

Syringic Acid Prevents and Reverses Ketamine-induced Schizophrenia-like Memory Impairment

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ABSTRACT

Background and Purpose: Alterations in the cholinergic-inflammatory pathway are believed to play a role in the cognitive symptoms of schizophrenia, a common neuropsychiatric condition characterised by altered perceptions of reality and impairments in learning and memory. In this study, we examined the preventive and reversal effects of syringic acid (SA), a naturally occurring phenolic metabolite with neuroprotective and anti-inflammatory properties, on ketamine-induced schizophrenia-like memory impairment, cholinergic deficits, and neuroinflammation.

Methods: In the preventive protocol, mice received SA (50 or 100 mg/kg, p.o.) or risperidone (0.5 mg/kg) for 14 days before ketamine (20 mg/kg, i.p., days 8-14), with 30 min between treatments. In the reversal protocol, mice received ketamine (20 mg/kg, i.p.) daily for 14 days, then SA (50 or 100 mg/kg, p.o.) or risperidone (0.5 mg/kg) from days 8-14. Thereafter, we conducted behavioural tests, including the Y-maze test (YMT) and novel-object recognition test (NORT). The following day, mice were euthanised, and relevant brain regions such as the prefrontal cortex (PFC), striatum, and hippocampus involved in the disease were isolated for biochemical analyses, including acetylcholinesterase activity and nitrite levels, as well as immune markers such as interleukin-1 β (IL-1 β), IL-10, and myeloperoxidase (MPO).

Results: SA prevented and reversed ketamine-induced memory impairments. SA attenuated nitroergic and cholinergic deficits, as shown by reduced brain nitrite and acetylcholinesterase levels in the PFC, striatum, and hippocampus. It also decreased MPO activity and IL-1 β , while increasing IL-10 in the PFC, striatum, and hippocampus.

Conclusion: Together, SA attenuates ketamine-induced schizophrenia-like memory impairment through its combined antioxidant and modulation of cholinergic-anti-inflammatory pathways in the brains of mice.

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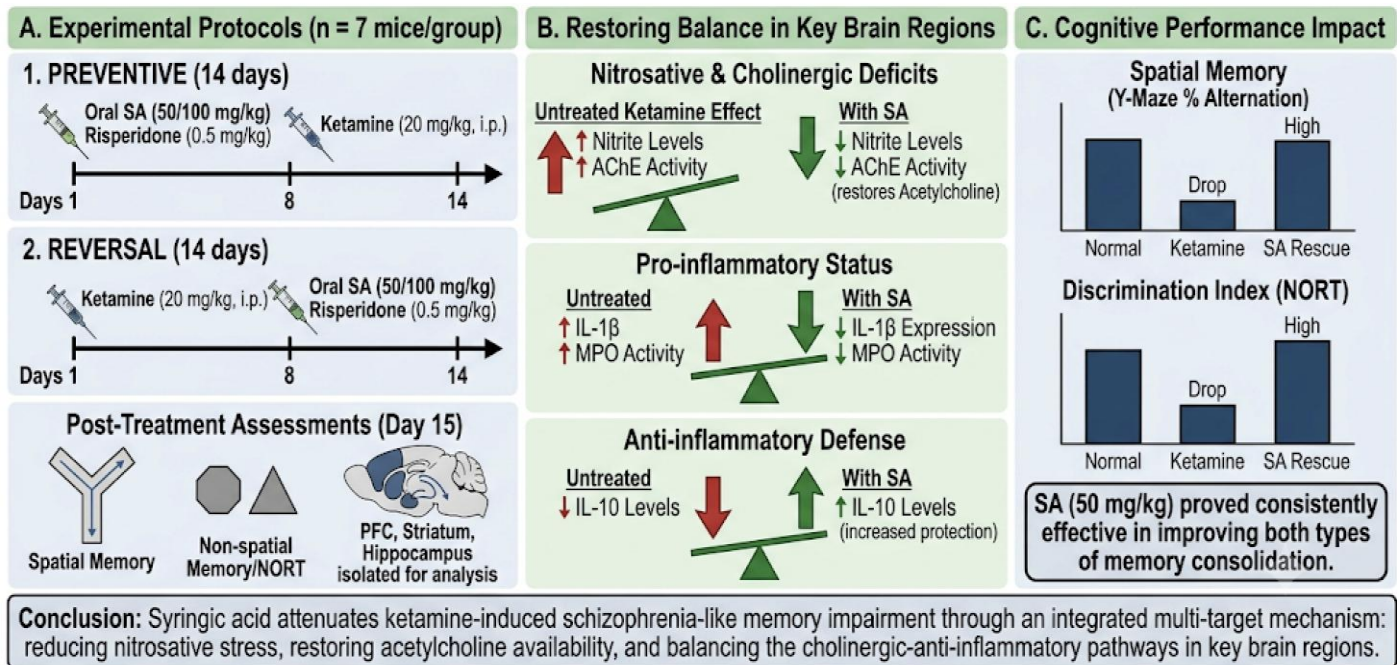


Figure 1: Graphical summary.

INTRODUCTION

Schizophrenia is a chronic, multisystemic psychiatric condition affecting more than 25 million people globally and is regarded as one of the most debilitating mental illnesses due to its profound impact on cognition, behaviour, and social functioning (Solmi *et al.*, 2023; Velligan and Rao, 2023). Clinically, schizophrenia is defined by three major clusters of positive, negative, and cognitive symptoms. While positive symptoms such as hyperlocomotion are often dramatic and easier to identify, cognitive impairments are pervasive, less overt, and strongly predictive of long-term disability and poor functional outcomes (McCutcheon *et al.*, 2023; Ben-Azu *et al.*, 2024a). The global burden of schizophrenia is reflected in high disability-adjusted life years (DALYs) and reduced life expectancy due to severe learning and memory impairment (Velligan and Rao, 2023). Importantly, cognitive dysfunction rather than psychosis itself is now recognised as the strongest determinant of patients' inability to work, maintain relationships, and live independently. This underscores the need for therapeutic strategies that specifically target cognitive symptoms.

The three symptom domains of schizophrenia arise from overlapping but distinct neurobiological disturbances. Positive symptoms are largely linked to mesolimbic dopamine hyperactivity, while negative and cognitive symptoms stem from dysfunctions in the prefrontal cortex and hippocampus, involving glutamatergic N-methyl-D-aspartate (NMDA) receptor hypofunction, which is linked to several neurochemical and cellular alterations, such as impaired GABAergic signalling and disrupted cholinergic

neurotransmission (Bighelli *et al.*, 2018). Neuroimmune and nitrosative disturbances, as well as abnormal cytokine hyperactivity, also play central roles as underlying factors associated with worsened cognitive symptoms (Momtazmanesh *et al.*, 2019; Reale *et al.*, 2021).

Within this framework, nitric oxide (NO) generation and the resulting peroxynitrite from the combination with superoxide radicals result in nitrosative stress, which can disrupt mitochondrial function, impair glutamatergic signalling, and damage synaptic proteins (Nakamura *et al.*, 2020; Üremiş and Üremiş, 2025). In parallel, the cholinergic system is profoundly disrupted, with increased acetylcholinesterase (AChE) activity limiting the availability of acetylcholine in cortical brain regions (Chatterjee *et al.*, 2012, 2021; Gasiorska *et al.*, 2021). This disruption impairs neural communication and information processing. However, clinical and experimental evidence indicates that targeting cholinergic dysfunction can normalise neurotransmission and improve outcomes, notably via mechanisms linked to increased acetylcholine in the medial prefrontal cortex (Ben-Azu *et al.*, 2024d). Importantly, these mechanisms are not isolated but interdependent, as nitrosative stress increases neuronal vulnerability to cholinergic deficits, while pro-inflammatory cytokines further compromise cholinergic signalling, establishing a cycle of oxidative injury, immune dysregulation, and neurotransmitter imbalance that sustains the neuropathological alterations in the schizophrenic condition (Li *et al.*, 2025; Singh *et al.*, 2024).

The ketamine model is commonly used to investigate schizophrenia-like phenotypes in rodents due to its non-

competitive NMDA receptor antagonistic action. Ketamine reliably reproduces a broad spectrum of clinical symptoms, especially spatial and non-spatial memory impairments, which are core features of the cognitive symptoms of schizophrenia, notably affecting males compared to females as presented in clinical settings (Ben-Azu et al., 2018a; Naz et al., 2023). Experimentally, ketamine administration induces memory deficits and impaired sensorimotor gating, closely resembling the cognitive domains of schizophrenia (Marchi et al., 2022; Santiago et al., 2023). These behavioural derangements are strongly associated with neuro-immune alterations and neurochemical changes such as cholinergic dysfunction in cortical brain regions (Santiago et al., 2023). In addition to behavioural changes, ketamine exposure triggers metabolic alterations, including upregulation of AChE enzyme activity, notably mirroring pathophysiological processes observed in patients, including AChE hyperactivity (Nogo et al., 2022; Uruaka et al., 2025). Importantly, investigations with ketamine-induced experimental psychosis and the underlying neurobiological alterations are reversible with atypical antipsychotic drugs, such as risperidone and clozapine, thereby confirming the face, construct, and etiological validity of the model (Vines et al., 2022). Collectively, these features make the ketamine model a robust and translationally relevant tool for investigating the neurobiology of schizophrenia and for evaluating novel therapeutic interventions.

Polyphenols are emerging leads with neuroprotective properties and have gained attention for their potential neuroprotective effects (Grabska-Kobylecka et al., 2023; Jalouli et al., 2025). Among them, syringic acid is widely distributed in edible plants, fruits, and medicinal herbs (Ogut et al., 2022). It is derived from the metabolism of anthocyanins and other polyphenols and possesses neuroprotective properties by enhancing endogenous antioxidant defences (Ogut et al., 2022; Zhao et al., 2025). Syringic acid ameliorates memory impairments, reduces neuroinflammation, and protects against neuronal degeneration in models of aging (Bartel et al., 2024), metabolic stress (Mashayekhi-Sardoo et al., 2025), and toxin-induced brain injury (Shi et al., 2024). Importantly, syringic acid has shown promise in restoring redox homeostasis and attenuating nitrosative stress (Ji et al., 2025). Although clinical investigations are still limited, its natural abundance in the diet and multitarget pharmacological profile make syringic acid a strong candidate for evaluation in neuropsychiatric conditions (Ogut et al., 2022). These properties highlight syringic acid as a potential therapy for disorders with oxidative stress, immune issues, and neurotransmitter imbalance. We tested its effects on ketamine-induced schizophrenia-like behaviour and mechanisms in mice brains, based on its antioxidant and anti-inflammatory evidence.

MATERIALS AND METHODS

Animals

Male Swiss albino mice (20–25 g), 7–8 weeks old, were obtained from the Laboratory Animal Centre of Delta State University (DELSU), Abraka. They were housed in plastic cages at $23 \pm 2^\circ\text{C}$, with a 12-h light/dark cycle and 40–70% humidity. They had free access to food and water. All procedures were approved by the Delta State University's Animal Care and Use Research Ethics Committee (REC/FBMS/DELSU/24/181). The sample size was determined based on a standard deviation of 31.28, an effective size of 50 for motor hyperactivity, and power analysis: Sample size = $2(31.28)^2(1.96+0.842)^2/(50)^2 = 6.12$. To account for 5% attrition, 7 mice per group were chosen using the formula: Final sample size = $6.12 / (1 - 0.05)$ (Charan and Kantharia, 2013).

Chemicals and Reagents

Syringic acid (95 % purity) and risperidone (98% purity) (Sigma-Aldrich, St. Louis, MO, USA) and ketamine hydrochloride (Rotex Medical, Germany) were used. Risperidone was dissolved in normal saline and served as the positive control because ketamine-induced schizophrenia-like behaviours are known to be responsive to atypical antipsychotics (Ben-Azu et al., 2019). Syringic acid was also dissolved in saline, and doses were based on established neuroprotective effects (Rashedinia et al., 2020; Adeyi et al., 2023). Diabetic rats treated with syringic acid for 6 weeks demonstrated improved learning and memory, increased antioxidant indices, and increased mRNA expression of cellular pathways such as nuclear factor erythroid 2-related factor 2 (Nrf2), which is involved in oxidative phosphorylation, energy metabolism, and mitochondrial biogenesis, and reduced AChE enzyme activity. This is consistent with other studies showing that syringic acid has antioxidant, anti-inflammatory, and antiapoptotic effects against dimethyl nitrosamine-induced hepatic injury in rats at doses of 50 and 100 mg/kg, reducing TNF- α , IL-1 β , and NF- κ B levels (Adeyi et al., 2023).

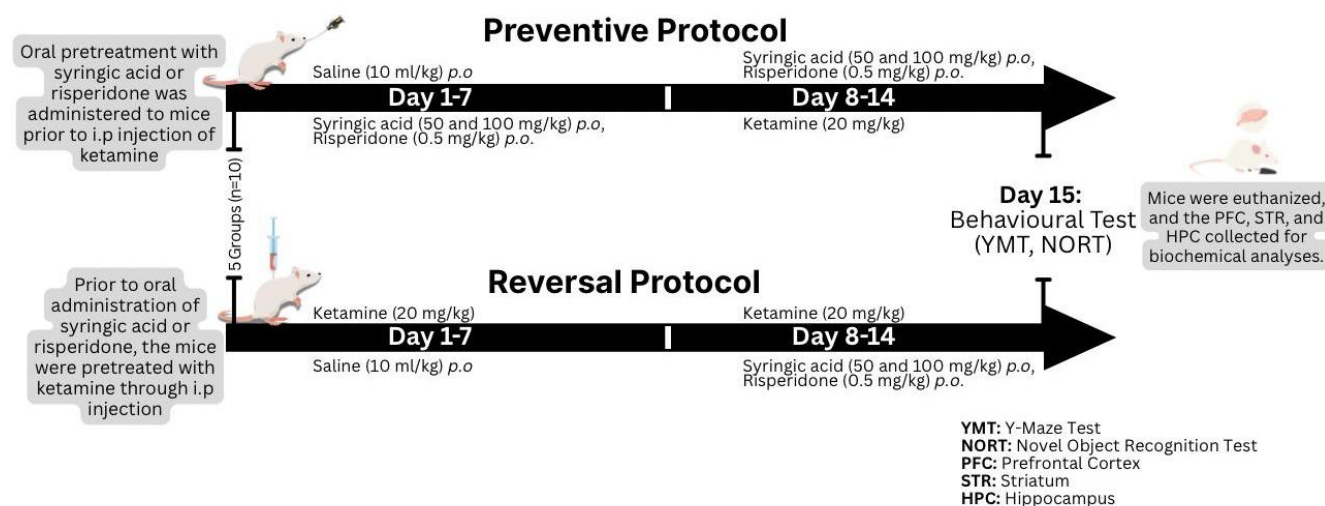
Assay reagents, including thiobarbituric acid (TBA), acetylcholine iodide, acetylthiocholine iodide, and Ellman's reagent (DTNB), were sourced from Sigma-Aldrich (St. Louis, USA). Other reagents included Tris-KCl buffer, acetic acid, sodium bicarbonate, sodium carbonate, hydrogen peroxide, adrenaline, trichloroacetic acid (TCA), and Tris buffer from various commercial suppliers of analytical-grade reagents. Cytokine kits, including IL-1 β and IL-10 ELISAs, were obtained from BioLegend (San Diego, USA).

Experimental Design

Two protocols ($n=7/\text{group}$) assessed syringic acid's preventive and reversal effects on ketamine-induced schizophrenia-like behaviours and neurochemical changes.

In the preventive protocol, mice were assigned to five groups: control, vehicle, syringic acid (50 or 100 mg/kg), and risperidone (0.5 mg/kg, p.o.). Groups 2-5 received ketamine from days 8–14. In the reversal protocol, mice received ketamine daily, then syringic acid or risperidone from days 8–14. Behavioural tests were performed on day 14, followed by euthanasia for biochemical analyses of

brain regions. Twenty-four hours after the final treatment (day 14), behavioural tests including the Y-maze test (YMT) and novel object recognition test (NORT) were conducted in the reported order. On the following day (day 15), mice were euthanised, and the prefrontal cortex (PFC), striatum (ST), and hippocampus (HC) were isolated for biochemical analyses (Scheme 1)



Scheme 1: Experimental design.

Behavioural Testing

Y-Maze Test

The Y-Maze Test (YMT) was used to assess spatial working memory on day 15, following treatment on day 14, serving as an important measure of cognitive function. It featured three identical arms (A, B, C), each measuring 33 × 11 × 12 cm, arranged at 120° angles in a Y-shape. Mice freely explored the maze's centre for 5 min. Alternation was defined as entering three different arms in sequence. The percentage of natural alternation, indicating spatial memory performance, was calculated as hitherto described (Ben-Azu et al., 2024b, 2024c).

Novel Object Recognition Test

We used the Novel Object Recognition Test (NORT) to assess non-spatial working memory (Amenotie et al., 2025), employing a white wooden chamber measuring 60 × 50 × 40 cm, based on the novelty preference one-trial model. This test was conducted on day 15 before the subsequent treatment of that day. During habituation, each mouse was placed equidistant from two similar objects (A and B). After a 4-hour interval, object B was replaced with novel object C, and the rat was reintroduced for recognition testing. Exploration was defined as nose contact within 1 cm or

interaction using nose or whiskers. Recognition memory was measured using the discrimination index derived from the time spent on the old and new objects (Ben-Azu et al., 2024d, 2026).

Brain Tissue Preparation

After the final test on day 15, animals were gently euthanised by cervical dislocation. Their brains were carefully removed, weighed, and segmented into the PFC, ST, and HC regions. Each part was quickly excised, rinsed in phosphate-buffered saline (PBS) (0.1 M, pH 7.4), and processed separately. The homogenates were gently centrifuged at 10,000 rpm for 10 min at 4°C, and the supernatants were collected and stored at -20°C for further biochemical analysis.

Estimation of Brain Nitrite Levels

Brain nitrite levels in the PFC, ST, and HC were measured using Griess reagent as an indicator of nitric oxide production. We added 100 μL of Griess reagent (a 1:1 mixture of 1% sulfanilamide in 5% phosphoric acid and 0.1% N-1-naphthyl ethylenediamine dihydrochloride) to 100 μL of the supernatant, then measured absorbance at 540 nm (Ben-Azu et al., 2024d,e). The nitrite concentration in the brain was calculated from a standard curve generated with sodium nitrite ranging from 0 to 100 μM.

Acetylcholinesterase (AChE) Activity

AChE activity, which reflects cholinergic function and cognitive performance, was measured using Ellman's colourimetric method (Ellman *et al.*, 1961). Brain homogenates were gently diluted and left to incubate at room temperature for 10 min. Then, 25 μ L of acetylthiocholine iodide (0.028 M) was added, and the mixture was carefully incubated for another 3 min. We measured absorbance at 412 nm before and after incubation to detect any changes. These changes helped us determine the AChE activity, which we expressed as μ mol/min/mg of tissue protein.

Neuroinflammatory Cytokine and Enzyme Assays

Pro-inflammatory cytokines such as IL-1 β and anti-inflammatory marker IL-10 were quantified in brain homogenates using ELISA kits by BioLegend (San Diego, USA) based on the manufacturer's protocol. Absorbances were then read per plate at 450 nm within 15 min using the Spectramax M-5 microplate reader, and the results were expressed as pg/mg protein (for more details, see Ben-Azu *et al.*, 2024d,f). Finally, myeloperoxidase (MPO) activity, an inflammatory enzyme, was determined following previously published protocols (Ben-Azu *et al.*, 2019). MPO catalyses the oxidation of substrates in the presence of hydrogen peroxide, and the resulting chromogen was quantified spectrophotometrically in a reaction mixture of brain homogenate in 5% hexadecyltrimethylammonium bromide in 50 mM potassium phosphate buffer (pH 6.0). The mixture was then frozen at -20 °C to facilitate supernatant extraction. The supernatant was freeze-thawed three times for 10 s each. Next, the reaction mixture was centrifuged at 15,000 rpm for 15 min at 4 °C. The supernatant was combined with 0.167 mg/mL O-dianisidine in 50 mM potassium phosphate buffer and 0.15 mM H₂O₂. The reaction mixture was then read at 450 nm using a SpectraMax device, and the MPO activity was expressed as units per mg of protein.

Statistical Analysis

We expressed our statistical data as mean $\pm$ SEM. All comparisons were performed using one-way and two-way analyses of variance (ANOVAs) with Tukey's post hoc test. A value of $P < 0.05$ was considered statistically significant. GraphPad Prism 9.0 was used for data analysis and graph plotting.

RESULTS

Syringic Acid Attenuated Ketamine-Induced Spatial and Non-Spatial Working Memory Deficits

The effect of syringic acid on ketamine-induced cognitive deficits is shown in Figure 1a-b. In the Y-Maze, ketamine (20 mg/kg) reduced correct alternations compared to saline,

indicating spatial working memory impairment, in both the preventive (Figure 2a) and reversal (Figure 2c) protocols. Syringic acid (50 and 100 mg/kg, p.o.) significantly improved performance in the preventive protocol, whereas in the reversal protocol, 50 mg/kg was effective, but 100 mg/kg was not. Risperidone (0.5 mg/kg) reversed ketamine impairment in both protocols. In the NORT, ketamine reduced the discrimination index in both protocols (Figure 2b; Figure 2d), indicating non-spatial memory issues. Syringic acid (50 and 100 mg/kg) showed no significant improvement in preventive treatment, but at 50 mg/kg and 100 mg/kg, it improved recognition memory in the reversal. Risperidone (0.5 mg/kg) significantly reversed ketamine's memory deficits in both protocols, supporting treatment efficacy.

Syringic Acid Ameliorated Ketamine-Induced Alterations in Nitrite Concentrations in the Prefrontal Cortex, Striatum, and Hippocampus of Mice

In the preventive protocol (Figure 3a), ketamine (20 mg/kg) significantly increased nitrite levels in the prefrontal cortex, striatum, and hippocampus versus saline, with syringic acid inhibiting all regions. Specifically, 50 mg/kg of syringic acid significantly decreased levels in the prefrontal cortex, striatum, and hippocampus, while 100 mg/kg reduced nitrite in these regions. Risperidone (0.5 mg/kg) also significantly reduced nitrite in all regions compared to ketamine. In the reversal protocol (Figure 3b), ketamine again elevated nitrite levels. Syringic acid showed dose-dependent effects: 50 mg/kg was non-significant in the prefrontal cortex, but 100 mg/kg significantly decreased nitrite. Both doses significantly reduced nitrite in the striatum and hippocampus ($P < 0.0001$), reversing increases. Risperidone also lowered nitrite in all regions, similar to higher syringic acid doses.

Syringic Acid Modulated Ketamine-induced Alterations in Acetylcholinesterase Activity in the Prefrontal Cortex, Striatum, and Hippocampus of Mice

Figure 4 shows syringic acid's effect on ketamine-induced changes in AChE activity in the prefrontal cortex, striatum, and hippocampus. In the preventive protocol (Figure 4a), ketamine (20 mg/kg) raised AChE activity, indicating cholinergic dysfunction. Syringic acid reduced this in all regions: at 50 and 100 mg/kg, it significantly decreased activity in the prefrontal cortex, striatum, and hippocampus. Risperidone showed non-significant effects. In the reversal protocol (Figure 4b), ketamine increased AChE activity in all regions. Syringic acid at both doses significantly reversed these increases, reducing activity close to normal, and risperidone also effectively reduced levels.

Syringic Acid Restores Ketamine-Induced Neuroimmune Challenge in the Prefrontal Cortex, Striatum, and Hippocampus of Mice

In the preventive protocol (Figure 4a), ketamine (20 mg/kg) raised MPO in the prefrontal cortex and striatum ($P < 0.001$) and hippocampus, increased IL-1 β in the prefrontal cortex, striatum, and hippocampus, and decreased IL-10 in the prefrontal cortex, striatum, and hippocampus (Figure 4a-c). Syringic acid (50 and 100 mg/kg, p.o.) reversed these changes in a region- and dose-dependent manner, reducing MPO in the prefrontal cortex and increasing IL-10 at 100 mg/kg. Neither dose significantly reduced IL-1 β ; in the striatum, both doses reduced MPO and IL-1 β and increased IL-10. In the hippocampus, both doses reduced MPO and IL-1 β but did not restore IL-10. Risperidone (0.5 mg/kg)

significantly reduced MPO and IL-1 β and increased IL-10 across regions.

In the reversal protocol, ketamine increased MPO (Figure 4d) and IL-1 β (Figure 4e) and decreased IL-10 (Figure 4f) in the prefrontal cortex, striatum, and hippocampus, and syringic acid reversed these effects in a dose- and region-dependent manner. In the prefrontal cortex, 50 mg/kg and 100 mg/kg reduced MPO; both doses reduced IL-1 β , and only 100 mg/kg restored IL-10. In the striatum, 50 mg/kg reduced MPO, both doses reduced IL-1 β , and both doses restored IL-10. In the hippocampus, both doses reduced MPO and IL-1 β , but neither restored IL-10. Risperidone reduced MPO and IL-1 β and restored IL-10 in all regions, confirming treatment efficacy.

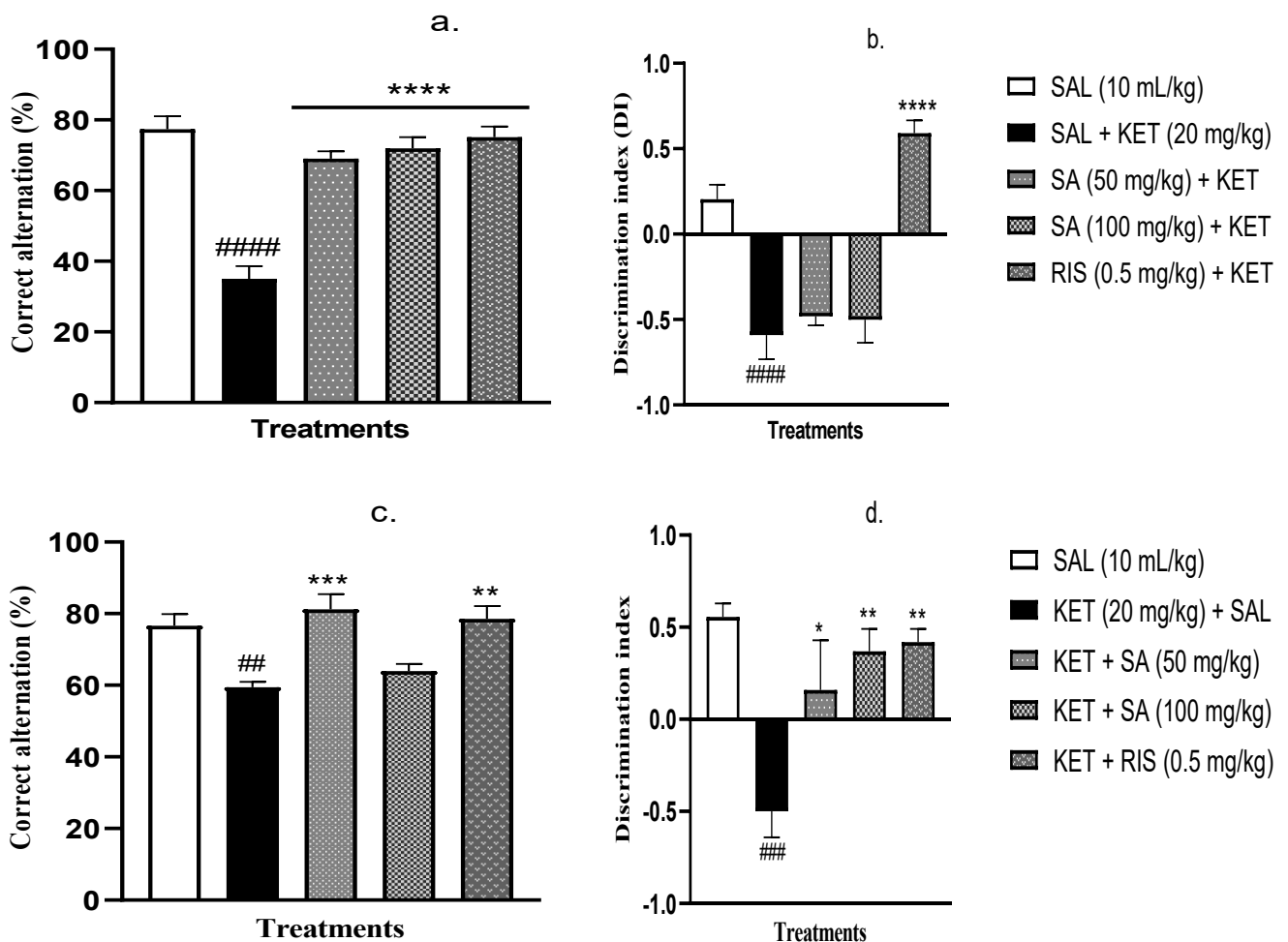


Figure 2a-d: Syringic acid attenuated ketamine-induced spatial (a, c) and non-spatial (b, d) working memory deficits in mice. Bars represent the mean $\pm$ S.E.M of 7 animals/group. ## $P < 0.05$, ### $P < 0.001$, #### $P < 0.0001$ compared to the saline group; * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$ compared to the KET group (one-way ANOVA followed by Bonferroni post-hoc test). SAL = Saline, KET = Ketamine, SA = Syringic Acid, RIS = Risperidone.

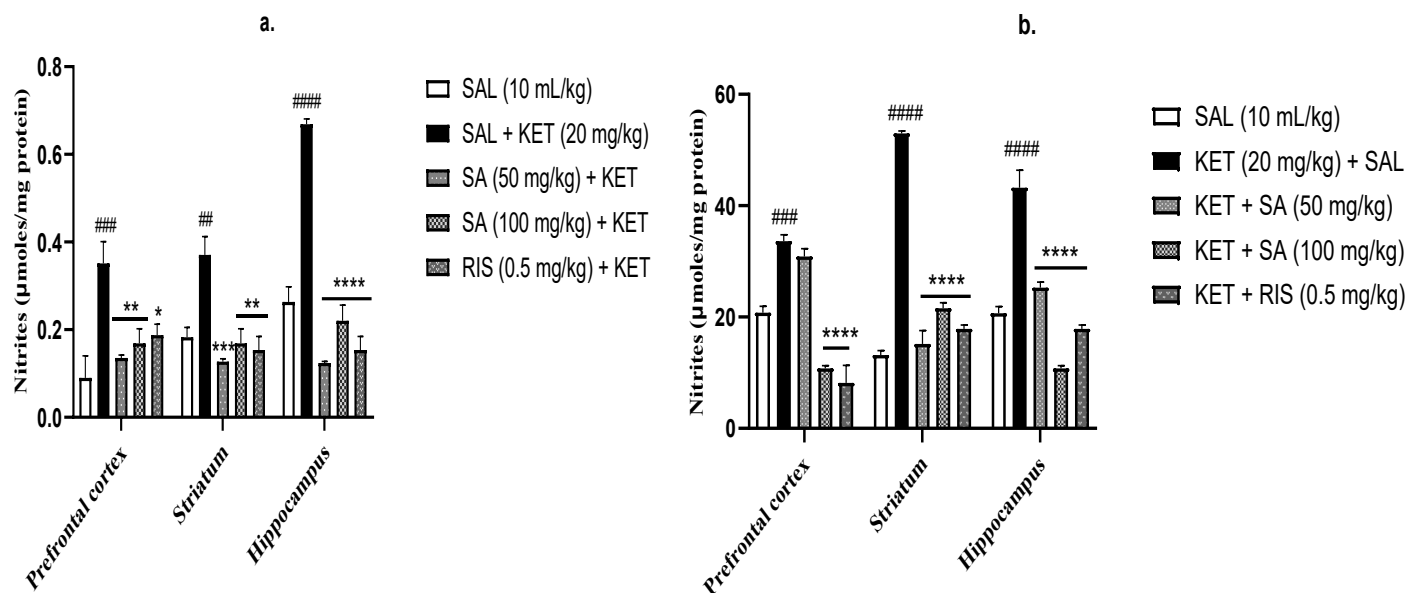


Figure 3a-b: Syringic acid prevented (a) and reversed (b) ketamine-induced alterations in nitrite concentrations in the prefrontal cortex, striatum, and hippocampus of mice. Bars represent the mean $\pm$ S.E.M of 7 animals/group. ^{##} $P < 0.01$, ^{###} $P < 0.001$, ^{####} $P < 0.0001$ compared to the saline group; ^{*} $P < 0.05$, ^{**} $P < 0.01$, ^{***} $P < 0.001$, ^{****} $P < 0.0001$ compared to the KET group. (two-way ANOVA followed by Bonferroni post-hoc test). SAL = Saline, KET = Ketamine, SA = Syringic Acid, RIS = Risperidone.

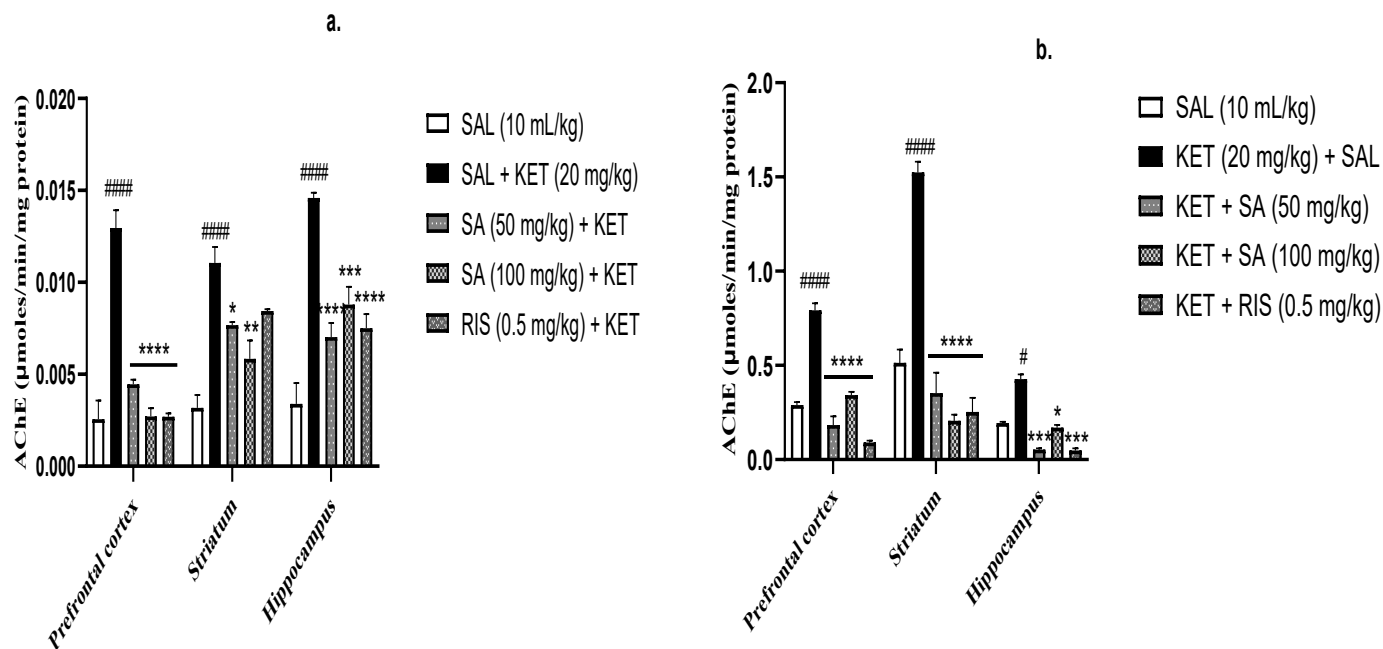


Figure 4a-b: Syringic acid reduces ketamine-induced alterations in acetylcholinesterase (AChE) activity in the prefrontal cortex, striatum, and hippocampus of mice in preventive (a) and reversal (b) protocols. Bars represent the mean $\pm$ S.E.M of 7 animals/group. [#] $P < 0.05$, ^{###} $P < 0.0001$ compared to the saline group; ^{*} $P < 0.05$, ^{**} $P < 0.01$, ^{***} $P < 0.001$, ^{****} $P < 0.0001$ compared to the KET group (two-way ANOVA followed by Bonferroni post-hoc test). SAL = Saline, KET = Ketamine, SA = Syringic Acid, RIS = Risperidone.

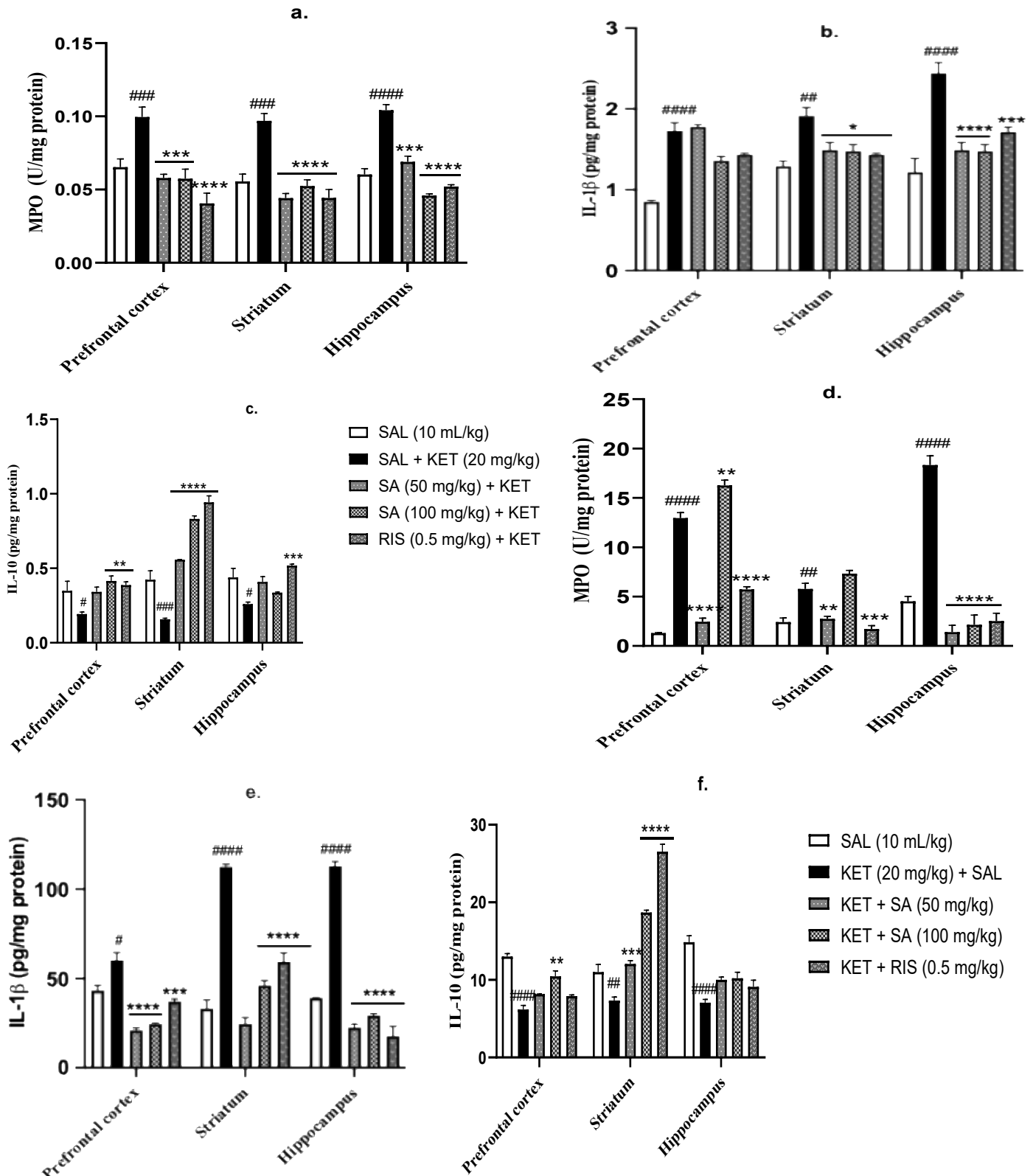


Figure 5a-f: Syringic acid restores ketamine-induced neuroimmune challenge in the prefrontal cortex, striatum, and hippocampus of mice. Bars represent the mean $\pm$ S.E.M of 7 animals/group. # P <0.05, ## P <0.01, ### P <0.001, #### P <0.0001 compared to the saline group; * P <0.05, ** P <0.01, *** P <0.001, **** P <0.0001 compared to the KET group (two-way ANOVA followed by Bonferroni post-hoc test). SAL = Saline, KET = Ketamine, SA = Syringic Acid, RIS = Risperidone.

DISCUSSION

Herein, we showed that syringic acid exerts cognitive-enhancing and neuroprotective effects beneficial in a psychotic-like condition in mice. Behavioural assessments showed that syringic acid significantly improved both spatial and non-spatial types of memories. These findings suggest that syringic acid has the capacity to ameliorate the cognitive impairments that are typically associated with schizophrenia. In addition to behavioural improvements, syringic acid markedly attenuated nitrosative stress, as evidenced by reduced brain nitrite levels, indicating its potent antioxidant potential. Furthermore, syringic acid restored cholinergic function by reducing AChE activity in key brain regions, thereby supporting enhanced acetylcholine availability for optimal synaptic transmission, an important biochemical mechanism that could be associated with its cognitive-enhancing property. The compound also modulated neuroimmune signalling, as shown by reduced MPO activity and IL-1 β levels, alongside elevated anti-inflammatory IL-10. Importantly, these effects were dose-dependent and region-specific, with the hippocampus and prefrontal cortex showing the most pronounced responses. In several parameters, the effects of syringic acid were similar to those of risperidone, the reference antipsychotic drug, underscoring its potential as a natural therapeutic alternative or adjunct in managing schizophrenia-like cognitive and neurochemical disturbances.

First, ketamine administration significantly increased nitrosative stress, a hallmark of NMDA receptor hypofunction models (Zhou *et al.*, 2024), by elevating brain nitrite levels. Syringic acid effectively counteracted this response, likely through increased endogenous antioxidant systems (Bartel *et al.*, 2024; Zhao *et al.*, 2025). By reducing the accumulation of nitric oxide and peroxynitrite, a toxic reactive species formed when nitric oxide reacts with the superoxide radical, syringic acid preserves mitochondrial function and limits oxidative damage to synaptic proteins, processes critical for sustaining neural connectivity and plasticity. Second, syringic acid prevents and reverses ketamine-induced immune dysregulation. Increased IL-1 β levels and MPO activity are linked to cortical neuroinflammation and abnormal microglial activation in schizophrenia models (Ben-Azu *et al.*, 2019; Fond *et al.*, 2020). Treatment with syringic acid significantly suppressed these inflammatory markers while simultaneously enhancing IL-10, an anti-inflammatory cytokine with neuroprotective roles. This dual action suggests that syringic acid not only dampens excessive inflammatory signalling but also promotes a protective immune environment that favours neuronal survival and synaptic plasticity (REF). Furthermore, syringic acid modulated the cholinergic system. Syringic acid effectively

reduced the increase in AChE activity induced by ketamine, thereby helping restore acetylcholine availability. By enhancing cholinergic neurotransmission, syringic acid may counteract the deficits in cortical communication that underpin cognitive dysfunctions in schizophrenia (Ben-Azu *et al.*, 2018b; Ben-Azu *et al.*, 2019). Notably, these mechanisms are not independent; rather, they converge to sustain syringic acid's therapeutic effects. The reduction of nitrosative stress decreases neuronal vulnerability to cholinergic dysfunction and further stabilises neurotransmitter systems (Kniffin *et al.*, 2024). Previous studies show that disruption in cholinergic signalling within the septohippocampal system due to disease-related AChE enzyme activity suggests the important role of the medial septal area in enhancing cognitive function, which is impaired in schizophrenia (Kniffin *et al.*, 2024). For instance, rats exposed to chronic stress have been shown to disrupt the septohippocampal system following excessive release of corticosterone (Tizabi *et al.*, 1989). This system is a crucial circuit that influences learning, memory, and the timing of hippocampal theta oscillations (Kniffin *et al.*, 2024). Moreover, previous findings have indicated that the medial septum is critical for the modulation of psychotic behaviour, such as delirium, through abnormally large-amplitude hippocampal gamma activity following ketamine injection in rats (Ma *et al.*, 2009). Therefore, the integrated modulation of redox and immune pathways, with normalisation of the cholinergic pathways, underscores syringic acid's unique psychotropic effects that can target the complex neurobiology of schizophrenia.

The effects of syringic acid in this study were, in several respects, comparable to those of risperidone, the reference atypical antipsychotic. Syringic acid and risperidone improved performance in spatial and recognition memory tasks and attenuated ketamine-induced heightened pro-inflammatory cytokine expression. However, syringic acid demonstrated a broader modulatory profile by simultaneously enhancing IL-10 while reducing IL-1 β and MPO activity, suggesting superior immune-balancing capacity. This immunomodulatory action is especially important when it comes to the cognitive symptoms of schizophrenia. Elevated levels of IL-1 β have been linked to difficulties in hippocampal neurogenesis, synaptogenesis, and memory consolidation, highlighting the role of the immune system in influencing brain function. By restoring cytokine balance and reducing neuroinflammation, syringic acid may help preserve neuronal integrity and support the cognitive processes disrupted in schizophrenia. Unlike risperidone, which primarily exerts its therapeutic effects through dopaminergic and serotonergic receptor antagonism, syringic acid's actions include antioxidant, anti-inflammatory, and cholinergic modulations, reflecting a distinct yet complementary mode of action. This difference highlights syringic acid's potential as a natural

adjunctive therapy, capable of targeting treatment-resistant domains such as inflammation and oxidative imbalance, with the added advantage of being less likely to cause the metabolic side effects often associated with atypical antipsychotics.

The neuroprotective profile of syringic acid aligns with evidence from other natural compounds, particularly polyphenols and nutraceuticals such as morin, diosmin, and silymarin, that have shown efficacy in schizophrenic mice (Ben-Azu *et al.*, 2018b; Ben-Azu *et al.*, 2022; Okubo *et al.*, 2020; Ben-Azu *et al.*, 2024a,b). Flavonoids such as quercetin and resveratrol, as well as amino acids like taurine, have been reported to ameliorate ketamine- or phencyclidine-induced psychosis via boosting the antioxidant system, modulating cytokine activity, and restoring neurotransmitter balance (Ben-Azu *et al.*, 2022; Juliani *et al.*, 2024). Syringic acid, as a hydroxybenzoic acid derivative, expands this body of evidence by demonstrating similar antioxidant and anti-inflammatory actions, while also exerting specific regulatory effects on the cholinergic system by inhibiting AChE enzyme activity. Its dietary abundance (Srinivasulu *et al.*, 2018) and established safety (Shimsa *et al.*, 2024) further support considering syringic acid as a promising adjunct in schizophrenia management. Its ability to cross the blood–brain barrier and exert multimodal actions, antioxidant, anti-inflammatory, and cholinergic regulation (Zhao *et al.*, 2025), makes it a strong candidate for adjunctive schizophrenia therapy. However, our study has limitations, including the use of a single animal model of schizophrenia and a lack of specific mechanistic evidence demonstrating the cellular mechanisms underlying syringic acid's antioxidant, anti-inflammatory, and cholinergic modulatory effects, warranting future mechanistic studies.

CONCLUSION

This study provides evidence that syringic acid prevents and reverses schizophrenia-like behaviour related to the cognitive symptoms induced by ketamine through its combined antioxidant, anti-inflammatory, and cholinergic modulatory effects (Figure 5). These findings highlight its promise as a safe, naturally occurring compound with potential adjunctive value in the management of schizophrenia, particularly for the poorly treated cognitive symptom domains.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHORS' CONTRIBUTION

Conceptualisation, formal analysis, Writing-original draft, Writing-review & editing, Funding acquisition: BB-A, BO, CPI and DTE; Methodology, Validation, Formal analysis: BSC, SGU, CPU, CIO, DDE, and SEK; Validation, Investigation: CPU, CIO, and JOTE.

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COMPLIANCE WITH ETHICAL STANDARDS

All experiments received approval from Delta State University's Animal Ethics Committee (REC/FBMS/DELSU/24/181).

AVAILABILITY OF DATA AND MATERIAL

Available on reasonable request.

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