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ORIGINAL RESEARCH

Mangiferin Mitigates Ketamine-Induced Dopaminergic and Glial Dysregulation and Modulates Nrf2 Expression in a Rat Schizophrenia-Like Model

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Introduction: Schizophrenia involves dopaminergic dysregulation, oxidative stress, and glial activation within motor–cognitive circuits. Mangiferin, a polyphenolic C-glucoside from *Mangifera indica*, exerts antioxidant and anti-inflammatory effects partly via modulation of nuclear factor erythroid 2–related factor 2 (Nrf2) signaling. This study evaluated whether mangiferin attenuates ketamine-induced behavioral and neurobiological alterations along the basal ganglia–substantia nigra–cerebellar axis in rats.

Methods: Male Wistar rats were assigned to seven groups (n = 6) and received vehicle, ketamine (50 mg/kg/day, i.p. 7 days), mangiferin (25–75 mg/kg, p.o. 14 days), ketamine plus mangiferin (25, 50, 75 mg/kg), or ketamine plus risperidone (2 mg/kg, p.o). Y-maze and open-field tests were conducted at baseline, after ketamine, and after treatment. Striatum, substantia nigra, and cerebellum were analyzed for dopamine (HPLC), oxidative stress markers, inflammatory mediators, and immunohistochemistry for GFAP and Nrf2.

Results: Ketamine produced behavioral alterations characterized by reduced exploratory activity, hyperlocomotion, and anxiety-like behavior, alongside elevated dopamine, reduced antioxidant enzyme activities, increased lipid peroxidation and pro-inflammatory mediators, enhanced GFAP immunoreactivity, and decreased Nrf2 immunoreactivity. Mangiferin, particularly at 50–75 mg/kg, increased Y-maze arm entries toward control values (indicating improved locomotor activity), restored antioxidant defenses, reduced oxidative and inflammatory indices toward control levels, reduced astrocytosis, and increased Nrf2 immunoreactivity. Risperidone improved behavior and neuroinflammatory indices but showed less consistent normalization of redox markers and Nrf2 compared with high-dose mangiferin.

Discussion: These findings indicate that mangiferin attenuates ketamine-induced behavioral, oxidative, inflammatory, and glial alterations in motor–cognitive circuits and are consistent with modulation of redox–glial interactions, including Nrf2-associated antioxidant signaling. Collectively, the results support further evaluation of mangiferin and related Nrf2-modulating natural products as adjunctive strategies targeting redox–glial dysfunction in schizophrenia.

Keywords: schizophrenia, mangiferin, oxidative stress, Nrf2 pathway, astroglial activation

Introduction

Schizophrenia is a long-term mental illness with an incidence of approximately 1% of the population, characterized by positive (hallucinations, delusions), negative (motivation, social withdrawal), and cognitive symptoms.[1,2] Motor abnormalities such as neurological soft signs, catatonia, and parkinsonism are prevalent, and both pre-treatment and drug side effects involve motor circuits in pathophysiology.[3]

Emerging evidence demonstrates that, beyond their classical motor roles, the basal ganglia and cerebellum significantly contribute to cognitive and affective functions. One of the key points of the dopamine hypothesis of psychosis is striatal dopaminergic dysregulation.[4] There are structural/metabolic anomalies in basal ganglia, including mitochondrial and oxidative impairments that could be the cause of psychosis and motor and cognitive impairment.[5] The Cerebellar

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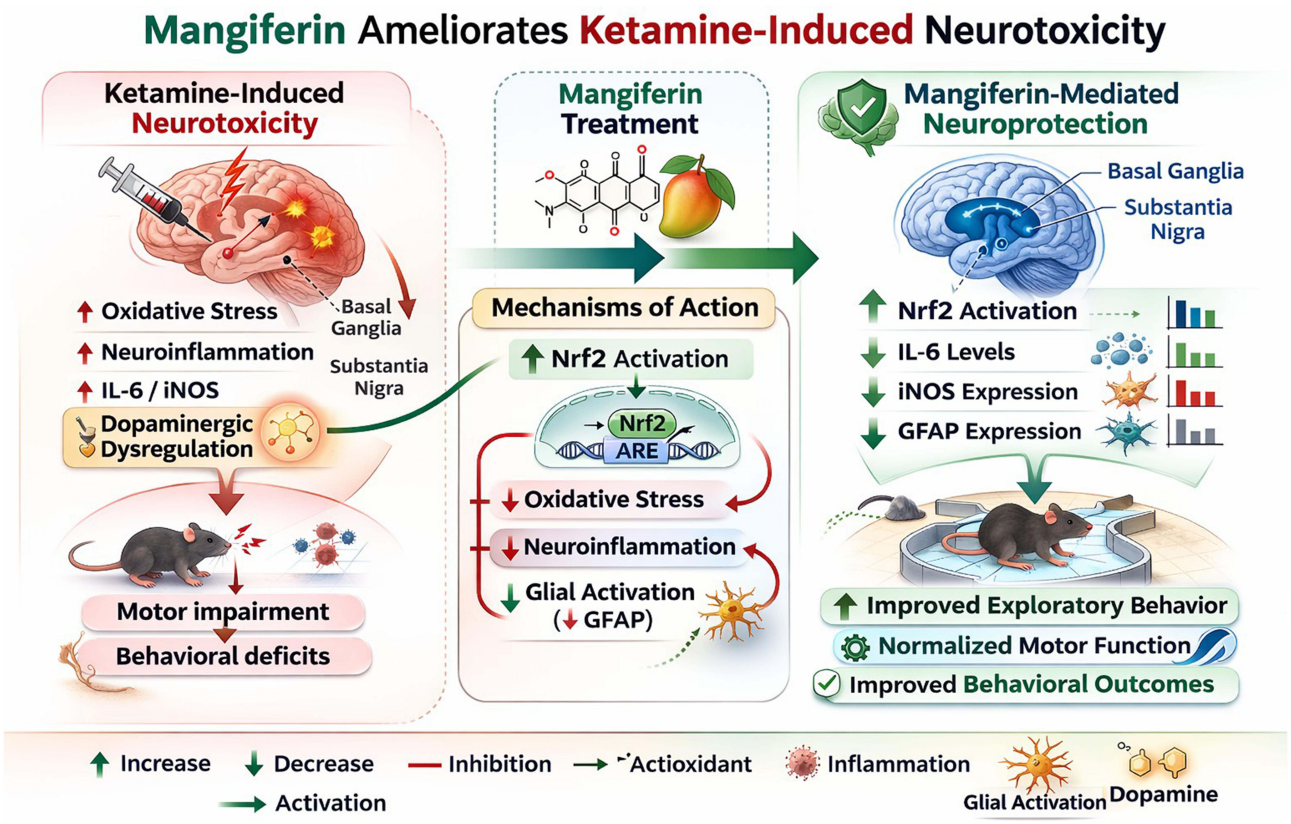
Graphical Abstract



involvement in cognitive dysmetria indicates impaired cortico-thalamo-cerebellar connectivity.[6,7] In some patients, structural and functional imaging studies also reveal reduced cerebellar volume or altered activation.[8] Notably, basal ganglia-cerebellar loops are linked, through thalamic relays. Dysconnectivity within this cerebello-basal ganglia circuitry has been associated with both negative symptoms and psychomotor poverty, and this supports a basal ganglia-substantia nigra-cerebellar axis in schizophrenia.[9,10] There is converging evidence that implicates neuroinflammation and oxidative stress. Elevated levels of pro-inflammatory cytokines (IL-6, IL-1β, TNF-α) have been observed even in first-episode, drug-naïve patients, and increased IL-6 is associated with more severe negative symptoms and treatment resistance.[11] The oxidative stress markers (lipid/DNA oxidation) are elevated, and the antioxidant defenses (eg., glutathione) are reduced.[12,13] The Nrf2 pathway is a key regulator of cytoprotective antioxidants genes (SOD, CAT, glutathione synthesis), and it does not seem to be sufficiently activated in schizophrenia.[14,15] The glial dysfunction also impairs redox and synaptic homeostasis: the activation of astrocytes is typical, and microglia are in primed/activated states with the release of cytokines and ROS.[16]

These mechanisms are induced with the ketamine model. Ketamine, an NMDA receptor antagonist, results in hyperlocomotion, working-memory impairment and social withdrawal, and triggers oxidative stress, interneuron dysfunction and dopaminergic dysfunction-in part through IL-6-dependent microglial ROS.[17] Although no model can fully recapitulate the complexity of the disorder, ketamine models key pathophysiological domains—glutamatergic dysfunction, inflammation, and redox imbalance—that are highly relevant for therapeutic development.[18]

Neuro-phytoremediation, involving the application of plant-derived compounds/mechanisms to counter neurotoxicity and facilitate neural repair has become an emerging interface between environmental remediation and neuroscience.[19–26] Traditional antipsychotics primarily target dopamine receptors and generally fail to sufficiently mitigate cognitive and

motor deficits or the underlying inflammatory/oxidative pathology.[27] This has prompted the development of adjunctive strategies with more extensive mechanisms of action.

Mango polyphenolic C-glucoside mangiferin (MGF) has antioxidant and anti-inflammatory properties. In addition to its redox modulating effects, mangiferin has shown anti-inflammatory activity by reducing the expression of key pro-inflammatory mediators, such as NF-kappa B, NLRP3 inflammasome components, TNF-a, IL-1-beta, IL-6, COX-2, and iNOS that mediate anti-inflammatory activity by reducing neuroinflammatory cascades involved in neurodegeneration and psychiatric disorders.[28–31]

Emerging data has also found that mangiferin acts on various intracellular signal pathways such as PI3K/Akt, and on the MAPK (JNK/p38), and apoptotic cascades, thus confirming its wide spectrum of cytoprotective and neuromodulatory properties in various experimental models.[32–35] Collectively, these mechanisms point to the fact that the effect of mangiferin may be directed toward pathways related to interconnected redox pathways, inflammatory pathways and neurotransmitter pathways, making mangiferin an interesting candidate for the reduction of ketamine induced dopaminergic, glial dysregulation. It activates Nrf2/ARE signalling, stimulates SOD/CAT/glutathione, suppresses lipid peroxidation, inhibits NF-κB–mediated cytokines, inhibits glial activation, and protects dopaminergic neurones in neurodegeneration models.[9,10,27,31] For instance, mangiferin protects against 6-hydroxydopamine (6-OHDA) lesions in a synergistic in vitro/in vivo model of Parkinson's disease, inhibiting dopaminergic neurone degeneration and oxidative injury.[36]

There is also emerging evidence on the role of mangiferin in neuropsychiatric studies. Preclinical studies have shown that mangiferin enhances the neurobehavioral and cognitive performance in models of depression and disorders involving stress, mainly through its actions on oxidative stress, inhibition of NLRP3/NF-kappa B mediated neuroinflammation and maintenance of mitochondrial function.[37–41] In addition, mangiferin has demonstrated positive effects in other neuropsychiatric settings, such as postpartum depression, epilepsy, and anxiety-related disease states, associated with modulation of microglial activation, regulation of neurotransmitters balance, as well as positive behavioral outcomes.[30,42,43] Systematic evidence further suggests that mangiferin has consistent effects to improve multiple domains of cognitive function in animal models through antioxidant, anti-inflammatory and neuromodulatory mechanisms.[28,44,45] Collectively, these findings support the emerging role of mangiferin as a multi-target neuroprotective agent with potential relevant to neuropsychiatric disorders, schizophrenia.

Cortical and hippocampal abnormalities are well-documented in schizophrenia, and mangiferin has demonstrated efficacy in hippocampal-dependent paradigms. However, the role of subcortical motor circuits—specifically the basal ganglia–substantia nigra–cerebellar (BG–SN–Cb) loop—in schizophrenia-related motor and psychomotor disturbances has been comparatively underexplored, despite persistent evidence of basal ganglia and cerebellar involvement.[46–48] By focusing on this subcortical axis, we sought to expand the current literature focused on the cortex and hippocampus, and to evaluate whether a redox- and glia-targeting natural product could restore dopaminergic and glial homeostasis within motor circuitry. Consequently, we evaluated the efficacy of mangiferin in restoring neuro-glial homeostasis along the BG–SN–Cb axis in ketamine-induced schizophrenia-like rats, as indicated by GFAP and Nrf2, and contrasted its effects with those of risperidone. We hypothesized that mangiferin would ameliorate behavioural deficits, diminish oxidative and inflammatory markers, and restore GFAP and Nrf2 levels in these subcortical areas.

Materials and Method

Animals and Housing

Forty-two adult male Wistar rats (8–10 weeks, approximately 170 g) were acquired from the animal breeding facility of the department of Anatomy Faculty of Basic Medical Sciences of University of Nigeria. The rats were kept five in a cage in controlled conditions (22 +- 2 deg C; 12:12 h light-dark cycle; 50–60% humidity) with food and water ad libitum. Enrichment of the environment (tunnels, nesting material) was given. All animals underwent behavioral assessments at baseline (day 0), after ketamine or vehicle treatment (day 7), and after the 14-day treatment phase (day 21). Following behavioral testing, three rats per group were randomly selected for biochemical and dopamine analyses, and three rats per group were processed for histology and immunohistochemistry. Thus, the sample size for behavioral analyses was n=6/group, for biochemical and dopamine measures n=3/group, and for histology/immunohistochemistry n=3/group.

Ethical Approval

All animal experiments were carried out based on the ARRIVE 2.0 recommendations on the care, use, and management of laboratory animals,[49] and approved of by the Institutional Research Ethics Committee of the University of Nigeria, Enugu with ethical number COMHREC/2025/01/012. The experimental standards complied with the National Institute of Health Guidelines, regarding Care and Use of Laboratory animals (NIH publication no. 8023, revised 1978).[50] All endeavors were made to lessen the pain of animals.

Sample Size/Power Calculation

The calculation of the sample size was performed with the software G*Power 3.1, based on the primary outcome superoxide dismutase (SOD) activity, expected effect size f = 0.55, level of significance a = 0.05, and power of 0.8. A total of 6 rats per group was needed to detect a 30% difference in the amount of SOD between the groups of rats that received ketamine alone and ketamine + mangiferin. Accordingly, 42 rats were used for 7 experimental groups (n = 6 per group). Animals were allocated into separate cohorts for behavioral (n = 6 per group) and terminal tissue-based analyses (n = 3 per group), as biochemical, neurotransmitter, and immunohistochemical assessments required euthanasia and could not be performed longitudinally in the same animals.

Statistical Analysis

Data were analyzed using SPSS version 25 and GraphPad Prism version 9. Behavioral data collected across multiple time points (baseline, post-induction, and post-treatment) were analyzed using repeated-measures ANOVA to account for within-subject variability, followed by Tukey's post hoc test for multiple comparisons. Biochemical, neurotransmitter, and immunohistochemical data, obtained from a separate terminal cohort of animals, were analyzed using one-way ANOVA followed by Tukey's post hoc test. All results are presented as mean ± SD, and statistical significance was set at $p < 0.05$. To evaluate group differences, we used one-way or two-way analysis of variance, according to the analysis. The two-way ANOVA contained factors of treatment (eg., ketamine, doses of mangiferin, risperidone, etc.) and time (eg., baseline, post-ketamine, post-treatment). Where applicable the assumption of sphericity was tested using Mauchly's test and Greenhouse-Geisser corrections were applied where necessary.

Randomization and Blinding

Rats were acclimatized and randomized in a computer-generated sequence after acclimatization. Scorers who performed behavioral scoring, biochemical assays, and histological staining were blinded to group assignment. No animal was excluded from analysis.

Dose Justification and Experimental Groups

Group A: Control (vehicle only)
Group B: Ketamine-only (50 mg/kg i.p.)
Group C: Mangiferin alone (50 mg/kg by mouth)
Group D: Ketamine and Mangiferin (25 mg/kg oraly)
Group E: Ketamine + Mangiferin (50 mg/kg oral)
Group F: Ketamine + Mangiferin (75 mg/kg oral)
Group G: Ketamine + Risperidone (2 mg/kg oral)

Ketamine-Induction

A 7-day, sub-anesthetic, subchronic ketamine (50 mg/kg/day, i.p.) induction was conducted according to validated models.[51] Group A and C were injected with saline.

Mangiferin Doses

Oral doses of 25–75 mg/kg (Fuma Natural Science, USA; Batch #FN-MGF-2023-05) were chosen based on previous efficacy research that demonstrated neuroprotective efficacy in the range of 10–100 mg/kg without toxicity.[36,52] The chosen oral doses of 25–75 mg/kg were based on evidence from several in vivo studies showing that mangiferin has dose-dependent neuroprotective, antioxidant and anti-inflammatory effects over a wide range of therapeutic doses. Systematic evaluation of preclinical models suggests that doses ranging from 10 to 200 mg/kg, but most often 10–50 mg/kg, improve cognitive and behavioral outcomes, including spatial and recognition memory, in preclinical models of neurodegeneration and neurotoxicity (Lum et al, 2020).

Additionally, studies have demonstrated the neuroprotective effect of mangiferin at doses of 10–60 mg/kg against neuroinflammation and oxidative brain damage, which supports its relevance in central nervous system disorders (Imran et al, 2017; Lum et al 2023; Mustafa et al, 2025).

The doses of 25, 50, and 75 mg/kg were chosen, based on this established therapeutic window, to represent graded low, intermediate, and higher pharmacologically active doses to test the effects of these doses on behavioral, neurochemical, and neuroglial parameters in the present study.

Risperidone Dose

Risperidone (2 mg/kg, oral; Juhel Pharm., Nigeria; Batch number:RS-0923) was used as a reference antipsychotic, which represents exposure to risperidone in rats that is relevant clinically.[27]

The treatments commenced 24 h following the final injection of ketamine and proceeded through 14 days. Daily observations were made on body weight, grooming, feeding, and overall movement.

Animal Humane Endpoints and Welfare

Daily monitoring of animals was done. Humane endpoints were a loss of more than 20% body weight, extreme dehydration, or failure to reach food/water. None of the animals reached these end points. Mild sedation was noted in risperidone-treated rats.

Euthanasia and Tissue Sharing

At the conclusion of the study, animals were euthanized under AVMA/IACUC-approved guidelines:

Biochemistry cohort (n=3/group): Rats were anesthetized with sodium pentobarbital (50mg/kg i.p.; Sigma, Cat. P3761) until pedal reflex loss, and then decapitation by guillotine to minimize stress and tissue integrity. Striatum, substantia nigra and cerebellum were dissected quickly and frozen in dry ice and kept in −80°C.

Histology cohort (n=3/group): Rats were anesthetized with pentobarbital (50 mg/kg i.p)., and transcardially perfused with phosphate-buffered saline (0.1 M, pH 7.4) and 4% paraformaldehyde (Sigma, Cat. #P6148). Brains were post-fixed overnight, cryoprotected in 30% sucrose, and embedded in paraffin for sectioning.

None of the animals recovered during or after anesthesia. Every procedure was in accordance with humane endpoints.

Behavioral Assessments

Three time points of behavioral testing were performed:

1. Baseline (Day 0): before any drug administration in order to determine basal parameters.
2. Post-induction (Day 7): to verify schizophrenia-like deficits, following injections of ketamine or vehicle.
3. Post-treatment (Day 21): This is done after 14 days treatment to assess recovery or improvement.

Tests were conducted in the light phase by blind observers who were not aware of group assignments. Between trials, apparatuses were washed with 70% ethanol to eliminate odor cues.

Y-Maze Test

The apparatus used for the Y-maze was three arms (40 cm in length, positioned at 120deg angles). Rats were placed in the maze and could move around freely for up to 8 minutes. An arm entry was recorded when the 4 paws of the animal all entered an arm. The total number of arm entries was taken as an index of exploratory and locomotor activity.[53] Baseline, post-induction, and post-treatment testing were performed.

Open Field Test (OFT)

It was performed in a 100×100 x 40 cm arena. The rats were put in the center and allowed to roam in the center within 10 min. Primary measures were in terms of total distance traveled/number of lines crossed (locomotor activity) and the time spent in the central zone (anxiety-related behavior). The qualitative recording of secondary behaviors (grooming, rearing) was done. OFT was given at the three time points.

Biochemical Assays

Three rats each group were euthanized 24hours after the final treatment with pentobarbital anesthesia (50mg/kg i.p.) and then decapitated. The striatum, substantia nigra, and cerebellum were quickly dissected, snap-frozen in liquid nitrogen, and stored at stored at −80 °C until analysis.

A glass-Teflon homogenizer was used to homogenize tissues in 10 volumes of ice-cold Tris-HCl buffer (50 mM, pH 7.4, 1.15% KCl and protease inhibitors). Homogenates were centrifuged at 10,000 x g in 15 min at 4 degC and supernatant collected to assays. An analysis of protein concentration was performed using a BCA kit (Thermo Fisher, Cat. #23225) to normalize results. Each sample and standard were run in duplicate.

Neurotransmitter Tests

In each rat, the substantia nigra, basal ganglia and cerebellum from one hemisphere were used for neurotransmitter analysis, whereas the same regions from the other hemisphere were processed for oxidative stress assays and immunohistochemistry (see below). For neurotransmitter measurements, tissue samples (≈50 mg) were homogenized in 0.1 M ice-cold perchloric acid (10% w/v) containing 0.02% ethylene diamine tetraacetic acid (EDTA) for precipitation of proteins and stabilization of monoamines. Homogenates were centrifuged at 12,000 x g for 15 min at 4 degC and their supernatant was collected for analysis.

Quantification of Dopamine by HPLC-Electrochemical Detection

Dopamine was measured in the same extracts by high performance liquid chromatography (HPLC) coupled with electrochemical detection. Separation was performed on a C18 analytical column, eluted at 0.7 mL/min with a mobile phase made up of citrate-acetate buffer (pH 3.5), 10% methanol, 1 mM octanesulfonic acid and 0.1 mM ethylenediaminotetraacetic acid. Dopamine was identified by its retention time (7–8 min) and quantified based on the peak height using an external standard curve.

Oxidative Stress Markers

- Superoxide dismutase (SOD; Elabscience®, Cat. #E-EL-S001) and catalase (CAT; Elabscience®, Cat. #E-EL-S0256) activities were measured by colorimetric ELISA at 450 nm and expressed as U/mg protein.
- Glutathione-S-transferase (GST; MyBioSource®, Cat. #MBS261231) activity was expressed in U/mg protein.
- Malondialdehyde (MDA; Abcam®, Cat. #ab118970), a lipid peroxidation index, was quantified at 532 nm and expressed as nmol/mg protein.

Inflammatory Mediators

- Interleukin-6 (IL-6; Cloud-Clone Corp., Cat. #SEA079Ra) and inducible nitric oxide synthase (iNOS; MyBioSource®, Cat. #MBS721222) levels were measured using sandwich ELISA kits. Concentrations were expressed as pg/mg and ng/mg protein, respectively.

Kit-supplied standards and calibrators provided quality control. Inter- and intra-assay coefficients of variation were less than 12% and all measurements were within linear ranges of detection.

Quantification of Immunohistochemical Staining

For each animal, three non-overlapping sections for each brain region (basal ganglia, substantia nigra, and cerebellum) were analyzed. Sections were chosen by systematic sampling approach where samples are picked at regular intervals to ensure representative coverage of each region.

Digital images were taken under the same microscope settings and analyzed with ImageJ software program (NIH, USA). Images were converted to 8-bit grayscale and a common threshold was used across sections of each staining batch to reduce variability.

For GFAP, quantification was done with the area fraction method in terms of the percentage of immunoreactive area with respect to the total field. For Nrf2, nuclear positivity was calculated using ImmunoRatio plugin. All image analyses were done by an investigator who was blinded to group allocation.

Statistical Analysis

Data were analyzed using SPSS version 25 and GraphPad Prism version 9. Behavioral data collected across multiple time points (baseline, post-induction, and post-treatment) were analyzed using repeated-measures ANOVA to account for within-subject variability, with treatment and time as factors where applicable, followed by Tukey's post hoc test.

Biochemical, neurotransmitter, and immunohistochemical data, obtained from a separate terminal cohort of animals, were analyzed using one-way ANOVA followed by Tukey's post hoc test. Assumptions of normality and homogeneity of variance were assessed using the Shapiro–Wilk and Levene's tests, respectively. For repeated-measures ANOVA, sphericity was evaluated using Mauchly's test, and Greenhouse–Geisser corrections were applied where necessary. All results are presented as mean ± SD, and statistical significance was set at $p < 0.05$.

ARRIVE Compliance Statement

All processes were in full compliance with the ARRIVE 2.0. Ethical approval, housing, randomization, blinding, sample size justification, humane endpoints and euthanasia protocols are clearly reported with the aim of ensuring transparency and reproducibility.[54]

Results

Mangiferin Improves Ketamine-Induced Behavioral Deficits

Y-Maze

In the Y-maze (Figure 1), ketamine significantly reduced the number of arm entries compared to the vehicle group, indicating decreased exploratory activity. Co-treatment with mangiferin dose-dependently attenuated this reduction, with the 50–75 mg/kg doses restoring arm entries toward control levels, comparable to risperidone. This restoration of exploratory behavior parallels the normalization of dopaminergic and redox-glial markers observed in mangiferin-treated groups, suggesting an overall improvement in neural function in this schizophrenia-like model.

Open Field Test (OFT)

The centre-square duration (Figure 2) was similar across all the groups at baseline. Ketamine significantly reduced centre time, indicating increased anxiety-like behaviour, but co-treatment doses significantly counteracted this reduction induced by ketamine. After treatment, the (50–75 mg/kg) doses mangiferins restored centre-square duration closer to control values, similar to risperidone, showing effective reversal of ketamine-evoked anxiety-like behaviour.

Ketamine had a significant effect on horizontal locomotion inhibition (Figure 3), that reflects reduced motor drive and disrupted basal ganglia-cerebellar function. Co-treatment with mangiferin dose-dependently reversed this suppression by ketamine. Following mangiferin treatment, the 50–75 mg/kg doses restored locomotor output towards control values, comparable to risperidone. This locomotor recovery is associated with normalization of dopaminergic tone and redox-glial indices by mangiferin, suggesting restoration of function of subcortical motor circuitry.

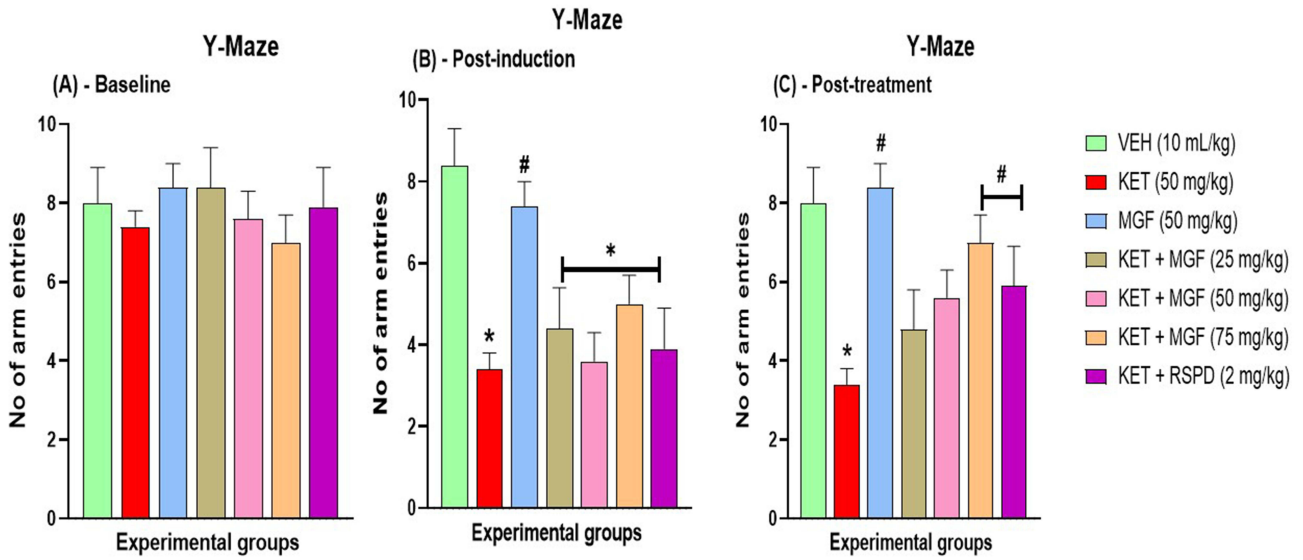


Figure 1 Effects of ketamine and mangiferin on exploratory behavior in the Y-maze. (**A**) Baseline measurements prior to treatment, (**B**) Post-induction (Day 7) following ketamine administration, (**C**) Post-treatment (Day 21) after mangiferin or risperidone intervention. Ketamine significantly reduced the number of arm entries, indicating decreased exploratory activity. Mangiferin treatment dose-dependently restored arm entries, with 50–75 mg/kg showing near-complete normalization comparable to risperidone. Data are presented as mean ± SD (n = 6). *p < 0.05 vs. VEH; #p < 0.05 vs. KET.

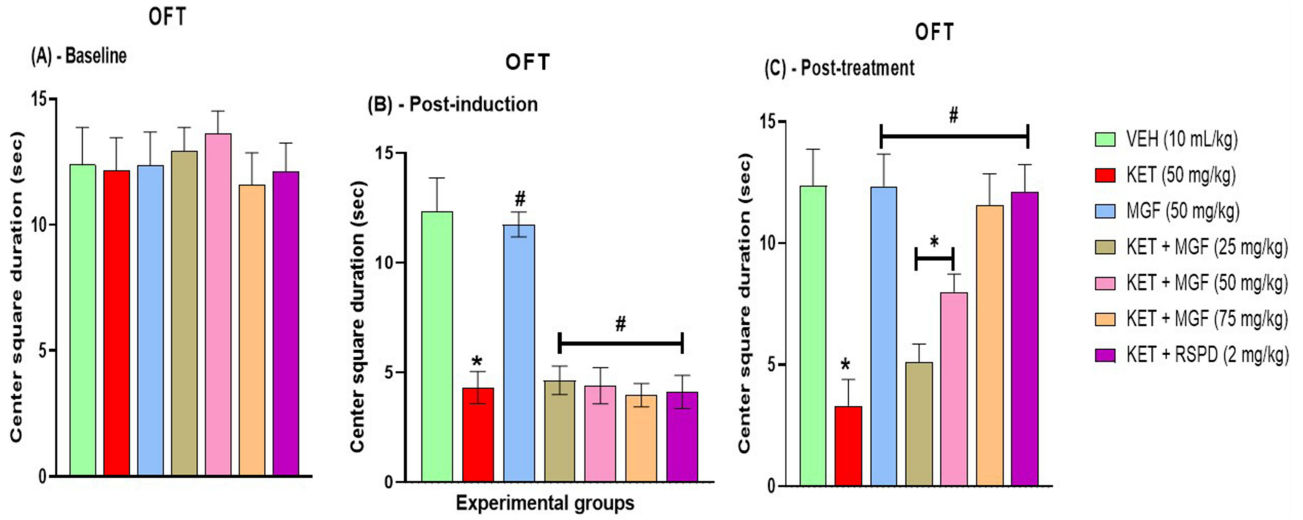


Figure 2 Effects of mangiferin on ketamine-induced anxiety-like behavior in the open field test. (**A**) Baseline center-square duration (s), (**B**) Post-ketamine induction (Day 7), (**C**) Post-treatment (Day 21). Ketamine significantly reduced center duration, indicating increased anxiety-like behavior. Mangiferin reversed this effect in a dose-dependent manner, with higher doses restoring values close to control and comparable to risperidone. Data are presented as mean ± SD (n = 6). *p < 0.05 vs. VEH; #p < 0.05 vs. KET.

Neurotransmitter Analysis

Ketamine caused a significant increase in tissue dopamine in the studied subcortical regions, thereby supporting the ketamine-induced dopaminergic dysregulation (Figure 4). In the rats exposed to ketamine, co-administration with mangiferin decreased the level of dopamine dose-dependently. The 50 and 75 mg/kg doses brought the dopamine levels near the norm. Risperidone also suppressed the increase in dopamine but the extent of normalization was lower than that seen with the larger doses of mangiferin. These findings indicate that mangiferin effectively counteracts ketamine-induced dopaminergic abnormalities, particularly at medium and high doses".

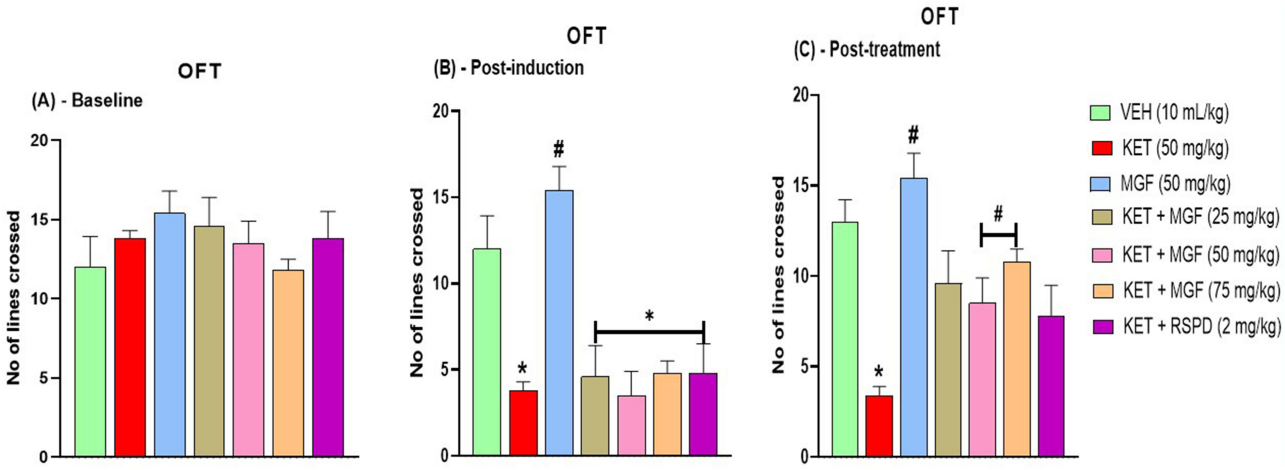


Figure 3 Effects of mangiferin on ketamine-induced locomotor activity in the open field test. (**A**) Baseline locomotor activity (number of lines crossed), (**B**) Post-ketamine induction (Day 7). (**C**) Post-treatment (Day 21), Ketamine reduced locomotor activity, while mangiferin dose-dependently restored movement, with higher doses approaching control levels and comparable to risperidone. Data are presented as mean ± SD (n = 6). *p < 0.05 vs. VEH; #p < 0.05 vs. KET.

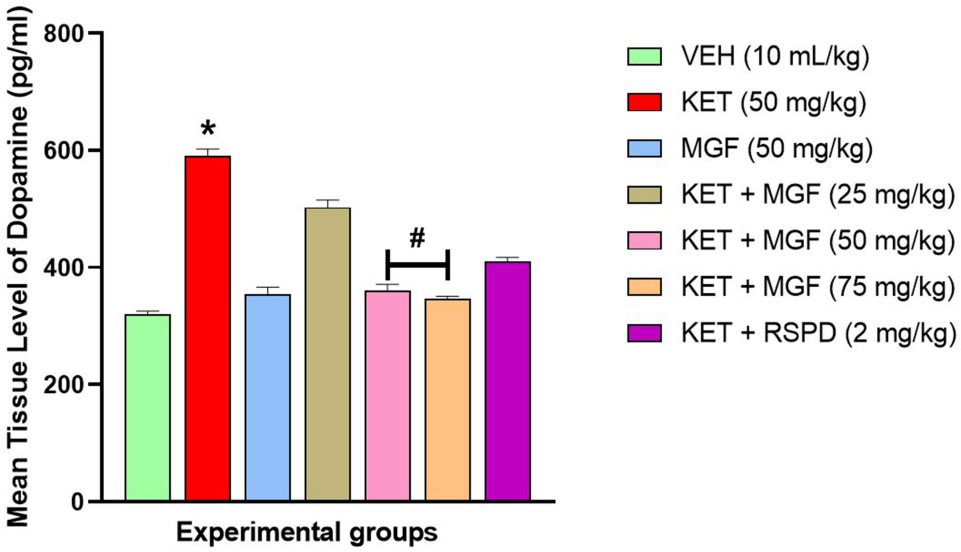


Figure 4 Effects of mangiferin on Dopamine levels in the basal ganglia across experimental groups. Ketamine significantly increased dopamine levels compared to the vehicle group. Mangiferin treatment dose-dependently attenuated this effect, with higher doses restoring levels toward control values, comparable to risperidone. Data are presented as mean ± SD (n = 3 per group). Data are presented as mean ± SD (n = 3). *p < 0.05 vs. VEH; #p < 0.05 vs. KET. Values represent total tissue dopamine levels and not extracellular synaptic release.

Mangiferin Reduces Oxidative Stress and Inflammation

Oxidative Stress

Ketamine exposure caused an imbalance of redox throughout the striatum, substantia nigra, and cerebellum, reducing antioxidant enzyme activities and increasing lipid peroxidation (MDA) (Figure 5A–D). These changes were reversed by mangiferin in a dose-dependent manner: high dose treatment restored the antioxidant levels to nearly normal levels and significantly decreased MDA, whereas medium dose gave partial and low dose only modest protection. Risperidone also enhanced the oxidative markers but in general was less effective than high-dose mangiferin. Notably, mangiferin as such never altered redox conditions in healthy rats.

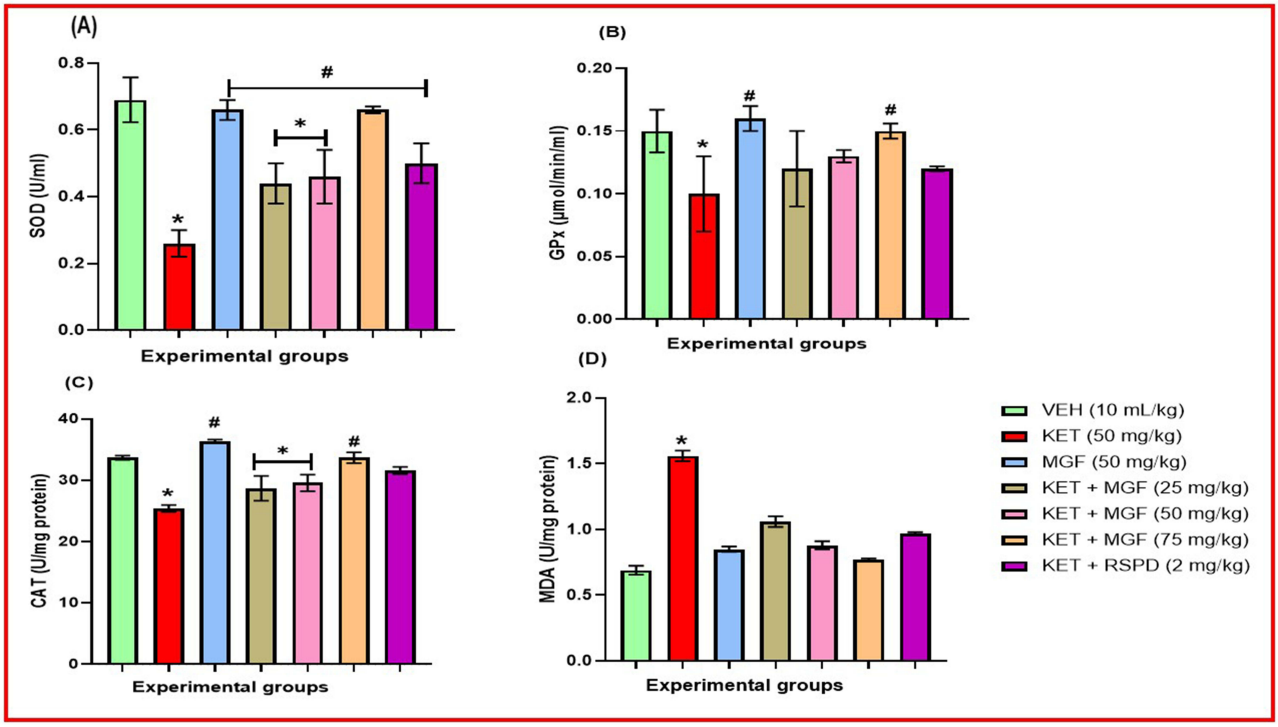


Figure 5 Effects of mangiferin on superoxide dismutase (SOD) activity following ketamine exposure. (**A**) Superoxide dismutase (SOD) activity, (**B**) glutathione peroxidase (GPx) activity, (**C**) catalase (CAT) activity, and (**D**) malondialdehyde (MDA) levels in brain tissue homogenates. Ketamine treatment significantly reduced antioxidant enzyme activities (SOD, GPx, CAT) and increased lipid peroxidation (MDA), indicating oxidative stress. Mangiferin treatment attenuated these alterations in a dose-dependent manner, with higher doses restoring antioxidant defenses and reducing lipid peroxidation toward control levels. Data are presented as mean ± SD (n = 3 per group). *p < 0.05 vs. VEH; #p < 0.05 vs. KET.

Inflammation

(Figure 6A and B) demonstrated that ketamine significantly elevated pro-inflammatory cytokines IL-6 and iNOS across all studied areas, which is also in line with neuroinflammatory activation. Mangiferin decreased both of the markers in a dose-dependent fashion, and the high dose treatment returned the values to near-control levels. Medium dose was moderate in its effect with low dose having minimal effect. Risperidone also reduced IL-6 and iNOS, with similar reduction effects as medium-dose mangiferin, but lacked the potent rejuvenating effect of antioxidant effects on mangiferin.

Collectively, these findings indicate that mangiferin reverses the action of ketamine-induced oxidative and inflammatory stress. Its capacity to simultaneously reverse antioxidant enzyme activity and inhibit inflammatory mediators are what makes it superior compared to risperidone, which had a significant effect on the inflammatory pathways yet was not able to completely restore redox homeostasis.

Immunohistochemical Analysis (Nrf2 and GFAP) and Preservation of Basal Ganglia, Substantia Nigra, and Cerebellum

Basal Ganglia (Figures 7 and 8)

Ketamine significantly increased GFAP immunoreactivity in the basal ganglia suggesting significant astroglial activation in response to oxidative and inflammatory stress. Mangiferin was dose-dependently effective in reducing this astrocyte reactivity and the 50–75 mg/kg doses increased levels of GFAP to baseline, performing as well as risperidone (Figure 7). This attenuation of astrogliosis is consistent with the Nrf2-mediated antioxidant action of mangiferin and its capacity to restore redox-glial signalling in the involved subcortical circuitry. Neuronophagia was prevented in risperidone but reactive astrocytes were left behind. Semi-quantitatively, ketamine caused a decreased number of neurons (~20% compared to control), which recovered to nearly 95–100% with high-dose mangiferin and almost 70–80% with risperidone.

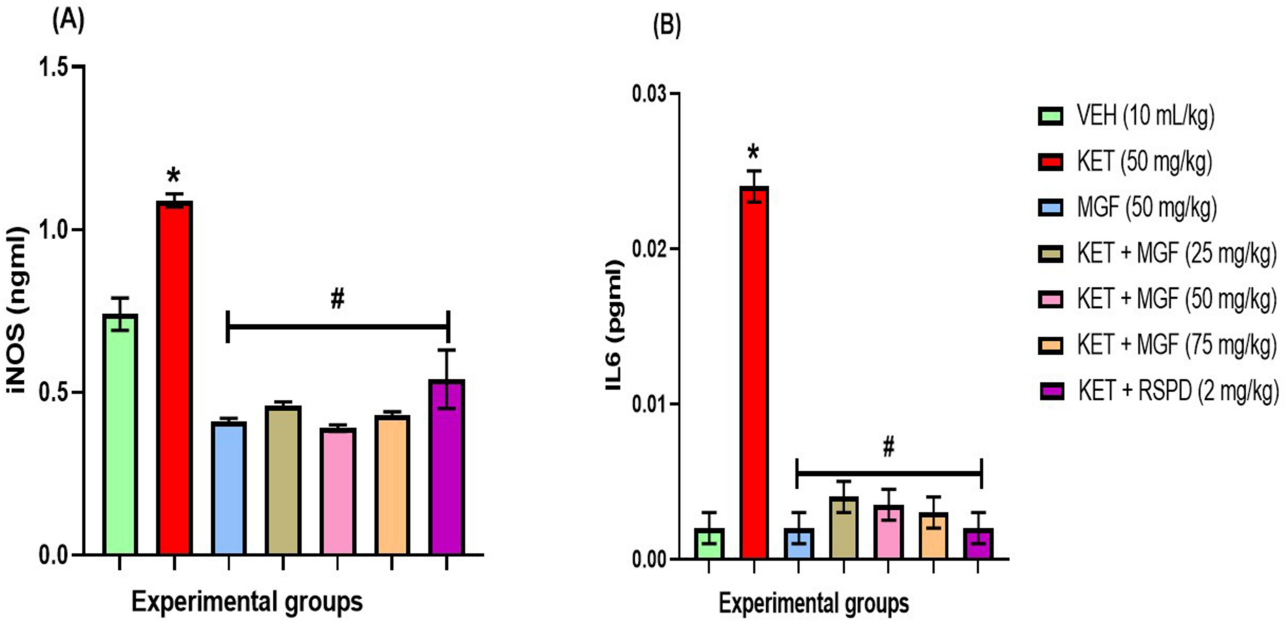


Figure 6 Effects of mangiferin on pro-inflammatory mediators following ketamine exposure. (**A**) Inducible nitric oxide synthase (iNOS) levels and (**B**) interleukin-6 (IL-6) levels in brain tissue homogenates. Ketamine treatment significantly increased iNOS and IL-6 levels, indicating enhanced neuroinflammatory activity. Mangiferin treatment attenuated these increases in a dose-dependent manner, with higher doses reducing pro-inflammatory mediators toward control levels. Data are presented as mean ± SD (n = 3 per group). *p < 0.05 vs. VEH; #p < 0.05 vs. KET.

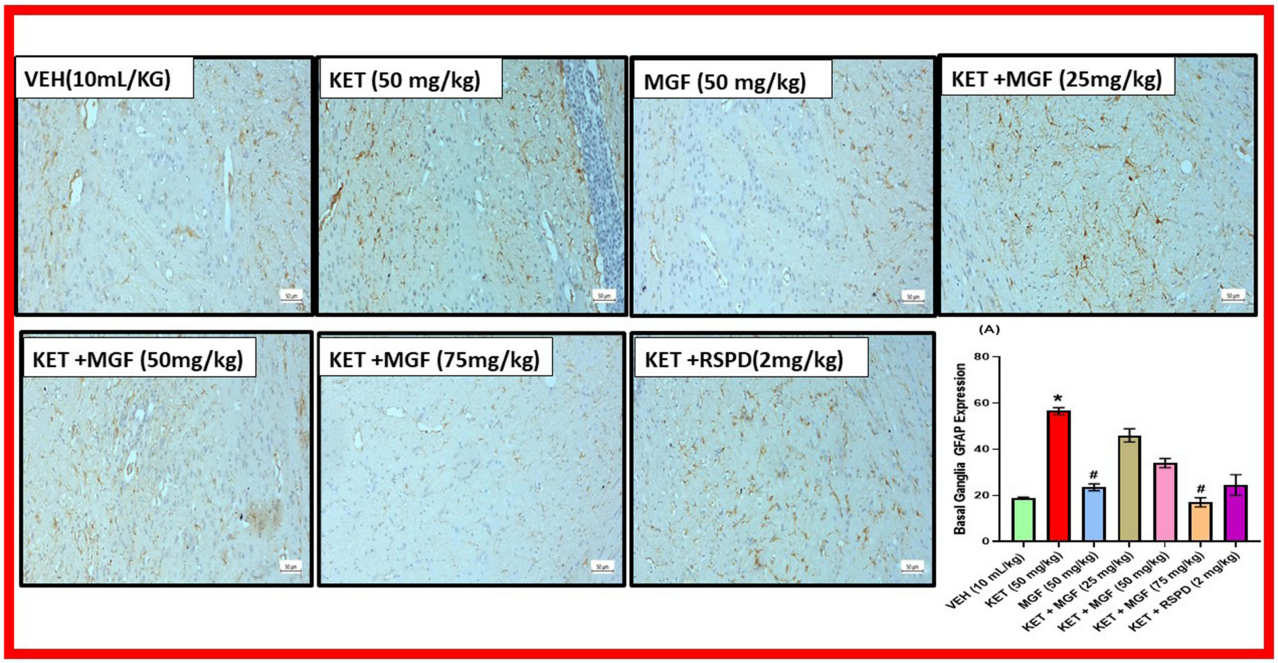


Figure 7 Effects of mangiferin on GFAP immunoreactivity in the basal ganglia. Representative photomicrographs showing astrocyte activation. VEH control: normal astrocytic morphology, KET: marked astrogliosis with hypertrophic astrocytes, KET + MGF (25, 50, 75 mg/kg): progressive attenuation of astrocyte activation, KET + RIS: moderate reduction in astrogliosis. Quantitative analysis confirms significant reduction in GFAP expression with mangiferin treatment. Scale bar = 50 μm. Data are presented as mean ± SD (n = 3). *p < 0.05 vs. VEH; #p < 0.05 vs. KET.

Ketamine caused a significant decrease in the immunoreactivity of Nrf2 in the basal ganglia (Figure 8). Mangiferin showed dose-dependently restored immunoreactivity of Nrf2, with the doses of 50–75 mg/kg showing substantial reactivation of the pathway and approaching the effect of risperidone. This recovery of Nrf2 is consistent with the

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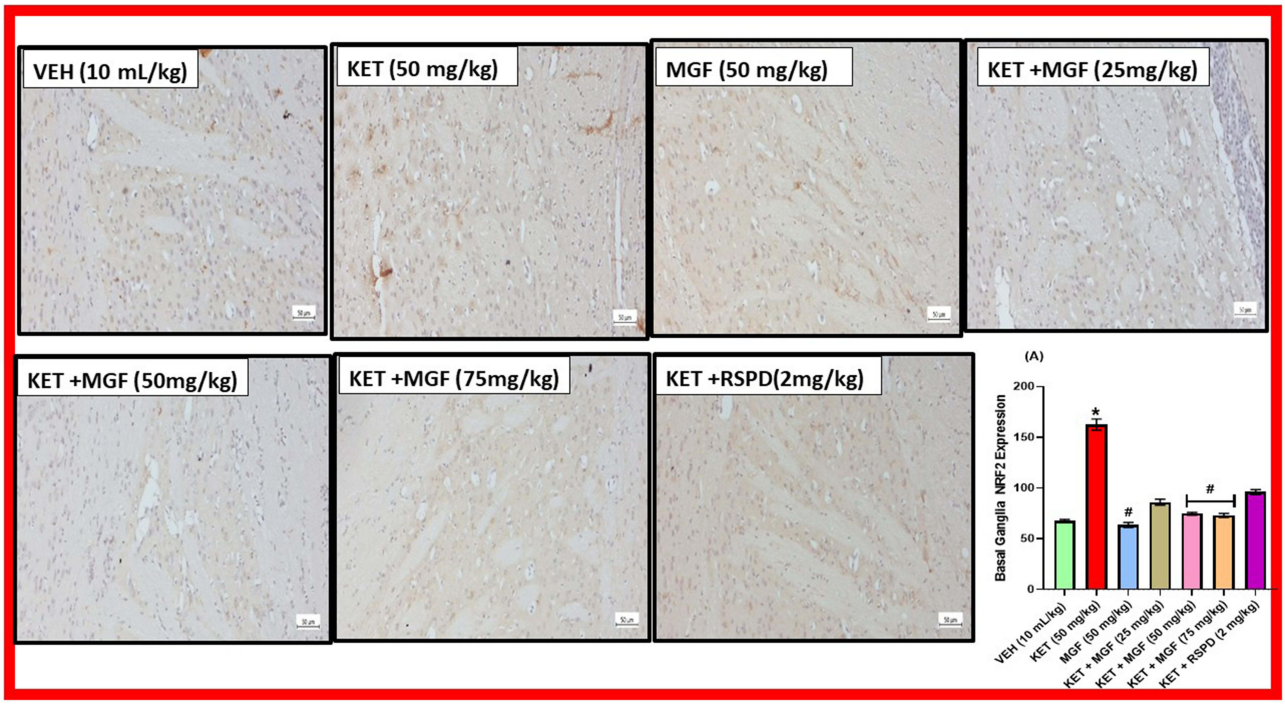

Figure 8 Effects of mangiferin on Nrf2 immunoreactivity in the basal ganglia. VEH: normal Nrf2 expression, KET: reduced Nrf2 expression, KET + MGF (25, 50, 75 mg/kg): dose-dependent restoration of Nrf2 expression, KET + RIS: moderate recovery. Mangiferin significantly enhanced Nrf2 activation, indicating restoration of antioxidant defense mechanisms. Scale bar = 50 μm. Data are presented as mean ± SD (n = 3). *p < 0.05 vs. VEH; #p < 0.05 vs. KET.

normalisation of redox balance and attenuation of glial activation by mangiferin, suggesting effective reinforcement of the antioxidant defence system in the brain by ketamine-challenged circuits.

Substantia Nigra (SN) (Figures 9 and 10)

Ketamine induced a significant increase in GFAP expression in the substantia nigra suggesting strong astroglial activation in response to oxidative and inflammatory stress. Mangiferin suppressed this glial reactivity in a dose-dependent way, with the 50–75 mg/kg doses having a significant inhibitory effect on GFAP upregulation and close to the effect of risperidone (Figure 9). This attenuation of astrogliosis represents the restoration of redox-glial homeostasis by mangiferin and contributes towards enhanced cellular resilience in ketamine-affected nigral circuitry.

Figure 10 illustrates the significant decrease in Nrf2 expression in the substantia nigra of the Ketamine-only group, suggesting inhibition of endogenous antioxidant signalling and increased susceptibility to oxidative injury. Mangiferin co-treatment restored Nrf2 immunoreactivity in a dose-responsive way, with doses of 50–75 mg/kg showing significant reactivation of the pathway and nearly the same as the effect of risperidone. This recovery of Nrf2 expression is consistent with the ability of mangiferin to rebalance redox-glia homeostasis in ketamine compromised nigral tissue. The ImageJ estimates add an internally consistent support to the visual immunohistochemistry results, and also reinforce the dose-dependent restorative effect of mangiferin on Nrf2 expression.

Cerebellum (Figures 11 and 12)

Ketamine induced a significant increase in cerebellar GFAP expression, indicating strong astroglial activation within cerebellar cortical layers. Mangiferin administration moderated this response in a clear dose-dependent manner with the 50–75 mg/kg doses significantly reducing the ketamine-induced astrocytosis (Figure 11). Risperidone brought about a moderate reduction, but not to the level seen with high-dose mangiferin. These results suggest that mangiferin is really efficient in stabilizing the reactivity of cerebellar glial cells under ketamine-induced oxidative-inflammatory stress.

Further highlights on how Ketamine significantly suppressed cerebellar Nrf2 expression are shown in Figure 12, indicating a breakdown of endogenous antioxidant signalling within cerebellar circuits. Mangiferin produced a clear

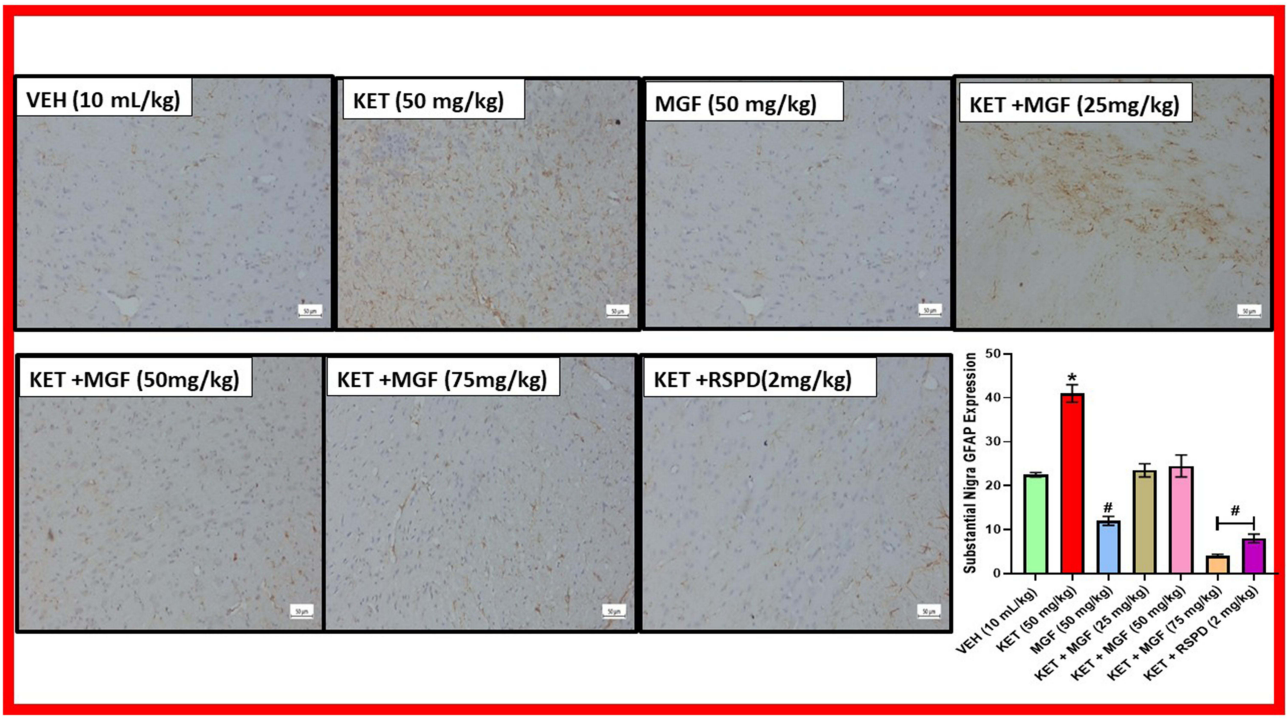

Figure 9 Effects of mangiferin on GFAP immunoreactivity in the substantia nigra. VEH: normal astrocytic architecture, KET: pronounced astrogliosis, KET + MGF (25, 50, 75 mg/kg): dose-dependent reduction in astrocyte activation, KET + RIS: partial improvement. Mangiferin restored redox-glial homeostasis in nigral circuitry. Scale bar = 50 μm. Data are presented as mean ± SD (n = 3). *p < 0.05 vs. VEH; #p < 0.05 vs. KET.

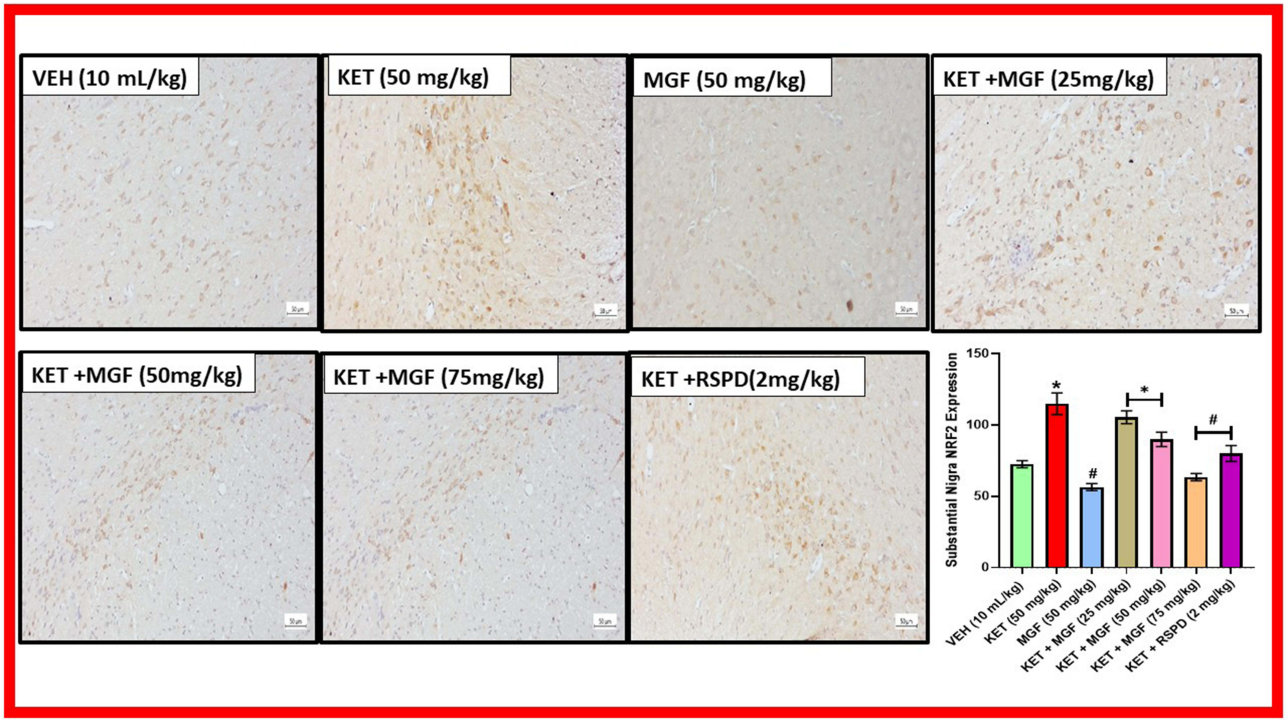

Figure 10 Effects of mangiferin on Nrf2 immunoreactivity in the substantia nigra. VEH: normal Nrf2 expression, KET: marked suppression of Nrf2, KET + MGF (25, 50, 75 mg/kg): dose-dependent restoration of Nrf2 expression, KET + RIS: moderate recovery. Quantitative ImageJ analysis supports the observed dose-dependent restoration. Scale bar = 50 μm. Data are presented as mean ± SD (n = 3). *p < 0.05 vs. VEH; #p < 0.05 vs. KET.

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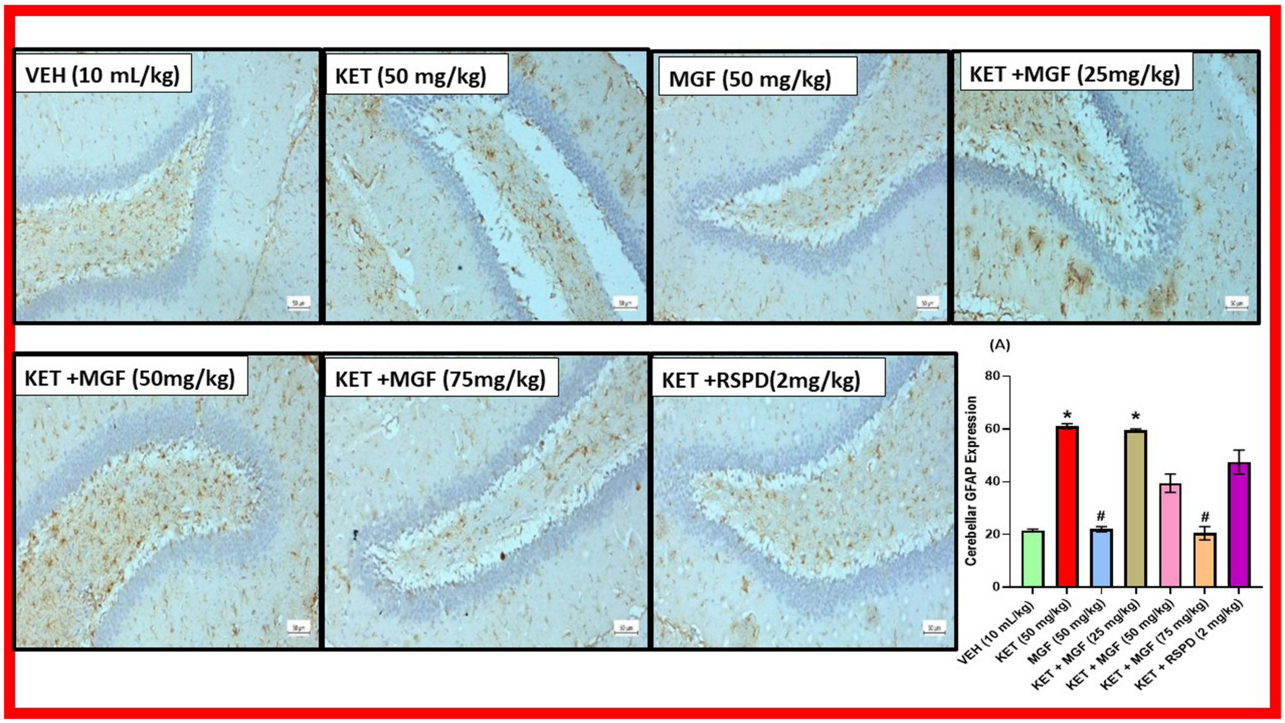

Figure 11 Effects of mangiferin on GFAP immunoreactivity in the cerebellum. VEH: normal glial morphology, KET: increased astrocyte reactivity, KET + MGF (25, 50, 75 mg/kg): progressive reduction in GFAP expression, KET + RIS: moderate reduction. Mangiferin effectively stabilized cerebellar glial responses under ketamine-induced stress. Scale bar = 50 μm. Data are presented as mean ± SD (n = 3). *p < 0.05 vs. VEH; #p < 0.05 vs. KET.

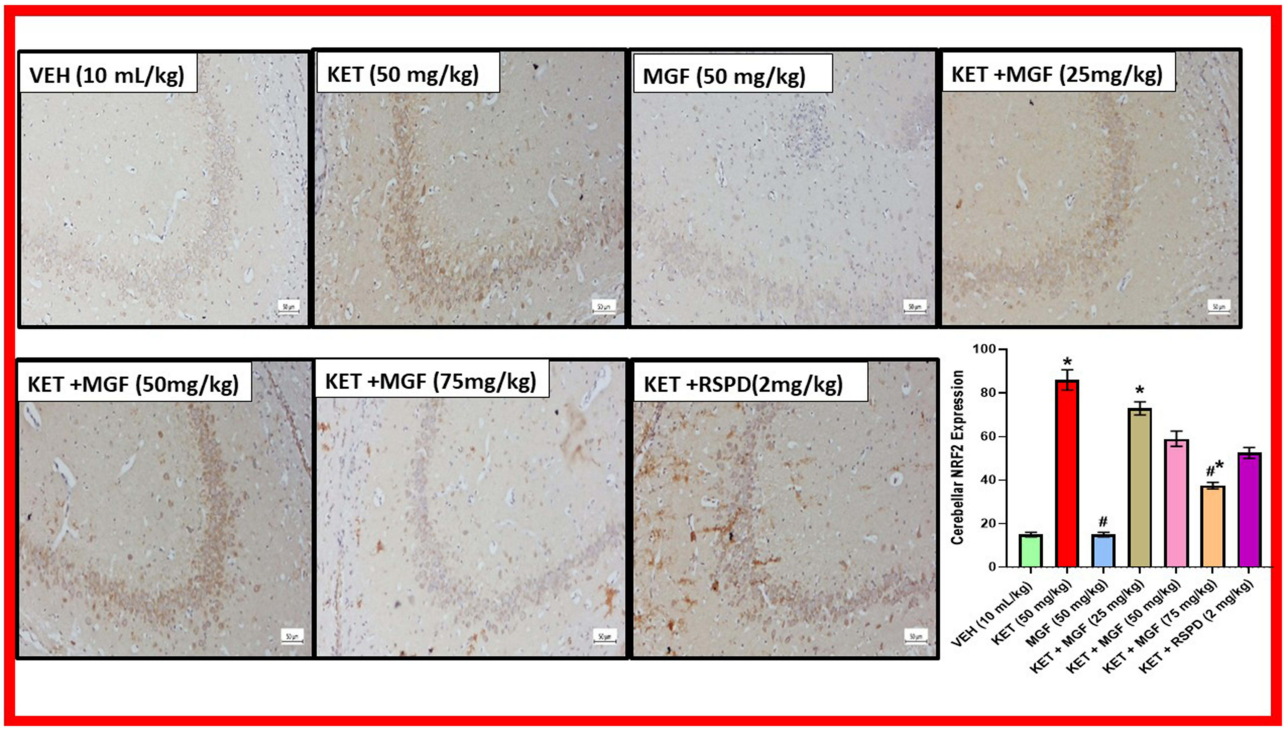

Figure 12 Effects of mangiferin on Nrf2 immunoreactivity in the cerebellum. VEH: normal Nrf2 expression, KET: significant suppression of Nrf2, KET + MGF (25, 50, 75 mg/kg): robust dose-dependent restoration of Nrf2 expression. KET + RIS: moderate improvement. Mangiferin re-established antioxidant signaling within cerebellar circuits. Scale bar = 50 μm. Data are presented as mean ± SD (n = 3). *p < 0.05 vs. VEH; #p < 0.05 vs. KET.

restorative effect, with the 50–75 mg/kg doses reactivating Nrf2 expression robustly and more effectively than the lower dose or risperidone. This recovery of Nrf2 aligns with mangiferin's broader redox-corrective actions, highlighting its capacity to re-establish antioxidant defence mechanisms in ketamine-challenged cerebellar tissue.

Integrative Summary

Through behavioral, biochemical, and immunohistochemical assessments, ketamine induced schizophrenia-like alterations characterized by oxidative and inflammatory stress, neuronal dysfunction in the striatum and substantia nigra, and glial activation within the cerebellum. Mangiferin had a dose-dependent effect: medium/high doses normalized cognition, decreased hyperactivity/anxiety, restored antioxidant capacity (↓MDA; ↑SOD/CAT/GST), suppressed IL-6/iNOS, preserved cytoarchitecture, reduced astrogliosis (GFAP), and activated Nrf2. High-dose mangiferin produced effects on redox balance and GFAP/Nrf2 expression that were comparable to those observed with risperidone. While risperidone appeared to confer greater protection in the cerebellum, residual gliosis in the striatum and substantia nigra and less consistent antioxidant enzyme recovery were noted across groups. These observations should be interpreted cautiously given the small sample size. Normal behavior was not impaired in non-ketamine rats by mangiferin.

Discussion

This study demonstrates that the naturally occurring polyphenol mangiferin substantially mitigates dopaminergic and glial dysregulation in a ketamine-induced rodent model of schizophrenia. We specifically targeted the basal ganglia–substantia nigra–cerebellar (BG–SN–Cb) loop, a subcortical network critically involved in motor control, cognition, and reward processing, domains frequently disrupted in schizophrenia.[46,47] Our findings can be summarized in three main points: (1) subchronic ketamine exposure induced pronounced oxidative stress, neuroinflammation, and neuron–glia pathology across the basal ganglia, midbrain, and cerebellum, recapitulating several pathological aspects reported in schizophrenia.[55,56] (2) Mangiferin treatment reversed these alterations in a dose-dependent manner, with parallel improvements in behavior, including reduced hyperactivity and anxiety-like responses. (3) These effects were associated with restoration of Nrf2-linked antioxidant defenses and attenuation of astroglial reactivity, implicating coordinated modulation of redox and glial pathways.

Basal Ganglia–Cerebellar Involvement in Schizophrenia and Ketamine Models

Our work adds to the growing recognition that schizophrenia reflects dysfunction of distributed brain circuits rather than a purely cortical or dopaminergic disorder, and that subcortical motor regions are integral to this network.[48] The dopamine hypothesis has long implicated the basal ganglia—particularly the striatum—because excessive dopamine signaling within striatal circuitry correlates with psychotic symptom severity.[57] Neuropathological changes in the basal ganglia in schizophrenia, however, are often subtle, primarily affecting molecular pathways such as oxidative balance, mitochondrial function, and synaptic density, rather than robust neuronal loss.[58] In contrast, our ketamine model produced overt neuronal loss and neuronophagia in the striatum, which likely exaggerates the degree of cell death observed in patients but underscores the susceptibility of basal ganglia neurons to excitotoxic and oxidative insults.[59,60] This is consistent with the notion that NMDA receptor hypofunction, as induced by ketamine, disinhibits glutamatergic neurons, leading to excessive glutamate release and potential excitotoxic damage to postsynaptic neurons in the striatum and other regions.

The presence of microglial activation and neuronophagic nodules in ketamine-only striatum aligns with reports of microglial overactivity and elevated microglia-derived proteins in schizophrenia brain and CSF, although human data remain heterogeneous, with inflammatory signatures present only in specific patient subgroups.[61] Our model therefore supports an immune–dopamine crosstalk framework in schizophrenia, in which microglial and astroglial responses in the striatum are modulated by cytokines such as IL-6, which can in turn influence dopamine signaling and create a vicious cycle of oxidative stress and neurotransmitter dysregulation.

The cerebellum has historically been under-appreciated in schizophrenia, yet converging evidence points to cerebellar involvement, including reduced volume, altered functional connectivity, and cognitive deficits attributable to impaired cerebellar coordination of mental processes.[8] In this context, our observation of ketamine-induced Purkinje cell loss is notable Purkinje neurons constitute the sole output of the cerebellar cortex and modulate deep cerebellar nuclei that

project to thalamic and basal ganglia targets.[62,63] Loss or dysfunction of Purkinje cells may therefore disinhibit downstream cerebellar projections and impact both cortical and basal ganglia circuits; similar Purkinje pathology has been reported in some models of autism and ataxia, conditions that share partial phenotypic overlap with schizophrenia.[63] Although overt Purkinje cell loss is not consistently demonstrated in patients, cerebellar hypoactivation on functional imaging during cognitive tasks may reflect related circuit-level disruption.

An emerging concept is the cerebello–basal ganglia network. Recent work, including a Schizophrenia Bulletin report,[10] indicates that cerebellar projections can modulate striatal dopamine release via thalamic relays and that this connectivity is impaired in schizophrenia, contributing to motivational and psychomotor disturbances.[10] Our findings provide experimental support for this model by demonstrating concurrent structural and glial pathology in cerebellar and striatal regions, consistent with a compromised cerebello–striatal circuit. The parallel treatment-related improvements we observed in both regions suggest that restoring function along this subcortical axis may contribute to behavioral normalization: improved striatal integrity may support normalized locomotor and novelty-seeking behavior, while preservation of cerebellar Purkinje neurons may facilitate procedural learning and motor coordination.

Neuroprotective Effects of Mangiferin: Nrf2 and Glial Modulation

A central outcome of this study is the convergent evidence that mangiferin exerts neuroprotective effects in the BG–SN–Cb axis through coordinated antioxidant and glial mechanisms. Mangiferin has previously been characterized as multimodal—antioxidant, anti-inflammatory, and potentially neurotrophic—in various experimental systems.[28,31,64,65] Although increased Nrf2 immunoreactivity was observed following mangiferin treatment, downstream antioxidant targets such as heme oxygenase-1 (HO-1) and NAD(P)H quinone oxidoreductase 1 (NQO1) were not assessed. Therefore, the involvement of the Nrf2 pathway should be interpreted as associative rather than definitive. Nrf2 is widely regarded as a master regulator of cellular antioxidant defense.[66] Under oxidative stress, Nrf2 dissociates from its inhibitor Keap1 and translocates to the nucleus, where it enhances transcription of genes encoding SOD, CAT, glutathione-synthesizing enzymes, HO-1, and related cytoprotective proteins. In chronic disorders such as schizophrenia, however, Nrf2 activity may be insufficient or dysregulated, possibly due to genetic factors or prolonged exposure to oxidative and inflammatory stressors; some studies have reported reduced nuclear Nrf2 in patient-derived cells, although the literature remains limited.[67]

The reduction in Nrf2 immunoreactivity observed in the ketamine group is consistent with impaired antioxidant signaling in the context of NMDA receptor hypofunction and oxidative stress. Mangiferin treatment increased Nrf2 immunoreactivity, in some instances approaching or exceeding control levels, suggesting a potential restoration of antioxidant capacity. This observation is consistent with past in vitro studies having reported Nrf2 modulating effects of mangiferin. For example, Zhou et al[61] reported that mangiferin upregulated Nrf2 and HO-1 in cellular models of Parkinson's disease, with concomitant reductions in ROS and improved cell survival, and similar Nrf2-dependent protective effects have been documented in diabetic wound models.[52] In our study, Nrf2 reinstatement by mangiferin was accompanied by restoration of antioxidant enzymes (SOD, CAT, GPx) and marked reductions in MDA, indicating attenuated lipid peroxidation and membrane damage.[68] These findings support a model in which mangiferin re-engages Nrf2-dependent antioxidant networks to counteract ketamine-induced oxidative stress.

Nrf2 is also increasingly recognized as an anti-inflammatory modulator via cross-talk with NF-κB and microglial signaling pathways. Nrf2 activation can attenuate NF-κB–driven transcription and promote a less reactive microglial phenotype.[54] The observed increase in Nrf2 immunoreactivity in mangiferin-treated groups, together with reduced IL-6 and iNOS levels, is consistent with an integrated antioxidant–anti-inflammatory effect, potentially contributing to the attenuation of interactions between oxidative stress, cytokine production, and glial activation.

The astrocytic effects of mangiferin are particularly relevant.[28] Astrocyte abnormalities in schizophrenia have been demonstrated in postmortem studies, although directionality (increased vs. decreased markers) appears to vary with brain region and illness stage.[69] Reactive astrogliosis can be beneficial in the acute phase by containing injury and providing antioxidant support but may become maladaptive if chronic, contributing to impaired glutamate clearance and persistent inflammatory signaling.[69] In our model, ketamine elicited a prominent astrocytic response in the striatum and SN, likely secondary to neuronal stress and degeneration. Mangiferin substantially reduced GFAP immunoreactivity in these regions, indicating attenuation of excessive astrogliosis.

Several non-mutually exclusive mechanisms may underlie this effect. First, by limiting neuronal injury, mangiferin would decrease ATP/glutamate release from dying cells, thereby reducing astrocyte recruitment and activation signals.[70] Second, mangiferin or related polyphenols may act directly on astrocytes to modulate NF-κB and iNOS expression; indeed, mangiferin has been shown in vitro to suppress astrocytic NF-κB and iNOS, consistent with our observed reduction in iNOS in vivo.[29] Third, increased Nrf2 immunoreactivity—although not cell-type specifically resolved in the present study—may be associated with a shift toward a more antioxidant, neuroprotective cellular environment rather than a pro-inflammatory. Collectively, these actions suggest that mangiferin fosters a microenvironment more conducive to neuronal recovery and network stabilization.

This glial profile may distinguish mangiferin from conventional antipsychotics. Risperidone improved behavior and modulated some inflammatory indices, but GFAP remained elevated, suggesting limited direct impact on chronic astrogliosis. This aligns with clinical observations that antipsychotic drugs predominantly alleviate symptoms without consistently normalizing underlying oxidative stress or gliosis.[71] In contrast, mangiferin's capacity to dampen astrocytic reactivity while restoring antioxidant defenses supports its potential as a complementary, pathophysiology-targeted intervention.

Dopamine Regulation

Dopamine measurements in our study represent total tissue content in homogenates and do not directly reflect extracellular or synaptic dopamine release. The robust dopamine elevation induced by ketamine in our study is consistent with established models in which NMDA antagonist administration perturbs mesocortical and subcortical dopaminergic circuits. Mangiferin acted as a regulator of monoaminergic neurotransmission by normalizing dopamine levels in a dose-dependent manner. This effect is likely indirect and mediated through antioxidant, anti-inflammatory, and mitochondrial-stabilizing mechanisms, rather than direct dopamine receptor antagonism. The graded dose–response pattern argues against a nonspecific reversal and supports a genuine pharmacological modulation.

Notably, higher doses of mangiferin normalized dopamine levels to a greater extent than risperidone in this model. This suggests that mangiferin acts upstream of dopamine receptors by targeting oxidative and inflammatory drivers of dopaminergic dysregulation, whereas risperidone primarily acts postsynaptically. The observed behavioral improvements, particularly in cognition and locomotor control, are therefore plausibly linked to mangiferin's ability to re-stabilize dopaminergic signaling within the broader context of restored redox and glial homeostasis.

Although the treatment with mangiferin was correlated with simultaneous improvements in oxidative stress markers, neuroinflammation, and dopaminergic markers, the direction of causation between these processes is not possible to demonstrate in the present study. It is plausible that attenuation of oxidative stress may contribute to stabilization of dopaminergic signaling, however this relationship remains inferential. Future studies using temporal analyses or pathway-specific modulation studies are needed to test if the redox changes are acting upstream of dopaminergic normalization. Taken together, these findings indicate that ketamine-driven oxidative stress and IL-6/iNOS-mediated neuroinflammation alter dopaminergic homeostasis within basal ganglia–cerebellar circuits, leading to the observed locomotor and working-memory deficits.[5,11,72] Mangiferin's ability to enhance Nrf2-dependent antioxidant defenses, attenuate glial activation, and normalize dopamine suggests a potential role for modulation of the redox–glia–dopamine axis in its antipsychotic-like effects in this model.

Behavioral Implications and Therapeutic Prospects

The neurobiological restorations observed in the BG–SN–Cb axis were accompanied by significant improvements in behavior. Mangiferin improved performance in the Y-maze test at higher doses which was reflected in an increased number of arm entries suggesting the recovery of exploratory and locomotor activity following ketamine-induced behavioral suppression.[72] In parallel, mangiferin ameliorated ketamine-induced hyperlocomotion and improved exploratory patterns in the open field, without evidence of sedation.[28] Rather than simply suppressing activity, mangiferin appeared to desensitize pathological hyperlocomotion by addressing upstream mechanisms such as NMDA hypofunction and striatal dopamine dysregulation.

Risperidone likewise reduced hyperactivity but did so in a manner consistent with partial sedation, as suggested by reduced activity even relative to controls. In contrast, rats treated with mangiferin—particularly at medium doses—exhibited locomotor behavior resembling normal exploration: absence of frantic agitation, increased center exploration

(suggestive of anxiolytic-like effects), and preserved capacity for coordinated movement. This distinction is conceptually important. An intervention that restores network-level balance via antioxidant and glutamatergic regulation may reduce aberrant motor activity without incurring the motor side effects associated with prolonged dopamine blockade, such as parkinsonism or tardive dyskinesia, which themselves may involve oxidative damage in basal ganglia circuits.[73]

Our findings also raise the possibility that combining mangiferin with low-dose antipsychotics could be beneficial. In principle, such an approach might allow lower antipsychotic doses (reducing receptor-mediated side effects) while mangiferin addresses redox and glial abnormalities. Mangiferin crosses the blood–brain barrier,[74,75] and has demonstrated CNS effects and cognitive benefits in other rodent models[28,74,75] and appears well tolerated in animals even at relatively high doses, with no overt toxicity reported up to 200 mg/kg in mice. The widespread human consumption of mango-derived products further suggests a favorable safety profile. Nonetheless, rigorous pharmacokinetic, pharmacodynamic, and long-term safety studies in humans will be essential before clinical translation can be considered.

More broadly, our data support the view that oxidative stress and neuroinflammation are central to schizophrenia pathophysiology and are attractive therapeutic targets. Multiple lines of evidence indicate that individuals with schizophrenia, and even high-risk populations, exhibit elevated inflammatory markers such as IL-6 and reduced antioxidant defenses such as glutathione early in the illness.[11] These imbalances may contribute to synaptic dysfunction and aberrant pruning. Interventions that enhance antioxidant capacity via Nrf2 or dampen inflammatory mediators could therefore complement neurotransmitter-based treatments and potentially modify disease trajectory. This conceptual framework aligns with emerging interest in natural compounds such as sulforaphane, curcumin, and resveratrol,[20,21,76–78] which share Nrf2-activating and anti-inflammatory properties. Mangiferin, with its multi-target effects and promising activity in our model, may represent another candidate within this class.

Conceptually, our data highlight a redox–glia–dopamine network as a tractable target in schizophrenia: subchronic NMDA receptor hypofunction shifts this network toward oxidative/inflammatory and hyperdopaminergic states, whereas mangiferin re-balances it toward antioxidant, neuroprotective, and behaviorally adaptive configurations.[11,14,47,72] This systems-level perspective may help rationalize the use of Nrf2-activating natural products such as mangiferin as adjuncts to dopamine receptor–based antipsychotic therapy.

Limitations and Future Directions

Some limitations should be acknowledged. Firstly, the subchronic ketamine paradigm captures aspects of hyperdopaminergia and cognitive impairment but does not fully model developmental, chronic, or negative-symptom dimensions of schizophrenia. Extending this work to chronic phencyclidine paradigms and genetic models, such as DISC1 or NMDA receptor knockdown, would enhance translational relevance.

Secondly, the present study deliberately focused on the BG–SN–Cb axis rather than cortical or hippocampal regions. Cortical and hippocampal abnormalities are well documented in schizophrenia and have been examined in different aspect of our report, including work showing beneficial effects on hippocampal-dependent functions,[28] whereas subcortical motor circuits and their contribution to schizophrenia-related motor and psychomotor disturbances have received comparatively less attention. By concentrating on this subcortical loop, our data complement the existing cortex- and hippocampus-centered literature and highlight motor circuitry as an additional, underemphasized dimension of the disorder. It is likely that mangiferin's neuroprotective actions extend across these interconnected cortical–subcortical networks, but a more comprehensive systems-level analysis will be needed to confirm this. Future work should prioritize brain-targeted pharmacokinetics, optimal dosing strategies, and formulation approaches (eg., phospholipid complexes or polyphenol combinations) to enhance bioavailability and CNS exposure.

Conclusion

In summary, this study shows that mangiferin improves subcortical brain integrity in a schizophrenia-like ketamine model by reducing astrocyte activation and enhancing Nrf2-mediated antioxidant defenses. Preservation of the basal ganglia, substantia nigra, and cerebellum was associated with more normalized motor and exploratory behaviors. These findings highlight the BG–SN–Cb axis as a potential therapeutic node where dopamine dysregulation, oxidative stress, and inflammation converge, and illustrate how targeting redox and glial pathways can complement traditional neurotransmitter-based approaches. Our

results provide a preclinical rationale for further development of Nrf2-activating agents such as mangiferin as adjunctive strategies in schizophrenia and potentially other neuropsychiatric disorders. Future studies incorporating downstream signaling markers are required to confirm pathway-specific mechanisms.

Statement of Human and Animal Rights

All procedures performed in this study involving animals comply with the ethical standards of the institution and adhere to the principles outlined in the 1964 Helsinki Declaration and its later amendments.

Ethical Approval

All experimental procedures involving animals were conducted in accordance with the guidelines and approval of the Ethical Committee of the Faculty of Basic Medical Sciences, College of Medicine University of Nigeria Enugu with ethical approval number COMHREC/2025/01/012.

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Disclosure

The authors declare that there is no conflict of interest regarding the publication of this paper.

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