze

We carried out the Y-Maze test to assess for short-term spatial memory as described previously (Faizi et al, 2012; Shamloo, 2024). The arms of the Y-Maze measured 75 cm long and 15 cm wide with a 120° angle. We placed the rats on the central square and allowed them to explore the maze for 5 minutes. Arm entry, or when both hind limbs were entirely in the arm, determined the result. Correct alternation was confirmed when the animal successfully explored each of the three arms in each exploration triad, such as ABC, BAC, or CAB. We considered an incorrect alternation after the animal explored two arms per exploration triad (eg, BAB, CAC, and AAB). The percentage of spontaneous alternation was calculated as follows: [successive triplet sets / (total number of arm entries−2)] ×100.

Novel Object Recognition Test (NORT)

We used NORT, as described by Vilar-Pereira et al,[36] and Fedosova and Sarkisova[37] to investigate the rodents' non-spatial recognition memory. NORT is based on the knowledge that animals naturally prefer engaging with unfamiliar

objects over those they are familiar with. The discriminated objects (A and B) were similar in size (10 cm in height and 5 cm in diameter) and cylindrical. Objects A were white, while object B was red. We divided the test into three phases: habituation, familiarization, and testing. In the habituation phase, we gave each rat complete freedom to explore the open-field box (60 cm x 50 cm x 40 cm) without any object present. In the familiarization phase, each rat spent 5 minutes in a box holding two identical objects, "A", which were white and cylindrical. We tested the animal's ability to remember the known object (A) and the new object (B) after 4 hours. We noted the amount of time the animal spent sniffing and probing each object. When an animal investigates objects, it makes contact with them at a distance of 2 cm, either with its nose or forepaws. To avoid bias from previous rats, we cleaned the test box and objects with 20% ethanol. The discrimination ratio was calculated by dividing the difference in time spent exploring the novel and familiar object by the total amount of time spent with both objects, which was used as a measure of non-spatial memory function.

Experimental Drugs and Chemicals

We purchased experimental drugs and chemicals: Morin (CAS Number: 654055–01-3) from Sigma-Aldrich in St. Louis, USA; METH (CAS Number: 537–46-2) from the National Drug Law Enforcement Agency (NDLEA) in Nigeria; and fluoxetine from VS International Pvt. Ltd.

Biochemical Assay

For all biochemical assays, blood samples were taken from each rat's ophthalmic artery through the orbital sinus 24 hours after the last neurobehavioral study. We placed the samples into an anticoagulant bottle. Blood samples were centrifuged at 3000 rpm for 10 minutes to obtain the serum, which was stored at −20 °C and used to assess oxidative stress and inflammatory markers.

Enzyme-linked immunosorbent assay (ELISA) kits for the assessment of rat Dopamine (Catalog No: MBS262606), rat acetylcholine (Catalog No: MBS282680), rat malondialdehyde (Catalog No: MBS268427), rat glutathione S-transferase (Catalog No: MBS8421449), rat interleukin-6 (Catalog No: MBS269892), and rat TNF-alpha (Catalog No: MBS2507393) were bought from MyBioSource, Inc, San Diego, USA. Sandwich ELISA techniques were used to determine the levels of Dopamine, acetylcholine, malondialdehyde, glutathione S-transferase, interleukin-6, and TNF-alpha in rat serum. All analyses were carried out according to the manufacturer's recommendations.

Immunohistochemistry

Immunohistochemistry was performed following the protocol outlined in the vector staining kit. The paraffin sections were heated in a microwave oven for 3 to 8 minutes, and then cooled for 5 minutes at room temperature using a citrate-based antigen unmasking solution (H-3300-250) from Vector Labs, CA, USA. This was then cooled for another 30 minutes at ambient temperature on a bench. Endogenous blocking was performed for 10 minutes using 0.3% hydrogen peroxide in Tris-buffered saline (pH 7.4). Sections were blocked in 2.5% normal horse serum (S-2012-50; Vector Labs, CA, USA) for 30 minutes and then incubated with the primary antibody; mouse anti-Neu N (1:800, Chemicon). Sections were further treated with 1:200 biotinylated horse anti-mouse IgG (BA-2000-1.5; rat absorbed, Vector LAB) for immunolabelling, followed by washing in PBS and a 3,3′-diaminobenzidine (DAB) peroxidase (HRP) substrate kit (SK-4100; Vector Lab, USA). Finally, sections were counter-stained with hematoxylin.

Histology

We sacrificed the rats immediately after blood collection, harvested their brains, and fixed them in 10% neutral buffered saline. We used the fixed brain tissue for histology and immunohistochemistry. As a guide, 5μm thick coronal sections of each tissue block were obtained from the fixed brain tissues that had been paraffinized, specifically from regions anterior to the bregma. The hematoxylin and eosin staining techniques were carried out as described by Fischer et al[38] and Oria et al.[21]

Immunohistochemistry

We followed the immunohistochemistry protocol as outlined in the vector staining kit. We heated the paraffin sections in a microwave oven for 3 to 8 minutes, and then cooled them for 5 minutes at room temperature using a citrate-based antigen

unmasking solution from Vector Labs, CA, USA. We allowed it to cool for 30 minutes at ambient temperature on a bench. We performed endogenous blocking for 10 minutes using 0.3% hydrogen peroxide in Tris-buffered saline (pH 7.4). Sections were blocked in 2.5% normal horse serum (Vector Labs, CA, USA) for 30 minutes and then incubated with the primary antibody; mouse anti-Neu N (1:800, Chemicon). Sections were further treated with 1:200 biotinylated horse anti-mouse IgG (rat absorbed, Vector) for immunolabelling, followed by washing in PBS and a 3,3′-diaminobenzidine (DAB) peroxidase (HRP) substrate kit (Vector Lab, USA). Finally, sections were counter-stained with hematoxylin.

Image Analysis and Cell Counting

For image analysis and cell counting, we captured panoramic photomicrographs of all sections using a digital brightfield microscope at a magnification of 100X. These images were imported into Image-J software (NIH, USA), and Neu-N-positive cells were identified and counted using the Image-J cell counter.[21,39]

Statistical Analysis

Statistical analysis was done using the GraphPad Prism programme (Version 9, GraphPad Inc., USA). We presented all results as mean and standard error of mean (SEM) using bar charts and tables. We used both two-way and one-way analysis of variance (ANOVA) when necessary to analyse the data. Tukey post hoc test was done for cases with statistically significant differences at $p<0.05$.

Results

In light of the established neurotoxic effects of METH, especially regarding its influence on oxidative stress, neuroinflammation, neurotransmitter equilibrium, and neuronal integrity, we aimed to evaluate Morin's potential to treat these METH-induced adverse effects. This investigation assessed oxidative stress markers, neuroinflammatory cytokines, as well as motor and cognitive functions, neurotransmitter levels, and both histological and immunohistochemical alterations within the basal ganglia, aiming to elucidate the degree of neuroprotection provided by Morin.

Morin Restores Oxidative Equilibrium Through the Modulation of Malondialdehyde (MDA), Superoxide Dismutase (SOD), and Catalase (CAT) Levels in Meth-Induced Neurotoxicity

Given that oxidative stress significantly contributes to neuronal damage induced by METH, we commenced the study of the MDA, a marker indicative of lipid peroxidation, alongside SOD and CAT, which are essential antioxidant enzymes in the various groups. METH exposure led to a significant elevation in MDA levels ($p<0.05$), signifying increased oxidative damage. Nonetheless, the Morin administration markedly mitigated this rise in a dose-dependent fashion, resulting in levels in the Morin-treated groups that were comparable to those in the control and Morin-only groups (Figure 1A). A significant decrease in SOD and CAT levels resulted from METH exposure ($p<0.05$) as presented in Figure 1B and C, an indication of impaired antioxidant defense mechanism. Following post-Morin treatment, SOD and CAT levels were normalized, exhibiting no significant differences between the high-dose Morin group and the control groups, indicating a potent antioxidant activity of Morin against METH-induced neurotoxicity.

Morin Reduces METH-Induced Inflammation Through the Inhibition of IL-6 and TNF-α Expression

We examined serum inflammatory cytokines IL-6 and TNF-α because of their crucial relationship with METH-induced neuronal injury (Figure 2). METH significantly increased IL-6 and TNF-α levels ($p<0.05$), supporting its role in the initiation of neuroinflammatory cascades. The Morin treatment, especially at elevated dosages, significantly decreased the levels of these cytokines, with IL-6 and TNF-α expression reverting to levels akin to those in the control groups. The data indicate that Morin possesses anti-inflammatory properties.

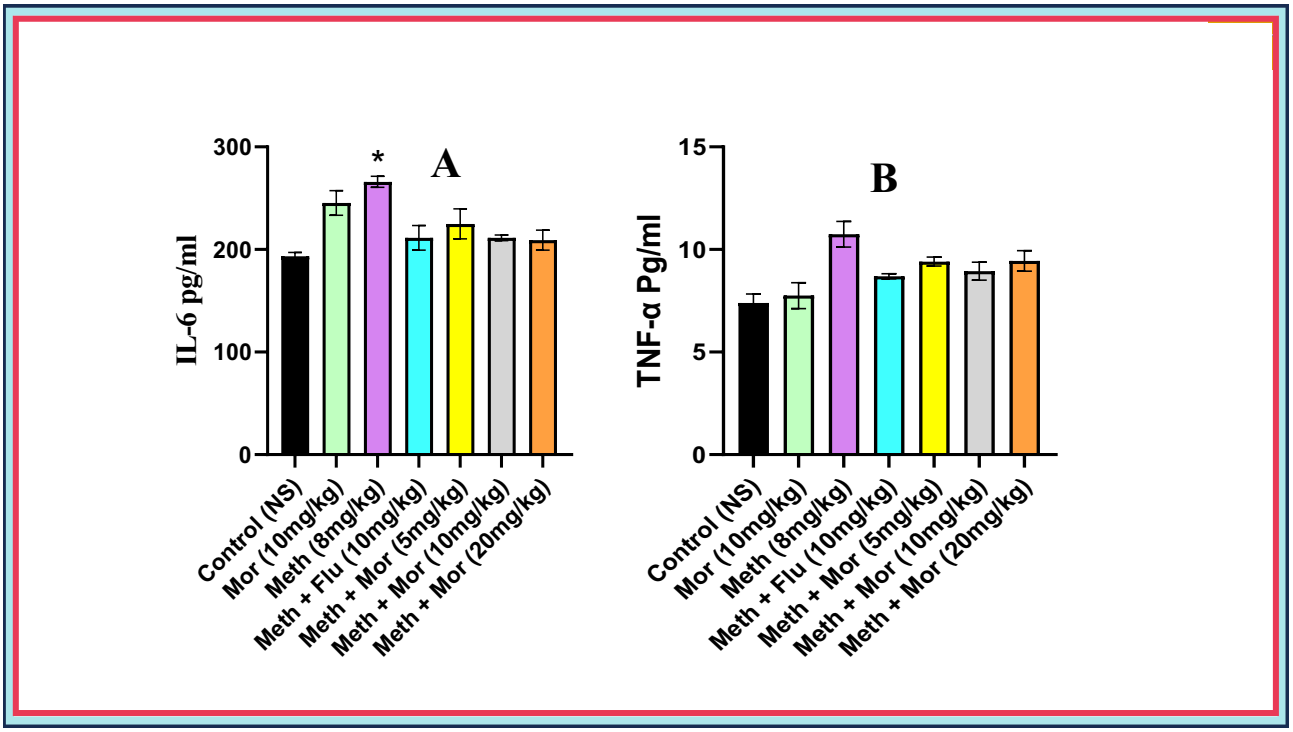

Figure 2 Effect of Morin on (**A**). IL-6 and (**B**). TNF- α in methamphetamine induced neurotoxicity. Values are expressed as mean ± SEM; *Indicates significant difference from control ($p<0.05$). One way ANOVA followed by Tukey post Hoc test.

Morin Mitigates METH-Induced Motor Impairment in the Walking Beam Assessment

Considering that motor impairments are characteristic of METH neurotoxicity, we then assessed motor coordination using the walking beam test. METH treatment resulted in a significant increase in both paw slips and crossing time ($p<0.05$), indicating compromised motor control (Figure 3A and B). Nonetheless, Morin therapy ameliorated these deficiencies, resulting in decreased crossing time and a reduction in paw slips. Significantly, motor performance in the Morin-treated groups was analogous to that of the control groups, indicating Morin's potential in reinstating dopaminergic function and motor coordination.

Morin Enhances Cognitive Performance in Y-Maze and Novel Object Recognition Assessments

We use the Y-maze test to assess spatial working memory and the Novel Object Recognition Test (NORT) to measure non-spatial memory in order to determine the effect of Morin on cognitive performance. METH treatment in the Y-maze test resulted to a significant decrease in percentage alternation ($p<0.05$), signifying compromised spatial memory (Figure 4). After Morin therapy, the percentage of alternation greatly improved, with no significant differences seen between the Morin-treated and control groups. In NORT, METH exposure resulted in a reduction of the discrimination ratio and exponential quotient ($p<0.05$), indicating impairments in recognition memory (Figure 5A and B). The Morin treatment, especially at elevated dosages, reinstated these parameters, showing its capacity to mitigate METH-induced cognitive impairment.

Morin Modulates Dopaminergic and Cholinergic Neurotransmitter Concentrations

We analyzed dopamine and acetylcholine concentrations in serum because of METH's strong influence on the dopaminergic system (Table 1). Prolonged exposure to METH led to an unusual increase in dopamine levels, likely due to heightened dopamine release and impaired reuptake processes ($p<0.05$). The Morin treatment stabilized dopamine levels, so averting more excitotoxic injury. Likewise, METH markedly decreased acetylcholine levels ($p<0.05$), a consequence linked to cognitive deficits. The Morin therapy successfully reinstated acetylcholine levels, indicating that its neuroprotective function encompasses not just the dopaminergic system but also cholinergic regulation.

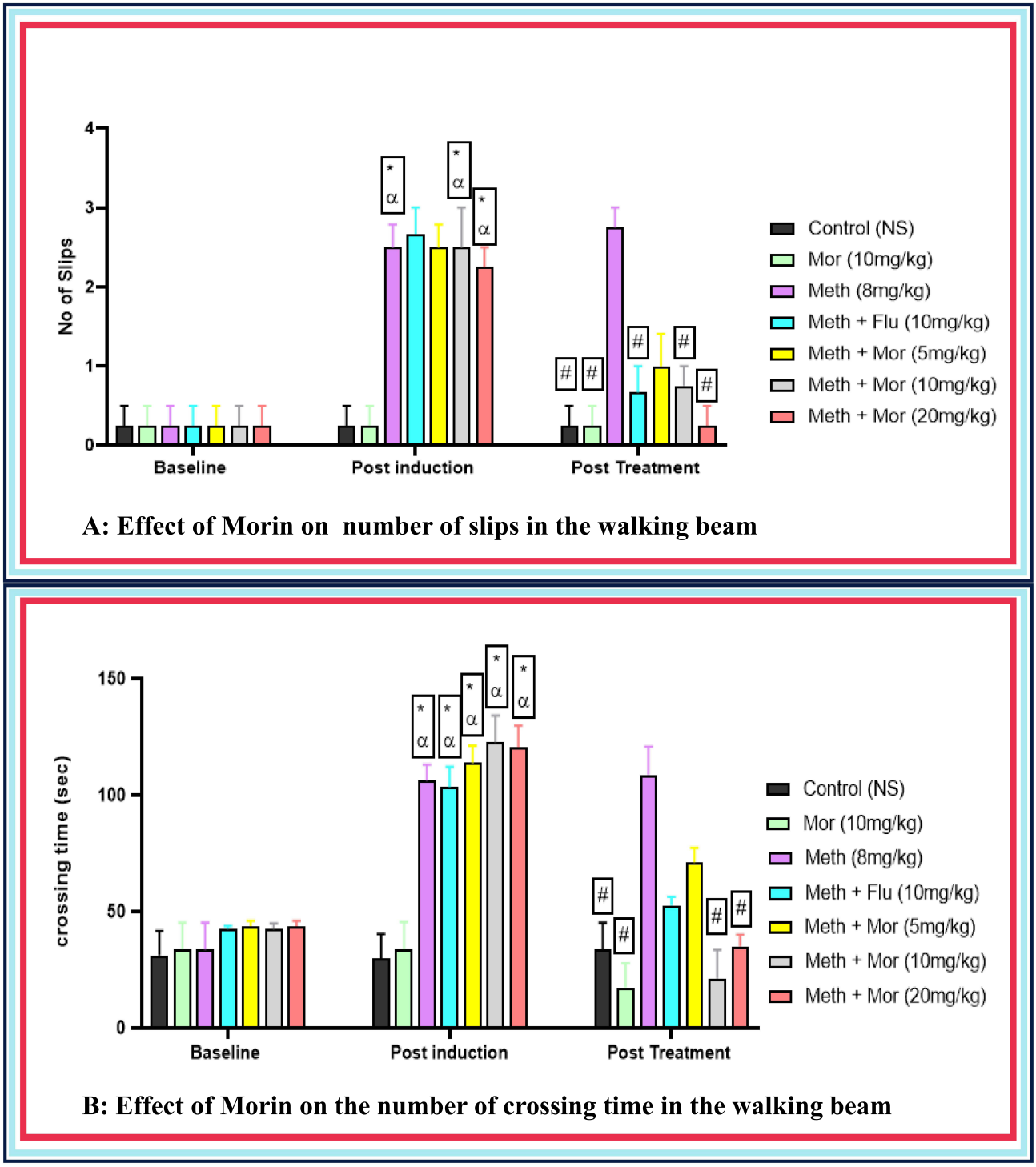

Figure 3 (**A** and **B**) Effect of Morin on number of slips (**A**) and crossing time (**B**) in walking beam test. Values are expressed as mean ± SEM; *Indicates significant difference from control group ($p < 0.05$), **α** indicates significant difference from Morin only group ($p < 0.05$) and #Indicates significant difference from Meth only group ($p < 0.05$), Two-way ANOVA followed by Tukey post Hoc test.

Morin Restores the Normal Histological Architecture of the Basal Ganglia

We assessed Morin's protective effects against METH-induced neuronal injury by analyzing hematoxylin and eosin (H&E) stained slices of the basal ganglia (Figure 6). Neuronal degeneration with pyknotic cells along with cytoplasmic fragmentation and altered neuropil architecture were noted in the METH-only group. The Morin-treated groups exhibited a significant

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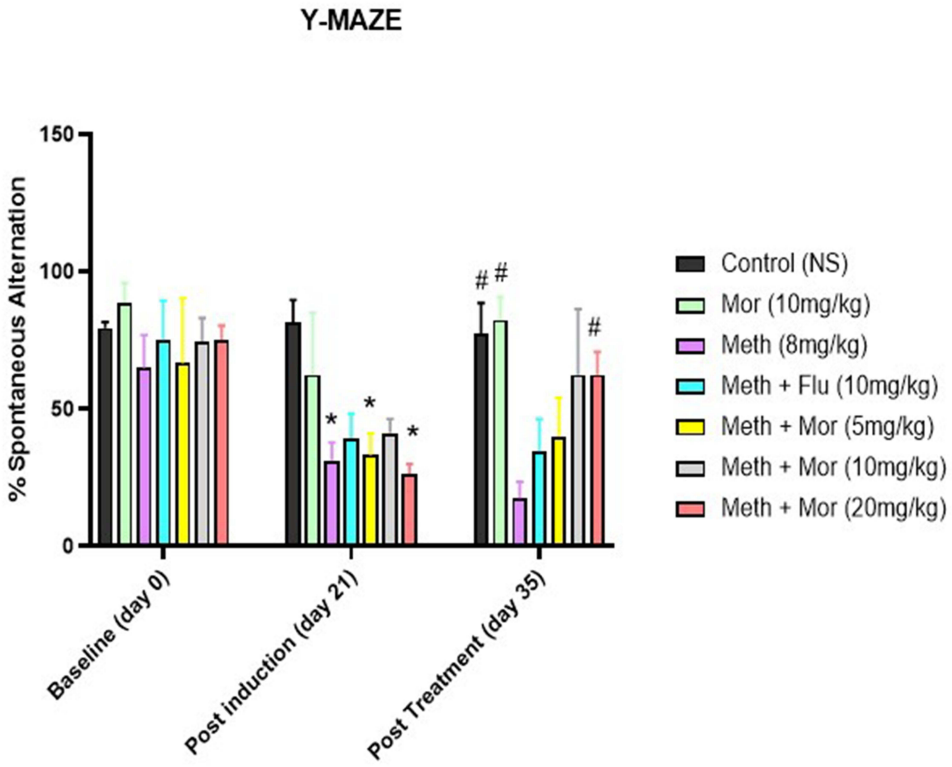

Figure 4 Effect of Morin on % spontaneous alternation in Y-maze test. Values are expressed as mean ± SEM; *Indicates significant difference from control ($p<0.05$), #Indicates significant difference from Meth only group ($p < 0.05$). Two way ANOVA followed by Tukey post Hoc test.

reduction in degenerative characteristics in a dose-dependent manner, with the high-dose Morin group demonstrating nearly normal neuronal morphology. Groups treated with Morin had intact neuronal architecture and increased Neu-N staining intensity, indicating improved neuronal survival or maintenance of neuronal integrity (Figures 7 and 8). To further examine the neuroprotective properties of Morin, we conducted Neu-N immunohistochemistry. Neu-N (Neuronal Nuclei) is a neuronal marker frequently employed to identify post-mitotic neurons, differentiating them from non-neuronal or proliferative cells. The Neu-N immunohistochemistry examination demonstrated a significant reduction in Neu-N staining intensity in the METH-only group, indicative of neuronal injury and compromised neuronal integrity. Conversely, the Morin-treated animals demonstrated increased Neu-N immunoreactivity, indicating improved neuronal preservation. While these data suggest possible neuroprotection, utilizing stereological techniques or supplementary neurogenesis markers is will validate and substantiate assertions on neuronal growth and alterations in neuronal populations.

Discussion

The present work shows that Morin mitigates motor and cognitive impairments, modulates dopamine and acetylcholine synthesis, and improves neuronal preservation in the context of METH-induced neurotoxicity. Morin markedly reduced the detrimental impacts of METH on oxidative stress indicators, including MDA, SOD, and CAT. It also lowers pro-inflammatory cytokines such as IL-6 and TNF-α.

The study's findings on oxidative stress markers indicate that prolonged METH treatment elevates MDA levels, signifying increased lipid peroxidation and oxidative stress. This also resulted in a notable decrease in SOD and CAT levels, which are essential enzyme antioxidants that neutralize ROS. Previous investigations have shown that METH increases oxidative stress through the production of ROS, which damage cellular structures and cause neurotoxicity.[1,19] Morin reversed this MDA elevation and SOD and CAT depletion, highlighting its ability to normalize lipid peroxidation, restore antioxidant enzyme activity; mitigating METH-induced oxidative damage.[27,40,41]

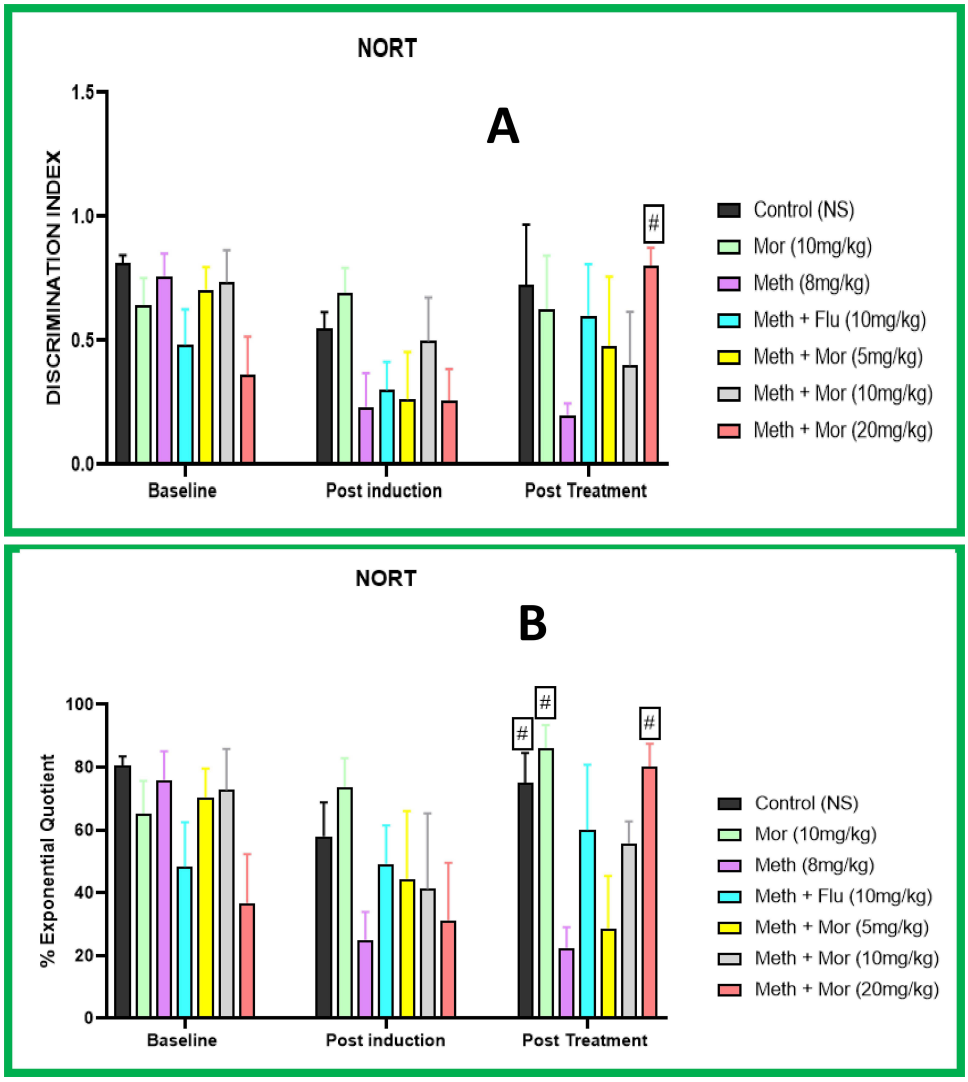

Figure 5 (**A**) Effect of Morin on discrimination ratio and (**B**) exponential quotient in Novel object test. Values are expressed as mean ± SEM; #Indicates significant difference from Meth only group ($p < 0.05$). One way ANOVA followed by Tukey post Hoc test.

Chronic METH exposure also elevated the pro-inflammatory cytokines IL-6 and TNF-α, which are critical in neuroinflammation. Increased levels of IL-6 and TNF-α are extensively reported in METH-induced neuroinflammation, resulting in neuronal damage and exacerbating neurotoxic effects.[42–44] Our study shows that Morin significantly lowered these cytokines, proving its anti-inflammatory effects. The decrease of IL-6 and TNF-α in Morin-treated groups is consistent with previous findings that have revealed that Morin has the potential to suppress microglial activation and pro-inflammatory cytokines.[41,45,46] Morin's ability to restore oxidative balance and reduce inflammation is evidenced by the restoration of oxidative stress markers (MDA, SOD, and CAT) and the reduction of inflammatory cytokines (IL-6 and TNF-α) in METH-induced neurotoxicity.

While fluoxetine reduces neuroinflammation and oxidative stress via its serotonergic routes where it indirectly lowers oxidative stress by regulating microglial activation and lowering pro-inflammatory cytokines like IL-6 and TNF-α,[47,48] Morin demonstrates antioxidant and anti-inflammatory capabilities by scavenging ROS, restoring the activity of antioxidant enzymes, and diminishing pro-inflammatory cytokines. The significant increase in serum levels of oxidative stress markers (MDA) and inflammatory cytokines (IL-6, TNF-α) following METH exposure suggests a systemic inflammatory response that aligns with established models of METH neurotoxicity.[42,49] While these markers are not exclusive to neural cells, previous research has demonstrated strong correlations between elevated serum pro-

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Table 1 Descriptive Statistics and ANOVA Values of Serum Dopamine and Acetylcholine Levels Expressed in Mean and Standard Error of Mean (SEM)

Groups	Dopamine		Acetylcholine	
	Mean	Sem	Mean	Sem
Normal saline only	0.72	0.02	1,49	0.15
Mor only (10mg/kg)	0.87	0.07	1.82	0.26
Meth only (8mg/kg)	1.47	1.12	0.58	0.13
Meth + flu (10mg/kg)	1.12	0.19	0.73	0.09
Meth + Mor (5mg/kg)	0.91	0.19	1.09	0.01
Meth + Mor (10mg/kg)	0.84	0.09	1.01	0.01
Meth + Mor (20mg/kg)	0.74	0.01	1.35	0.11
F stat	4.13		4.19	
P value	0.14		0.14	

inflammatory cytokines and neuroinflammation within the CNS, particularly in the dopaminergic pathways of the basal ganglia.[43,44] Additionally, METH has been shown to compromise the integrity of the blood-brain barrier (BBB), allowing peripheral inflammatory mediators to exacerbate neuroinflammation and oxidative damage in the basal ganglia.[18] Future studies should incorporate direct quantification of oxidative stress markers and inflammatory cytokines within the basal ganglia to further confirm these systemic-brain interactions.

The study's findings indicated that METH induction resulted in impaired motor coordination and balance, as seen by the induced rats exhibiting increased paw slips and prolonged crossing durations. Previous studies have reported that METH induction leads to motor dysfunction.[4,50,51] The motor dysfunctions that are associated with METH toxicity are due to damage to the dopaminergic neurons that are involved in the regulation of motor control, reward processing, motivation, and cognitive functions.[29,52–54] Our findings indicate that Morin administration restored dopamine and

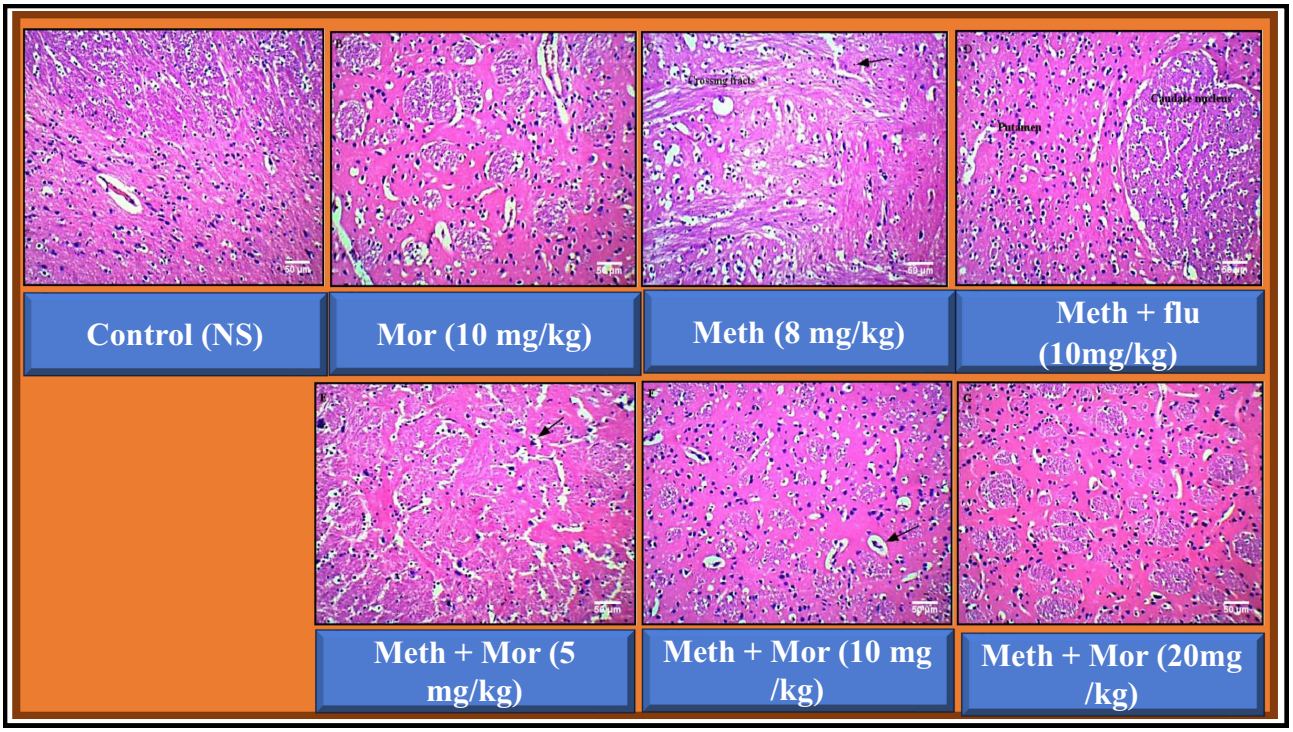

Figure 6 H&E-stained photomicrographs showing panoramic views of basal ganglia general micromorphological presentations in Wistar rats across the study groups. Magnification: 100 X; scale bars: 50μm. Black arrows indicate profiles with degenerative changes.

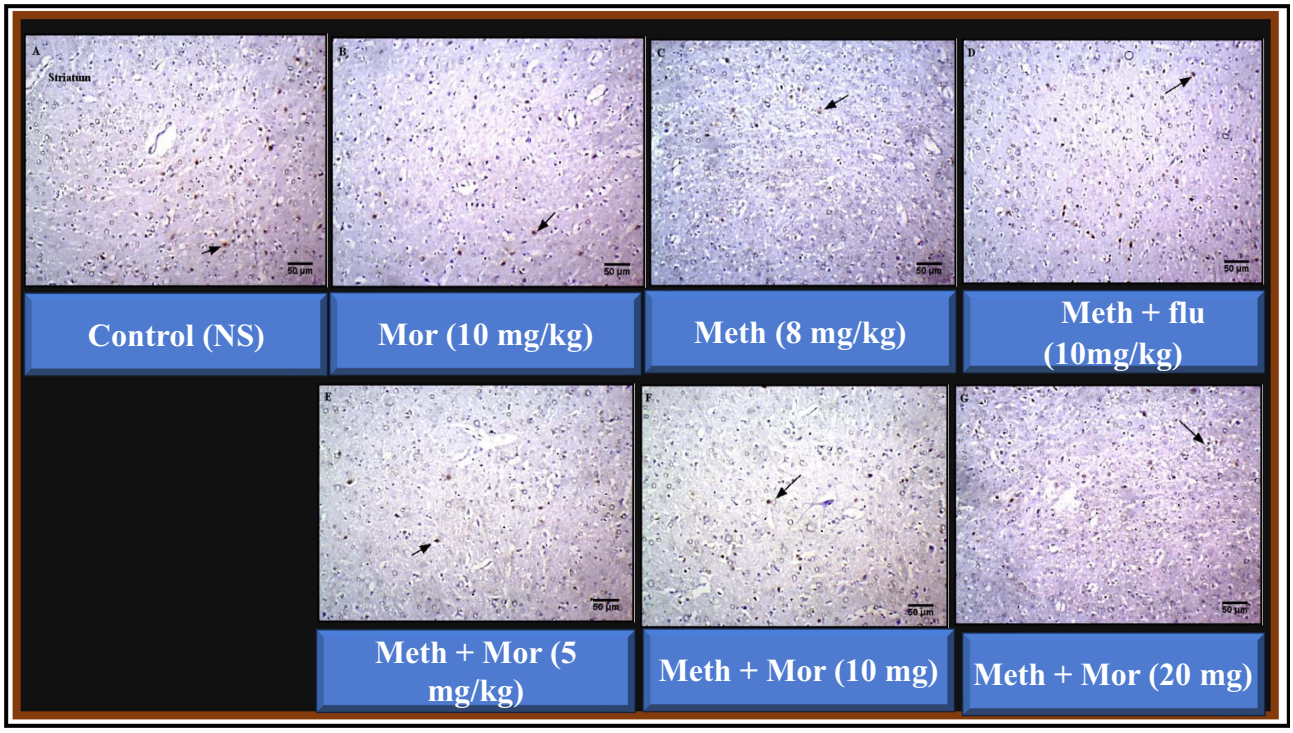

Figure 7 Anti-Neu-N immunostaining photomicrographs showing panoramic views of striatum general micromorphological presentations in Wistar rats across the study groups (**A**–**G**). Magnification: 100X; scale bar: 50μm. Black arrows indicate cells positive for Neun-N antibody.

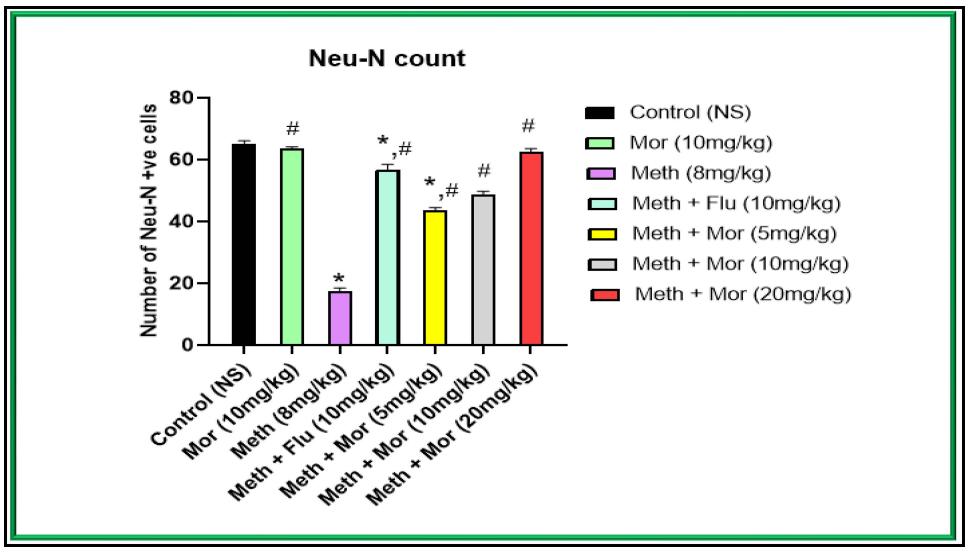

Figure 8 Image J analysis of Neu-N positive cells in the basal ganglia. Values are expressed as mean± SEM, *Indicates significant difference from control ($p<0.05$), #Indicated significant difference from Meth only group ($p < 0.05$). One-way ANOVA followed by Tukey post hoc test.

acetylcholine levels that were altered by METH exposure. Given that dopamine depletion is a hallmark of METH-induced neurotoxicity, this suggests that Morin may exert neuroprotective effects through dopamine system stabilization. Additionally, the reversal of acetylcholine deficits aligns with prior research indicating that flavonoids can modulate cholinergic neurotransmission.[33] While these results suggest a role for Morin in neurotransmitter homeostasis, tissue-based markers will offer more definitive regional neurotransmitter dynamics.

The nigrostriatal pathway which principally is made up of dopaminergic neurons and mostly those emanating from the substantia nigra and projecting to the striatum are essential for the initiation and modulation of voluntary movements.

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A decrease in dopaminergic activity in this pathway is essential to the motor symptoms of Parkinson's disease, including tremors, rigidity, and bradykinesia. METH has been shown to cause motor impairment in several studies and it has been associated with damage in the basal ganglia.[55–58] Treatment with Morin improved these deficits and produced a marked decrease in paw slips and crossing time than the METH-only group. The Morin-treated group exhibited motor performance comparable to that of the control and Morin-only groups, indicating that Morin may facilitate the restoration of motor coordination in METH-treated rats. This outcome aligns with other studies indicating that flavonoids possess motor-restorative effects attributable to their antioxidant and anti-inflammatory characteristics.[29,33,59,60]

The restoration of motor function in Wistar rats induced by METH and treated with Morin can be attributed to the strong oxidative and anti-inflammatory properties of Morin. METH-induced neurotoxicity leads to motor dysfunction through increased oxidative stress and the activation of inflammatory responses in the brain. Morin's anti-inflammatory properties enable reduction in the production of pro-inflammatory cytokines, including TNF-α and IL-6. Suppression of microglial activation and reduction of cytokine expression will contribute to the prevention of further inflammation-induced neuronal damage. Inflammatory cytokines are known for their impact on altering normal neuronal signaling and motor function. Morin contributes to the recovery of neuronal health by mitigating inflammatory responses, which facilitates the restoration of motor function. This suggests that Morin's therapeutic potential is linked to its capacity to reduce the neurotoxic effects of METH by modulating oxidative and inflammatory pathways.

The cognitive-enhancing effects of Morin were assessed using the Y-maze test which is a test for spatial working memory in terms of percentage alternation. From our study, METH exposure for a long period reduced the percentage alternation showing that the animals had cognitive dysfunction. This is in agreement with previous studies which have shown that METH neurotoxicity caused hippocampal and cortical damage that affected memory and learning.[21,33] Morin treatment mitigated the cognitive impairments induced by METH, restoring percentage alternation to levels comparable to those of the control and Morin-only groups. Morin's mitigation of METH-induced cognitive deficits stems greatly from its ability to diminish oxidative stress and inflammation, which are major recognized factors in METH-related cognitive deterioration.[24,27,33] Earlier reports have also noted that Morin enhanced cognitive function, particularly memory and learning, in neurodegenerative models like Alzheimer's disease.[41,61,62]

To assess cognitive function, the Novel Object Recognition Test (NORT) was applied to calculate the discrimination ratio and exponential quotient. METH-induced neurotoxicity affected both measures significantly, thus pointing to a defect in recognition memory. Previous studies have indicated that METH affects cognitive flexibility and recognition memory, and this is mainly due to the damage to dopaminergic and cholinergic systems. to a substantial reduction in both measurements, indicating impairments in recognition memory. Earlier reports have noted that METH compromises cognitive flexibility and recognition memory, and this is mostly attributable to impairment in dopaminergic and cholinergic systems.[4,9,51] Dopaminergic neurons in the mesocortical pathway run from the ventral tegmental area to the prefrontal cortex, playing a role in higher cognitive tasks like attention, decision-making, and working memory. Disruption in this system is frequently linked to schizophrenia and cognitive impairments, as dopamine plays a crucial role in regulating executive functions and cognitive flexibility. Morin administration, especially at higher doses, ameliorated both the discrimination ratio and exponential quotient deficits, which implies that it can improve recognition memory. This function can be attributed to Morin's ability to reduce oxidative damage and inflammation, hence preserving neuronal integrity and neurotransmitter balance in the brain. The neuroprotective effects of Morin are corroborated by studies indicating its enhancement of recognition memory in several neurotoxic models.[41,61]

METH-induced neurotoxicity is marked by the dysregulation of essential neurotransmitter systems, notably dopamine and acetylcholine. Prolonged METH use, usually results in a substantial increase in serum dopamine levels, signifying malfunction within the dopaminergic system. Increased dopamine levels after METH injection are associated with excessive release and compromised absorption, leading to oxidative stress and neuronal injury.[49,63–65] Morin treatment reversed this increase in dopamine levels thus normalizing the dopaminergic system. Earlier research has established that flavonoids such as Morin can affect dopamine release and have neuroprotective effects against dopaminergic toxicity.[29,33] Similarly, METH decreased the levels of Acetylcholine; a neurotransmitter essential for cognitive functions supporting earlier reports that flavonoids may enhance cholinergic transmission and protect against cognitive decline.[29,33]

The presence of METH-induced neuronal damage in the basal ganglia was validated through H&E staining, revealing pyknotic neurons alongside alterations in cell morphology. The histopathological changes are characterized by oxidative stress, excitotoxicity, and neuroinflammation, which eventually result in neuronal apoptosis.[18,19] Morin treatment prevented these neurodegenerative alterations; however, higher doses provided a nearly normal histological organization of the basal ganglia. The neuroprotective action of Morin may be attributed to its antioxidant and anti-inflammatory activities which prevent neuronal death and maintain the cellular structure. It has been found that Morin can protect against neurodegeneration in models of Parkinson's disease in which dopaminergic neurons are also lost.[29] To further support this finding, we performed Neu-N immunohistochemistry and found that METH treatment significantly reduced the number of Neu-N-positive cells in the basal ganglia. This decrease in neuronal markers may be suggestive of dopaminergic neuronal loss which is a characteristic feature of METH-induced neurotoxicity.[66] However, in our Morin-treated group, Morin significantly elevated the Neu-N positive neurons in a dose-dependent manner neuronal regeneration. These neuro-regenerative effects of Morin are in agreement with other findings which have indicated that flavonoids can enhance neurogenesis. While our observed increase in Neu-N immunoreactivity in Morin-treated groups may suggest a protective effect against METH-induced neurotoxicity, an indication of preserved neuronal architecture, future studies using stereological techniques and additional markers of neuronal survival or proliferation (eg, Ki67, BrdU) will further elucidate the mechanisms underlying these neuroprotective effects.

While our results demonstrate that METH significantly impaired recognition memory in the Novel Object Recognition Test (NORT), this effect cannot be attributed solely to dopaminergic dysfunction in the basal ganglia. Unlike motor coordination deficits, which are strongly linked to dopaminergic damage in the basal ganglia, novel object recognition primarily relies on the hippocampus and prefrontal cortex. Previous studies, including,[51] suggest that METH does not consistently impair hippocampal-dependent behaviors, indicating that other mechanisms may underlie these cognitive deficits. Given the known effects of METH on cortical excitotoxicity and hippocampal structural integrity,[18,64] it is likely that METH-induced neurotoxicity extends beyond dopaminergic neurons, affecting cholinergic and glutamatergic systems as well. Future studies incorporating direct hippocampal and prefrontal cortex analyses are needed to confirm these mechanisms.

In conclusion, the present work reveals that Morin ameliorates motor and cognitive deficits, modulates neurotransmitter systems and protects dopaminergic neurons from METH-induced neurotoxicity. Thus, it is possible to consider Morin as a potential therapeutic agent for the prevention of the long-term consequences of METH abuse on the brain due to its antioxidative, anti-inflammatory, and neuro-preservative potential. Given the findings from our study, several future directions and additional studies are necessary to further explore the potential of Morin as a therapeutic agent for METH Use Disorder (MUD). These studies should aim to (1) further validate Morin's mechanism of action, (2) enhance translational relevance, and (3) evaluate its clinical efficacy in human populations.

Disclosure

The authors report no conflicts of interest in this work.

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