African Journal of Pharmaceutical Research and Development
Available online at https://ajopred.com
Vol. 17 No.2; pp. 180-199 (2025)

Original Research Article

Ficus patyphylla STEM BARK EXTRACT REVERSES KETAMINE-INDUCED SCHIZOPHRENIC–LIKE BEHAVIORS IN RATS VIA MODULATION OF CHOLINERGIC, NITRERGIC AND OXIDATIVE PATHWAYS

BEN AHMED CHINDO[1,*], ZAINAB ADAMU[1], MUHAMMAD AMINU MUSA[1], PETER MAITALATA WAZIRI[2], ALIYU ADAMU[3], ZAKARI LADAN[4], SAMSON AMOS[5]

1. Department of Pharmacology and Toxicology, Faculty of Pharmaceutical Sciences, Kaduna State University, Kaduna, Nigeria.
2. Department of Biochemistry, Faculty of Life Sciences, Kaduna State University, Kaduna, Nigeria.
3. Bioinformatics Unit, Department of Microbiology, Faculty of Life Sciences, Kaduna State University, Kaduna, Nigeria.
4. Department of Chemistry, Faculty of Physical Sciences, Kaduna State University, Kaduna, Nigeria.
5. School of Pharmacy, Cedarville University, Ohio, USA.

ABSTRACT

Ketamine challenge is a suitable animal model for evaluating cognitive, positive and negative symptoms of schizophrenia, besides oxidative stress, cholinergic, dopaminergic, GABAergic and nitrergic dysfunctions observed in the disease. Effects of *Ficus platyphylla* (FP) methanol extract on behavioral alterations triggered by ketamine were investigated in forced swim, open field, and new object identification tests. To examine the part played by nitrergic, cholinergic, and oxidative pathways in the antipsychotic properties of FP, acetylcholinesterase activity, levels of oxidative stress biomarkers, and nitrite in the brain were also evaluated. *In silico* molecular docking analysis was conducted to predict the interactions between bioactive compounds from FP and potential drug targets for the treatment of schizophrenia. FP administered alone or in conjunction with risperidone (RIS) significantly reversed ketamine-induced schizophrenic-like behaviors in rats; the increased brain levels of glutathione, catalase and superoxide dismutase activities, the decreased acetylcholinesterase activity, levels of nitrite and malonyladehyde in ketamine-treated rats. The bioactive compounds from FP demonstrated binding affinities for the recognized drug targets for pharmacotherapy of schizophrenia, including dopamine, serotonin and metabotropic glutamate receptors, and phosphodiestrases. Our findings revealed that cholinergic, nitrergic, and oxidative pathways were modulated by FP alone or in conjunction with RIS to reverse symptoms akin to schizophrenia triggered by ketamine. These findings further suggest that co-administration of *Ficus platyphylla* extracts and risperidone may improve the ameliorative effects of risperidone on cognitive, negative, and positive symptoms of schizophrenia.

ARTICLE INFO

Received 16 July 2025
Accepted 11 August 2025
Published 26 September 2025

KEYWORDS

Ficus platyphylla,
Ketamine,
Schizophrenic-like behaviors,
Cholinergic pathways,
Nitrergic pathways
Oxidative pathways

INTRODUCTION

Schizophrenia is a complex and diverse mental illness characterized by persistently disturbed thinking, paranoid delusions, emotional disengagement, as well as auditory and visual hallucinations [1]. It is an idiopathic, highly complex and polygenetic brain order that is linked with neurodevelopmental and environmental risk factors [2[, and characterized by negative, positive, disorganized symptoms [3]. The positive

***Corresponding author:** bachindo@kasu.edu.ng, +234 803 289 9112

https://doi.org/10.59493/ajopred/2025.2.8 ISSN: 0794-800X (print); 1596-2431 (online)

symptoms include hallucinations, auditory and visual delusions, thought disorder, conceptual disorganization and paranoia [4]. The negative symptoms include depression, deficiencies in social interactions, motivation and expression, emotional blunting, avolition, anhedonia, poverty of thought, and speech content [1]. These deficiencies have a unique psychopathological component that sets them apart from cognitive impairment, disorganization, and reality distortion [5]. Compromised working memory, executive functioning and attention are cognitive dysfunctions linked to this crippling mental illness [4].

Although the exact cause of schizophrenia is unknown, studies have demonstrated multiple pathophysiologic abnormalities in brain functions and structures that may have significant roles in the pathophysiology of this mental illness. A neuro-developmental model with evidence supplied by the abnormal neural migration that most schizophrenic brains exhibit suggests that an unidentified *in utero* disruption takes place, most likely during the second trimester of pregnancy. In addition to functionally leading to the creation of aberrant brain circuits, these "schizophrenic lesions" may cause anomalies in cell shape, location, symmetry, and connection [6–7]. It is believed that the secondary "synaptic disorganization" that results from such injuries does not cause overt clinical signs of psychosis until adolescence or early adulthood, when neural development occurs [8].

Additionally, research has linked schizophrenia to obstetric problems or neonatal hypoxia. A glutamatergic cascade that leads to enhanced neuronal pruning is thought to be triggered by obstetric difficulties, hypoxia, and a genetic susceptibility associated with genes governing N-methyl D-aspartate (NMDA)-receptor activity [9]. Other research linked schizophrenia to low birth weight (less than 2.5 kg) [11] and upper respiratory infections in the second trimester of pregnancy [10].

Several other theories have emerged, suggesting many possible causes of schizophrenia. According to psychological beliefs, some people with schizophrenia have left hemisphere limbic dysfunction, and others have a diminished capacity to manage the volume and velocity of incoming perceptual stimuli [12]. Schizophrenia may be caused by disruptions in family connections or communication, according to a widely accepted sociological idea that is unsupported by scientific data [12].

The pathophysiology of schizophrenia also involves the malfunctioning of many neurotransmitter systems, besides the genetic, neuro-developmental, psychological, and social factors. Schizophrenia is caused by a distinct imbalance in neurotransmitter systems, although patients may be predisposed to the disorder by abnormal neuro-developmental processes [13]. Many neurotransmitter systems, including serotonergic, glutamatergic, dopaminergic and GABAergic systems, may be sites of major pathophysiologic anomaly in schizophrenia, with alterations in other neurotransmitters occurring secondarily [8].

Currently, schizophrenia is thought to be a systemic illness that involves disorders of the immune system, the endocrine and the cardiovascular systems [14]. Increased levels of immunological response, inflammation and oxidative stress are observed in schizophrenics [15], besides aberrations in dopaminergic, GABAergic, glutamatergic and serotonergic neurotransmission systems [16], one-carbon (C1) metabolism and membrane lipid composition [17, 18].

Schizophrenia is accompanied by severe physical, social and psychological apprehensions that transcend racial, social, age, sexual or geographical borders. Schizophrenia prevalence varies from 0.6% to 1.9% worldwide, with an average of about 1% [19], making it the most prevalent psychiatric condition often linked to significant economic and social consequences [20]. Males and females have the same prevalence of schizophrenia, but males typically develop the illness earlier. Males commonly experience their initial episodes in their early twenties, while females typically experience them in their late twenties to early thirties [21–22]. While the frequency of schizophrenia is increasing in developing nations, schizophrenic patients in Sub-Saharan Africa do not receive adequate care [23]. Traditional antipsychotic drugs have not achieved the expected results in schizophrenia treatment. The most significant limitations in schizophrenia treatment are the demoralizing adverse reactions of conventional antipsychotics, coupled with their inability to adequately manage core negative symptoms and cognitive dysfunctions of the disease [4], while giving the patients' quality of life little to no discernible increase. To overcome these barriers, schizophrenia research is increasingly focusing on the development of novel antipsychotic medications that are accessible, affordable, and effective. The medicinal plants are desirable targets in the quest for novel medications and lead compounds to treat these crippling mental illnesses [24–25]. For many years, traditional Nigerian medicine has utilized extracts from *Ficus platyphylla* Delile (Moracea) to treat schizophrenia with generally acclaimed efficacy among rural communities of Northern Nigeria. Previous studies on extracts from *Ficus platyphylla* demonstrated the plant's safety [26], and central nervous system activities [27–30] that suggest antipsychotic properties. In order to validate the antipsychotic potentials of FP shown in previous studies, we examined its effects on behaviors resembling schizophrenia induced by ketamine in this study and examined the roles of nitrergic, cholinergic and oxidative mechanisms in the antipsychotic properties of FP. Effects of continuous administration of FP on schizophrenic-like behaviors were evaluated alongside, to determine the effects of treatment with the extract in rats. We also conducted *In silico* molecular docking analysis to predict the interactions between potential therapeutic targets for the treatment of schizophrenia and the bioactive compounds from FP.

MATERIALS AND METHODS

Animals

For this study, we used nine-week-old, wiser rats (weighing 180–200 g), bought from Kaduna State University's (KASU)

Animal House and kept in cages made of clear plastic cushioned with wood shavings under conventional 12/12 h (dark/light) cycles, temperature, and humidity settings. The animals were given regular feeds and unlimited water following approval by the Animal Ethics Committee of the university (No. KASU/AEC/2025/0002). The study was conducted in compliance with the 2011 revised publication of the National Institutes of Health on the use and care of laboratory animals (NIH Publications No. 80–23).

Extract Preparations

Mallam Ibrahim Muazzam of the National Institute for Pharmaceutical Research and Development (NIPRD), Abuja, Nigeria, identified and authenticated the stem bark of FP after collection. A voucher sample (No. 4035) has been stored in the Herbarium of NIPRD for reference. A pestle and mortar were used to grind the bark into a coarse powder after it had been cleaned, sliced, and allowed to air dry. A Soxhlet extractor was used to extract the coarse powder (100 g) for 12 h using 500 mL of methanol until it was completely extracted. A rotary evaporator set at 40 °C was then used to remove the solvent, yielding 34.8% (w/w) of the crude methanol extract used in the investigation.

High Performance Liquid Chromatographic (HPLC) and **Gas Chromatography-Mass Spectrometric** (GC–MS) Analysis

Acute toxicity testing, HPLC analysis, and preliminary phytochemical screening were performed on FP, and the outcomes have been published [28, 31]. Additionally, the Shimadzu GC–MS QP2010 ultra model and the chromatographic technique previously outlined by Beschi et al. [32] were used to analyze FP.

Drugs and Chemicals

Adrenaline (Sigma-Aldrich), ellman Reagent [5',5'-Dithiobis-(2-nitrobenzoate) DTNB] (Sigma-Aldrich), hydrogen peroxide (H_2O_2) (BDH Chemicals Ltd.), Ketamine (Rotexmedica, Germany), risperidone (Jassen-Cilag), trichloroacetic acid (TCA) (Burgoyne Burbidges & Co., India), thiobarbituric acid (TBA) (Guanghua Chemical Factory Co. Ltd., China) were employed in this investigation.

Drug Preparations and Treatments

Physiological saline solution was used as solvent to re-suspend FP and risperidone (RIS) and also used for other drugs. KET was administered intraperitoneally (i.p.), while FP and RIS were given orally (p.o.). Volumes of 10 mL/kg of the vehicle (physiological saline solution) were administered. Doses of RIS (0.5 mg/kg), KET (20 mg/kg) and FP (25, 50, and 100 mg/kg) used in this investigation were selected from earlier research [28, 31, 33–34].

Experimental Protocol

With slight modifications, the method outlined by Ben-Azu and colleagues [34] was employed to produce biochemical alterations and behaviors resembling schizophrenia in rats. The rats (n = 8) were randomly divided into 12 groups. For 14 days, groups 2–7 got ketamine (KET) (20 mg/kg, i.p.) once daily, while group 1 received saline (10 mL/kg, p.o.). KET (20 mg/kg, i.p.) plus FP (25 – 100 mg/kg, p.o.) was administered to groups 3–5 from day 8 to day 14. Group 6 received KET (20 mg/kg, i.p.) plus RIS (0.5 mg/kg, p.o.), and Group 7 received both FP (50 mg/kg, p.o.) and RIS (0.5 mg/kg, p.o.) plus KET (20 mg/kg, i.p.) once daily with a one-hour break between therapies. From the eighth to the fourteenth day, different sets of animals in groups 8–10 received FP (25 – 100 mg/kg, p.o.), RIS (0.5 mg/kg, p.o.) in group 11, and FP (50 mg/kg, p.o.) and RIS (0.5 mg/kg, p.o.) in group 12 once daily (Figure 1).

Behavioral Studies

Negative, cognitive and positive symptoms are hallmarks of schizophrenic disorder [3]. The effects of FP on ketamine-induced hyperlocomotion, cognitive deficits and depressive behavior, which correspond to the positive, cognitive and negative symptoms of the disease, were investigated here using the open field, new object recognition and forced swim tests 24 h after the last administration of Sal, FP, RIS, and KET. Trained observers conducted all behavioural tests from 8:00 am to 3:00 pm.

Open-field test

To assess the locomotor behavior in rats, we used an open-field (35 × 30 × 23 cm) featuring a glass front wall, 36 squares (20 cm × 20 cm), and a central square (20 cm × 20 cm) divided by lines [35]. The open field was situated in a soundproof room with the lighting adjusted to about 90 lux. Lines crossing activity served as the primary basis for the open-field test (OFT). Rats were kept for at least 1 h in the test room before the OFT to reduce anxiety. Each rat was positioned at the open field's back left square, and given five minutes to investigate the equipment. Line crossings were counted and recorded. Between sessions, 70% ethanol was used to clean and dry the equipment to eliminate any odour cues from the prior animal [36–37].

Forced swim test (FST)

There were two sessions for the FST [38]. During the pretest (first day), each rat was given 15 minutes to swim in a glass cylinder measuring 46 cm in height by 20 cm in circumference, filled with water 30 cm deep and at 25 **^{0}C** [1]. Following the pretest, the rats were returned to their cages after being dried in a heated arena. After 24 h, each rat was put back in the water, made to swim, and their five-minute immobility period was noted [39]. If a rat stayed passive or did nothing but make small movements to maintain its head above the water, it was considered immobile [1, 36].

Novel object recognition test (NORT)

Twenty–four hours following ten minutes of free exploration in an open field raised 27 cm from the ground and measured 52 cm by 52 cm by 31 cm. Each rat was given two identical objects

to examine for five minutes. One of the identical objects was swapped out for an unfamiliar object on the second day. Five minutes were allotted to each rat's exploration of the known (tA) and novel (tB) objects [40]. Rats were deemed to have inspected an object if they touched or poked their snout at it within two millimeters [41]. For every rat [41], the preference (PI) and discrimination (DI) indexes were computed as follows: PI = (tB/(tB + tA) X 100, and DI = (tB – tA/tB + tA).

Biochemical Assays

Preparations of brain tissue

Following the behavioral evaluations, rats were placed in bell jars filled with cotton wool soaked in ether to be decapitated under deep ether anaesthesia [34, 42–44]. The tissues of the entire brain were then promptly removed. The following biochemical parameters were assessed after the brain samples were centrifuged for 10 minutes at 10,000 × g force at 4 0C after being homogenized in a standard phosphate buffer.

Superoxide dismutase activity

In a spectrophotometer set at 480 nm, superoxide dismutase (SOD) activity was assessed by suppressing superoxide-dependent adrenaline auto-oxidation. [45]. Freshly made 0.3 mM adrenaline was used to start the reaction after 2.5 milliliters of 0.05 M carbonate buffer (pH 10.2) were mixed with the diluted brain supernatant. A blank sample comprising 0.3 mL of substrate (adrenaline), 2.5 mL of buffer, and 0.2 mL of distilled water was used to measure the absorbance at 480 nm and 25 °C.

Catalase activity

The activity of catalase (CAT) was determined by measuring the amount of hydrogen peroxide (H_2O_2) that vanished when an enzyme source (catalase) was present [46]. The brain supernatant of the homogenate combined with distilled water was added to 4 mL of H_2O_2 solution and 5 mL of phosphate buffer (pH 7.0), and the mixture was slowly stirred at room temperature. After adding some of the combination to 2 milliliters of the dichromate/acetic acid reagent, the absorbance was measured at 570 nm. The catalase activity was expressed as micromoles of H_2O_2 degraded per minute per milligram of protein.

Glutathione concentration

The addition of 5', 5'-dithio-bis-(2-nitrobenzoic acid) (DTNB) to sulfhydryl compounds produced a rather stable (yellow) color that was used to determine the concentration of glutathione (GSH) [47]. After adding an equal volume of 20% trichloroacetic acid (TCA), brain homogenates were gently swirled and centrifuged at 5400 g for 20 minutes in a cool (4 °C) centrifuge. Phosphate buffer (0.2 M, pH 8.0) was used to raise the final volume of the solution to 3 mL after 0.25 mL of the supernatant was added to 2 mL of 0.6 mM DTNB. In comparison to a blank reagent [2 mL of 0.6 mM DTNB + 1 mL of phosphate buffer (0.2 M, pH 8.0)], the absorbance was measured at 412 nm using a spectrophotometer. Nanomoles per gram of tissue (nmol/mg protein) was the unit of measurement for the brain tissues' reduced GSH content.

Malondialdehyde

The amount of malondialdehyde (MDA) in the brain was assessed based on the unstable lipid peroxides that are produced by lipid peroxidation and decompose to yield a complex series of molecules, including reactive carbonyl compounds [48]. The Ohkawa et al. (1979) approach was used to detect the MDA levels in tissue samples. Aliquots of brain supernatant, Tris-KCl buffer, thiobarbituric acid (TBA), and 30% TCA were progressively mixed and then placed on a water bath heated at 80 °C for 45 minutes. After cooling, the mixture was centrifuged at 1800 × g force for 15 minutes. After obtaining a pink supernatant, the absorbance at 532 nm was measured with reference blanks of pure water. Moles per gram of tissue were used to express the MDA levels.

Brain nitrite level

Nitrite levels were assessed as previously described [49], to ascertain how drugs affect the synthesis of nitric oxide (NO). After the supernatant was incubated with Griess reagent at room temperature for ten minutes, the absorbance was measured at 550 nm. The level of nitrite in the brain was measured in nmol/g of tissue.

Acetylcholinesterase activity

A previously described method was employed to gauge the acetylcholinesterase (AChE) enzyme's activity [50]. After mixing 0.4 mL of the homogenate, (0.1 M, pH 7.4), 0.1 mL of DTNB, 0.1 mL of acetylthiocholine iodide solution, and 2.6 mL of phosphate buffer, the absorbance at a wavelength of 412 nm was measured using a spectrophotometer. The color increased by the interaction of thiocholine and DTNB was used to gauge the rate of acetylcholinesterase activity. The unit of measurement for acetylcholinesterase activity was µmoles/min/g tissue.

Molecular docking studies

The methods [51–52] as previously described were used to conduct *in silico* molecular docking examination to predict the interactions of pentadecanoic acid, 2, 3-dimethylphenylisothiocyanate, and 11-octadecenoic acid from FP with proteins such as serotonin receptors, metabotropic glutamate receptors, phosphodiesterase, and dopamine receptors, which are acknowledged drug targets for pharmacotherapy of schizophrenia. The ligands and proteins were processed using AutoDockTools4 [53]. Torsion angles within the ligand were identified; polar hydrogens were added, and water molecules were removed from the proteins to avoid empty atom groups and unnecessary interactions with the ligands. Grid (affinity) maps of 120 × 120 × 120 grid points with a spacing of .375 Å that covered the entire protein chain containing the active site were generated. AutoDock Vina 1.1.2 was used to perform the molecular docking calculations [54].

Statistical Analysis

Two-way ANOVA and either the Bonferroni or Turkey post hoc tests were used to analyze the data using Graph Prism version 4.00 (GraphPad Software, Inc., La Jolla, CA, USA). The findings, which were presented as mean ± S.E.M., were significant at $p < 0.05$. For every experiment, "n" represents the number of animals in each group.

RESULTS

Bioactive compounds in *F. platyphylla*

Twenty bioactive compounds were identified by GC–MS analysis, with the main compound being pentadecanoic acid (13.10 %), 2, 3-dimethylphenylisothiocyanate (13.47 %), and 11-octadecenoic acid (14.35 %) (Data not yet published). FP's HPLC fingerprint has previously been published [31].

Effect of FP on ketamine-induced hyperlocomotion

Repeated exposure of rats to FP and RIS significantly decreased locomotor activities ($F_{5, 31} = 9.700$, $p < 0.0001$; *$p < 0.05$; ***$p < 0.001$; **$P < 0.01$) in contrast to the controlled rats treated with saline (Fig. 2A). Sub-chronic intraperitoneal injections of ketamine substantially ($^{+}p < 0.05$) increased locomotor activities in rats in contrast to rats treated with saline. Ketamine administration with FP (25 – 100 mg/kg), RIS 0.5 mg/kg and FP 50 mg/kg + RIS markedly ($F_{5, 20} = 29.40$, $p < 0.0001$; ***$p < 0.001$) reversed hyperlocomotion triggered by ketamine in rats. Concomitant administration of both FP 50 mg/kg + RIS to ketamine treated rats significantly ($^{XX}p < 0.01$) attenuated ketamine enhanced hyperlocomotion compared to administration of RIS 0.5 mg/kg only (Figure 2B).

Effects of FP on Forced Swim Test Immobility Time

Recurrent administration of FP and RIS significantly ($F_{5, 31} = 15.59$, $p < 0.0001$; *$p < 0.05$; ***$p < 0.001$) decreased the immobility time by the rats during the mandatory swimming period relative to saline-treated group. Administration of both FP 50 mg/kg +and RIS significantly ($^{\&\&}p < 0.01$) compared to administration of FP 50 mg/kg alone (Fig. 3A). Repeated administration of ketamine substantially ($^{+}p < 0.05$) inccreased immobility time in contrast to saline treated rats. Concomitant administration of ketamine with RIS (0.5 mg/kg), FP (50 and 100 mg/kg) and FP 50 mg/kg + RIS) substantially ($F_{5, 32} = 6.925$, $p = 0.0003$; *$p < 0.05$; **$p < 0.01$) reversed ketamine augmented immobility in rats treated with ketamine (Fig. 3B).

Effects of FP on rats' performance on the Novel Object Recognition Test (NORT).

Repeated administration of FP substantially ($F_{5, 25} = 12.11$, $P < 0001$; *$p < 0.05$) increased exploration of a familiar object (Fig. 4A). Continuous injections of ketamine had no significant effects on the exploration of a familiar object in contrast to rats that received saline. Administration of ketamine with FP (25 – 100 mg/kg), RIS 0.5 mg/kg or FP 50 mg/kg + RIS significantly ($F_{5, 37} = 14.36$, $p < 0.0001$; ***$p < 0.001$) reduced exploration of familiar object by ketamine treated rats (Fig. 4B). Administration of FP RIS 0.5 mg/kg, (25 – 100 mg/kg) or FP 50 mg/kg + RIS significantly ($F_{5, 30} = 11.29$, $p < 0.0001$; **$p < 0.01$; ***$p < 0.001$) reduced exploration of novel object by rats treated with saline, while concurrent administration of RIS and FP 50 mg/kg substantially ($^{X}p < 0.05$) reduced novel object exploration in contrast with administration of RIS 0.5 mg/kg alone (Fig 4C). Repeated ketamine treatments markedly ($^{+++}p < 0.001$) decreased exploration of novel objects in contrast to the group treated with saline. Concurrent treatment with of FP, RIS and FP 50mg/kg + RIS substantially ($F_{5, 36} = 4.237$, $p=0.0047$; *$p<0.05$; **$p < 0.01$) increased exploration of the novel object in ketamine treated rats (Fig. 4D). Repeated treatments with FP (25 – 100 mg/kg), RIS 0.5 mg/kg, FP 50 mg/kg + Ris had no significant ($F_{3, 24} = 0.5002$, $p= 0.7723$) effects on the recognition index of control treated rats (Fig 4E). Rats treated with only ketamine markedly (+$p < 0.05$) decreased recognition index in contrast to the group that received saline. Concurrent treatments of ketamine with Ris 0.5 mg/kg, FP (25 – 100 mg/kg), FP 50 mg/kg + Ris significantly {($F_{5. 20} = 8.564$, $p < 0.0001$; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$) increased the recognition index (Fig, 4F). Recurrent oral administration of FP 50 mg/kg, FP 50 mg/kg + RIS significantly ($F_{3, 26} = 12.11$, $p < 0.0001$; *$p<0.05$; ***$p < 0.001$) reduced the discrimination index compared to those treated with saline. Concurrent administration of FP 50 mg/kg and RIS substantially ($^{XXX}p < 0.01$) reduced the discrimination index in contrast to administration of RIS 0.5 mg/kg alone (Fig. 4G). Recurrent ketamine treatments substantially ($^{+++}p < 0.001$) reduced the discrimination index in contrast to rats treated with only saline. Recurrent administration of ketamine with RIS 0.5 mg/kg, FP (25 – 100 mg/kg), FP 50 mg/kg + RIS significantly ($F_{5, 27} = 52.89$, $p < 0.0001$; ***$p < 0.001$) augmented the index of discrimination (Figure 4G).

Effects of FP on malondialdehyde (MDA) and glutathione (GSH) levels in the brain

Repeated administration of significantly ($F_{5, 23} = 16.14$, $p < 0.0001$; ***$p < 0.001$)
increased the brain's levels of glutathione. FP 50 mg/kg and Ris 0.5 mg/kg administered together significantly ($^{\&\&}p < 0.01$) reduced the brain's concentrations of GSH compared to administration of FP 50 mg/kg only (Figure 5A). Continuous injections of ketamine substantially ($^{+++}p < 0.001$) decreased the brain's concentrations of GSH, while co-administration of ketamine with FP, RIS and FP + RIS significantly ($F_{5, 24} = 19.17$, $p < 0.0001$; ***$p < 0.001$) elevated the brain concentrations of glutathione compared to animals that received ketamine only (Fig. 5B). Repeated administration of FP had no significant ($F_{5, 19} = 1.010$, $p = 0.4477$) effects on brain concentrations of malondialdehyde (MDA) (Fig. 5C); injections of ketamine

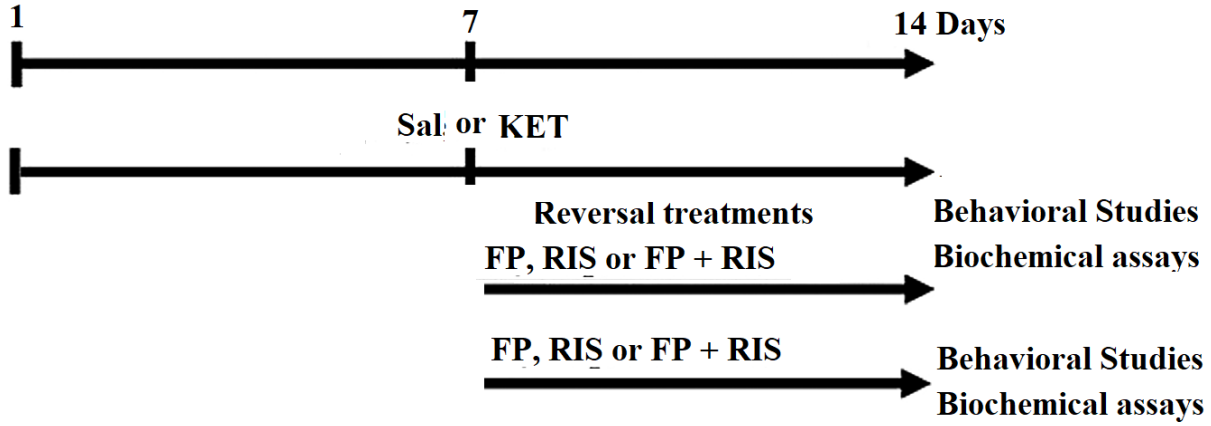


Figure 1: Treatment protocol: Sal = Saline solution, KET = Ketamine, FP = *Ficus platyphylla*, RIS = Risperidone

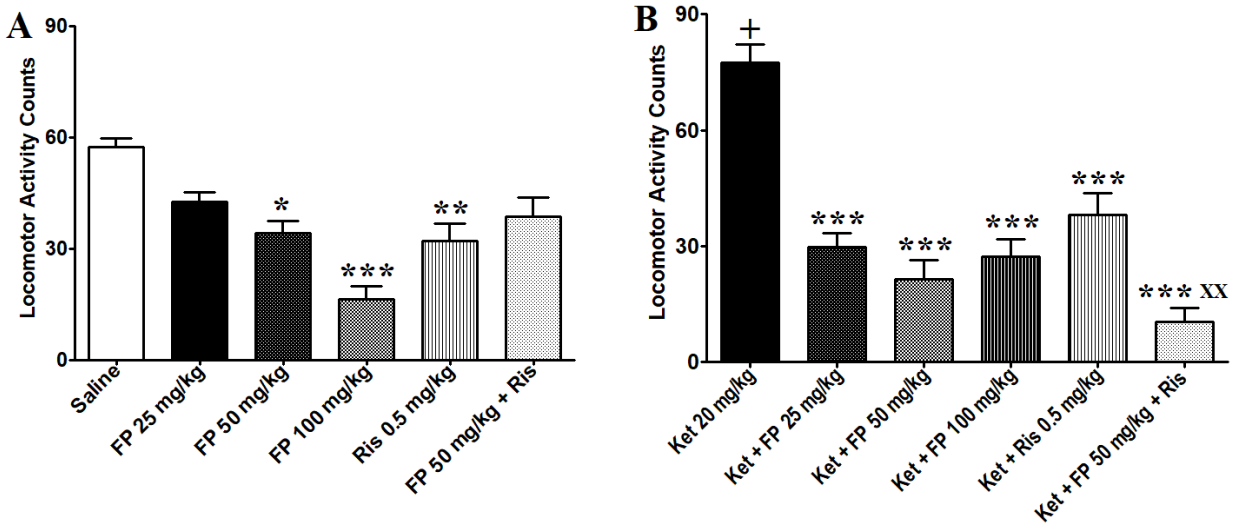


Figure 2: Effects of repeated administration of *Ficus platyhylla* on Locomotor activities **A)** Control rats {($F_{5, 31}$ = 9.700, p < 0.0001; *p < 0.05 (Saline vs FP 50 mg/kg, ***p < 0.001 (Saline vs FP 100 mg/kg), **P < 0.01 (Saline vs Ris 0.5 mg/kg)}. **B),** ketamine-enhanced locomotion {($F_{5, 20}$ = 29.40, p < 0.0001; +p < 0.05 (Saline vs Ket 20 mg/kg); ***p < 0.001 (Ket 20 mg/kg vs Ket + FP 25 mg/kg; Ket 20 mg/kg vs Ket + FP 50 mg/kg; Ket 20 mg/kg vs Ket + FP 100 mg/kg; Ket 20 mg/kg vs Ket + Ris 0.5 mg/kg; Ket 20 mg/kg vs Ket + FP 50 mg/kg + Ris); ^{XX}p < 0.01 (Ket + Ris 0.5 mg/kg vs Ket + FP 50 mg/kg + RiS)} in rats.

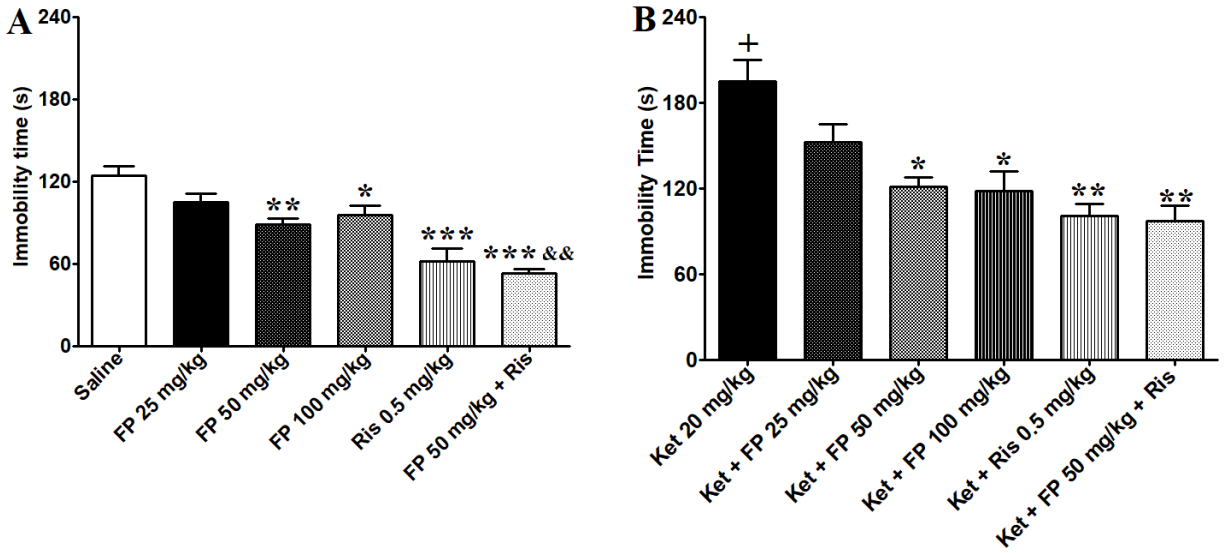
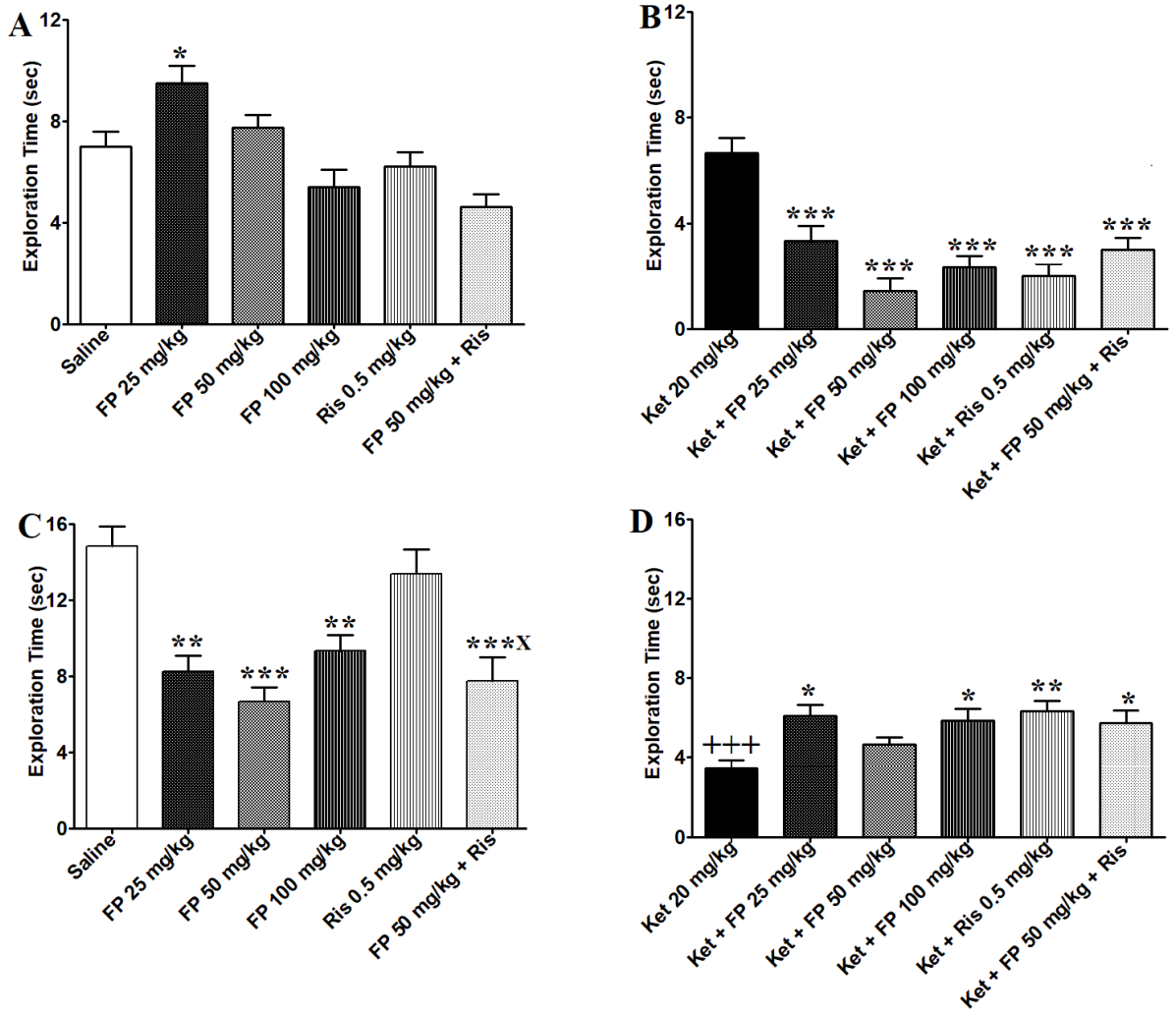


Figure 3: Effects of FP on ketamine-enhanced immobility in the forced swim test. A) Controlled rats {(F5, 31 =15.59, ***p < 0.0001; *p < 0.05 (Saline vs FP 100 mg/kg), **p < 0.01 (Saline vs FP 50 mg/kg), ***p < 0.001 (Saline vs Ris 0.5 mg/kg; Saline vs FP 50 mg/kg + Ris), &&p < 0.01 (FP 50 mg/kg vs FP 50 mg/kg + Ris). B) ketamine-enhanced immobility in rats {(F 5, 32 = 6.925, p = 0.0003; +p < 0.05 (Ket 20 mg/kg vs Saline); *p < 0.05 (Ket 20 mg/kg vs Ket + FP 50 mg/kg; Ket 20 mg/kg vs Ket + FP 100 mg/kg); **p < 0.01 (Ket 20 mg/kg vs Ket + Ris 0.5 mg/kg; Ket 20 mg/kg vs Ket + FP 50 mg/kg + Ris)}.



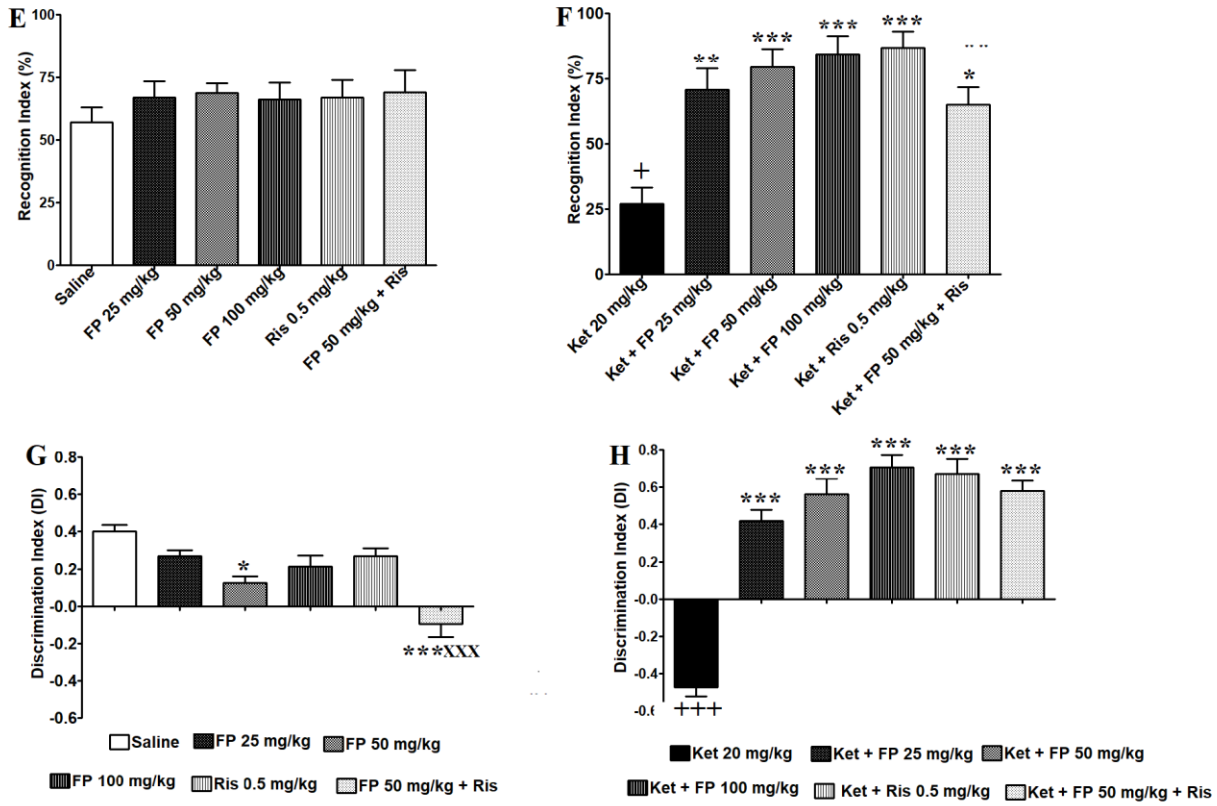


Figure 4: Effects of FP on novel object recognition test (NORT) in rats. **A)** Familiar objects exploration by controlled rats {($F_{5, 25}$ =12.11, P<0001; *p < 0.05 (Saline vs FP 50 mg/kg)}. **B)** Exploration of familiar object induced by ketamine {($F_{5, 37}$=14.36, p < 0.0001; ***p <0.001 (Ket 20 mg/kg vs Ket + FP 25 mg/kg; Ket 20 mg/kg vs Ket + FP 50 mg/kg; Ket 20 mg/kg vs Ket + FP 100 mg/kg; Ket 20 mg/kg vs Ket + Ris 0.5 mg/kg; Ket 20 mg/kg vs Ket + FP 50 mg/kg + Ris)} **C)** Novel object exploration by controlled rats {($F_{5, 30}$ =11.29, p < 0.0001; **p < 0.01 (Saline vs FP 25 mg/kg; Saline vs FP 100 mg/kg); ***p < 0.001 (Saline vs FP 50 mg/kg; Saline vs FP 50 mg/kg + Ris0; ^{x}p < 0.05 (Ris 0.5 mg/kg vs FP 50 mg/kg + Ris)}. **D)** exploration of novel object induced by ketamine {(F5, 36 = 4.237, p=0.0047; +++p < 0.001 (Saline vs Ket 20 mg/kg); *p<0.05 (Ket 20 mg/kg vs Ket + FP 25 mg/kg; Ket 20 mg/kg vs Ket + FP 100 mg/kg; Ket 20 mg/kg vs Ket + FP 50 mg/kg + Ris); **p < 0.01 (Ket 20 mg/kg vs Ket + Ris 0.5 mg/kg)}. **E)** Index of recognition of control treated rats (F3, 24 = 0.5002, p= 0.7723). **F)** Index of recognition of ketamine treated rats {($F_{5, 20}$ = 8.564, p < 0.0001; +p < 0.05 (Saline vs Ket 20 mg/kg); **p < 0.01 (Ket 20 mg/kg vs Ket + FP 25 mg/kg); ***p < 0.001 (Ket 20 mg/kg vs Ket + FP 50 mg/kg; Ket 20 mg/kg vs Ket + FP 100 mg/kg; Ket 20 mg/kg vs Ket + Ris 0.5 mg/kg); *p < 0.05 (Ket 20 mg/kg vs Ket + FP 50 mg/kg + Ris)}. **G)** Index of discrimination of controlled rats {(F3, 26 = 12.11, p < 0.0001; *p<0.05 (Saline vs FP 50 mg/kg); ***p < 0.001 (Saline vs FP 50 mg/kg + Ris) **H)** Index of discrimination of ketamine treated rats {($F_{5, 27}$ = 52.89, p < 0.0001; +++p < 0.001 (Saline vs Ket 20 mg/kg); ***p < 0.001 (Ket 20 mg/kg vs Ket + FP 25 mg/kg; Ket 20 mg/kg vs Ket + FP 50 mg/kg, Ket 20 mg/kg vs Ket + FP 100 mg/kg, Ket 20 mg/kg vs Ket + Ris 0.5 mg/kg, Ket 20 mg/kg vs Ket + FP 50 mg/kg + Ris)}.

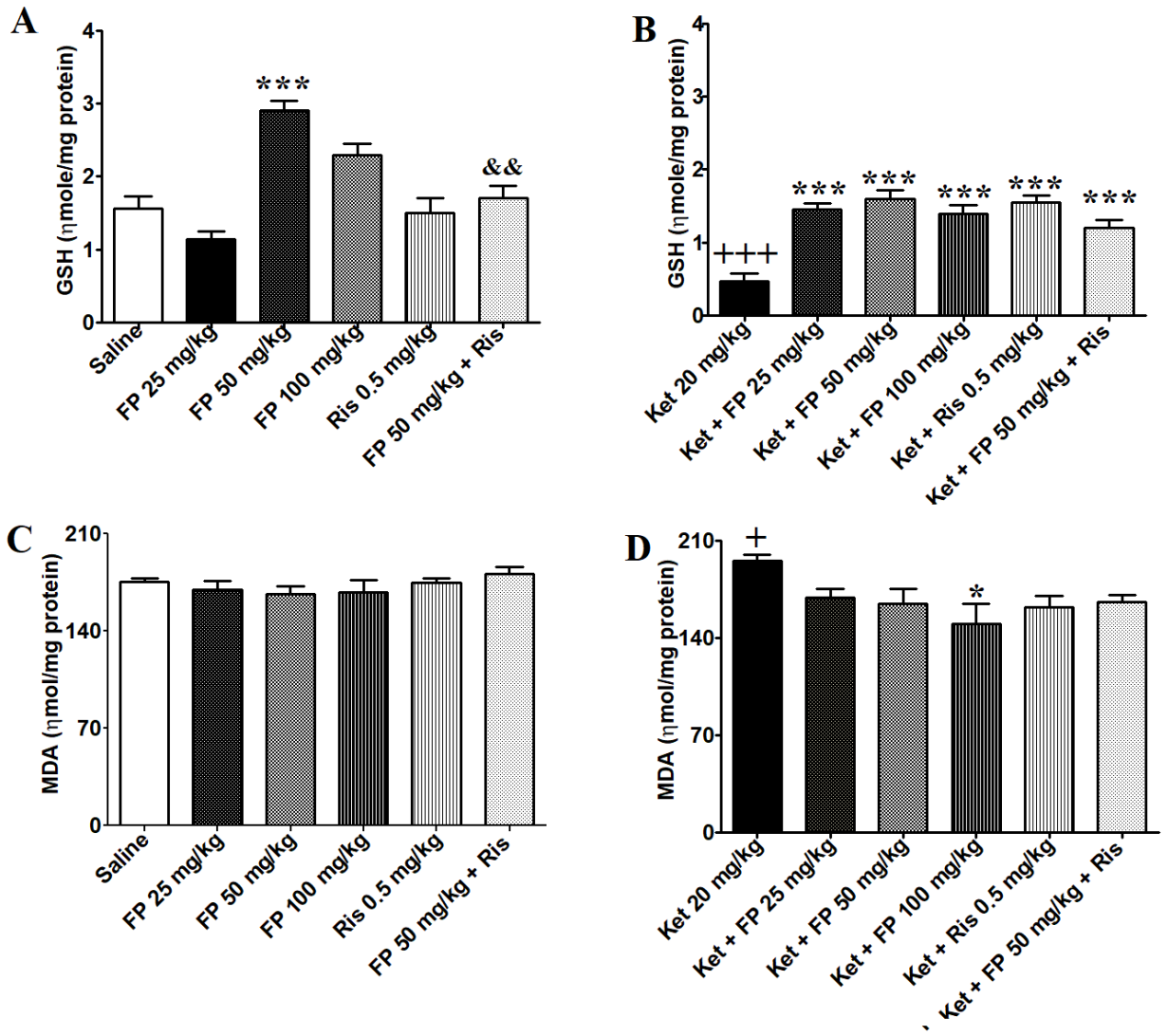


Figure 5: Effects of FP on oxidative stress markers in brains of controlled and ketamine treated rats. (A) Levels of glutathione (GSH) concentrations in controlled treated rats {(F5, 23 =16.14, p < 0.0001; P < 0.001 (Saline vs FP 50 mg/kg); &&p < 0.01 (FP 50 mg/kg vs FP 50 mg/kg + Ris). (B) Levels of glutathione (GSH) in ketamine treated rats {(F5, 24 = 19.17, p < 0.0001; $^{+++}$p < 0.001 (Saline vs Ket 20 mg/kg); ***p < 0.001 (Ket 20 mg/kg vs Ket + FP 25 mg/kg, Ket 20 mg/kg vs Ket + FP 50 mg/kg, Ket 20 mg/kg vs Ket + FP 100 mg/kg, Ket 20 mg/kg vs Ket + Ris 0.5 mg/kg, Ket 20 mg/kg vs Ket + FP 50 mg/kg + Ris). (C) Malondialdehyde (MDA) levels in controlled treated rats ($F_{5, 19}$ =1.010, p = 0.4477); (D) MDA levels in ketamine treated rats {($F_{5, 20}$ =3.506, p = 0.0268; +p < 0.05 (Saline vs Ket 20 mg/kg); *p < 0.05 (Ket 20 mg/kg vs Ket + FP 100 mg/kg)}.

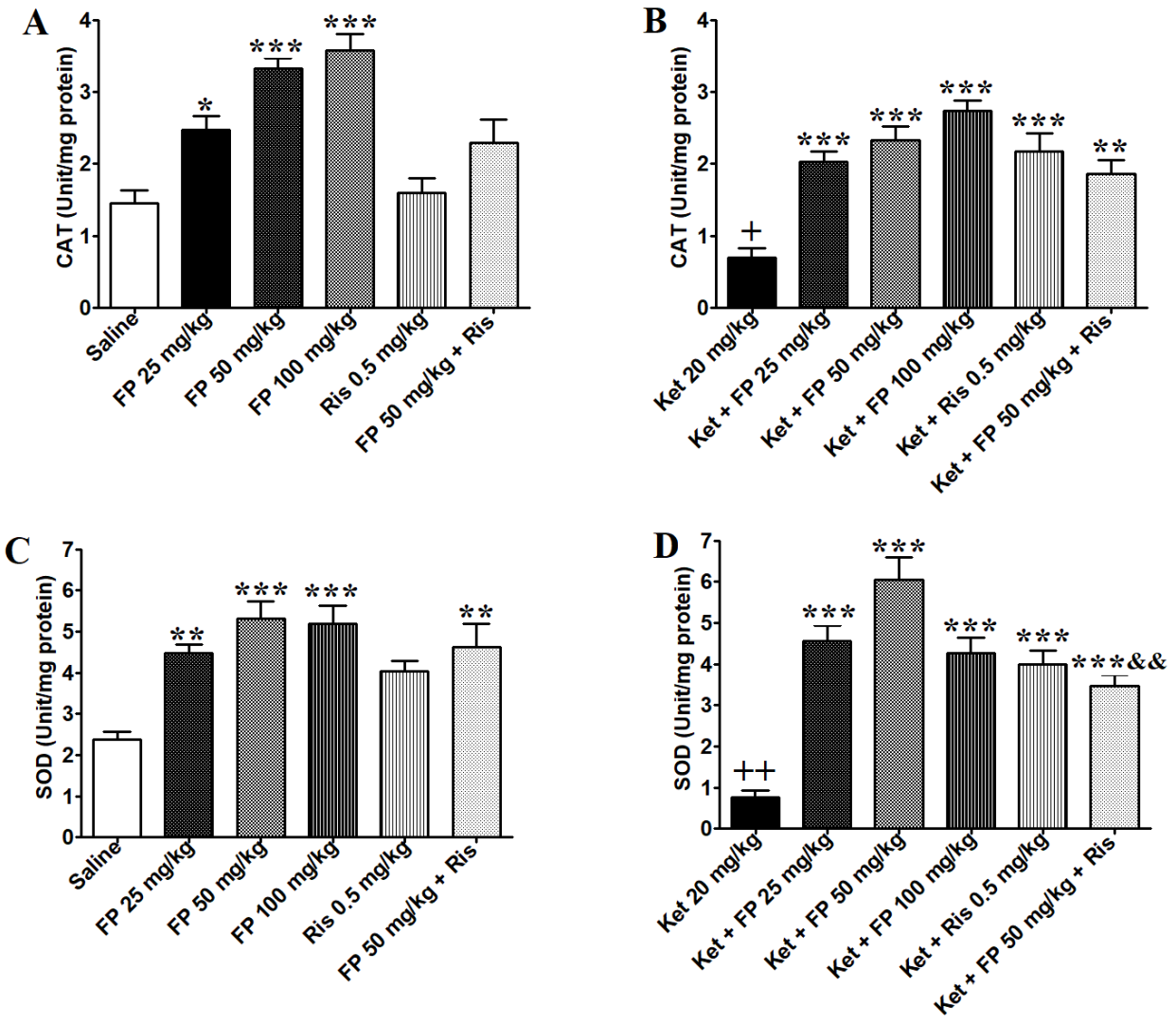


Figure 6: Effects of FP on oxidative stress biomarkers in the brains of controlled and ketamine treated rats. (A) Catalase (CAT) activity in brains of control-treated rats {($F_{5, 26}$ =17.55, $p < 0.0001$; *$p < 0.05$ (Saline vs FP 25 mg/kg); ***$p < 0.001$ (Saline vs FP 50 mg/kg, Saline vs FP 100 mg/kg)}. (B) CAT activity in ketamine treated rats {($F_{5, 22}$ = 18.11, $p < 0.0001$; +$p < 0.05$ (Saline vs Ket 20 mg/kg); **$p < 0.01$ (Ket 20 mg/kg vs Ket + FP 50 mg/kg + Ris); ***$p < 0.001$ (Ket 20 mg/kg vs Ket + FP 25 mg/kg; Ket 20 mg/kg vs Ket + FP 50 mg/kg; Ket 20 mg/kg vs Ket + FP 100 mg/kg; Ket 20 mg/kg vs Ket + Ris 0.5 mg/kg)}. (C) Activity of superoxide dismutase (SOD) in brains of control-treated rats ($F_{5, 21}$ =9.801, $p = 0.0002$; **$p < 0.01$ (Saline vs FP 25 mg/kg; Saline vs FP 50 mg/kg + Ris); ***$p < 0.001$ (Saline vs FP 50 mg/kg; Saline vs FP 100 mg/kg)}. (D) Activity of SOD in brains of ketamine treated rats {($F_{5, 22}$ = 35.43, $p < 0.0001$; ++$p < 0.01$ (Saline vs Ket 20 mg/kg); ***$p < 0.001$ (Ket 20 mg/kg vs Ket + FP 25 mg/kg; Ket 20 mg/kg vs Ket + FP 50 mg/kg; Ket 20 mg/kg vs Ket + FP 100 mg/kg; Ket 20 mg/kg vs Ket + Ris 0.5 mg/kg; Ket 20 mg/kg vs Ket + FP 50 mg/kg + Ris); $^{\&\&}p < 0.01$ (Ket + FP 50 mg/kg vs Ket + FP 50 mg/kg + Ris).

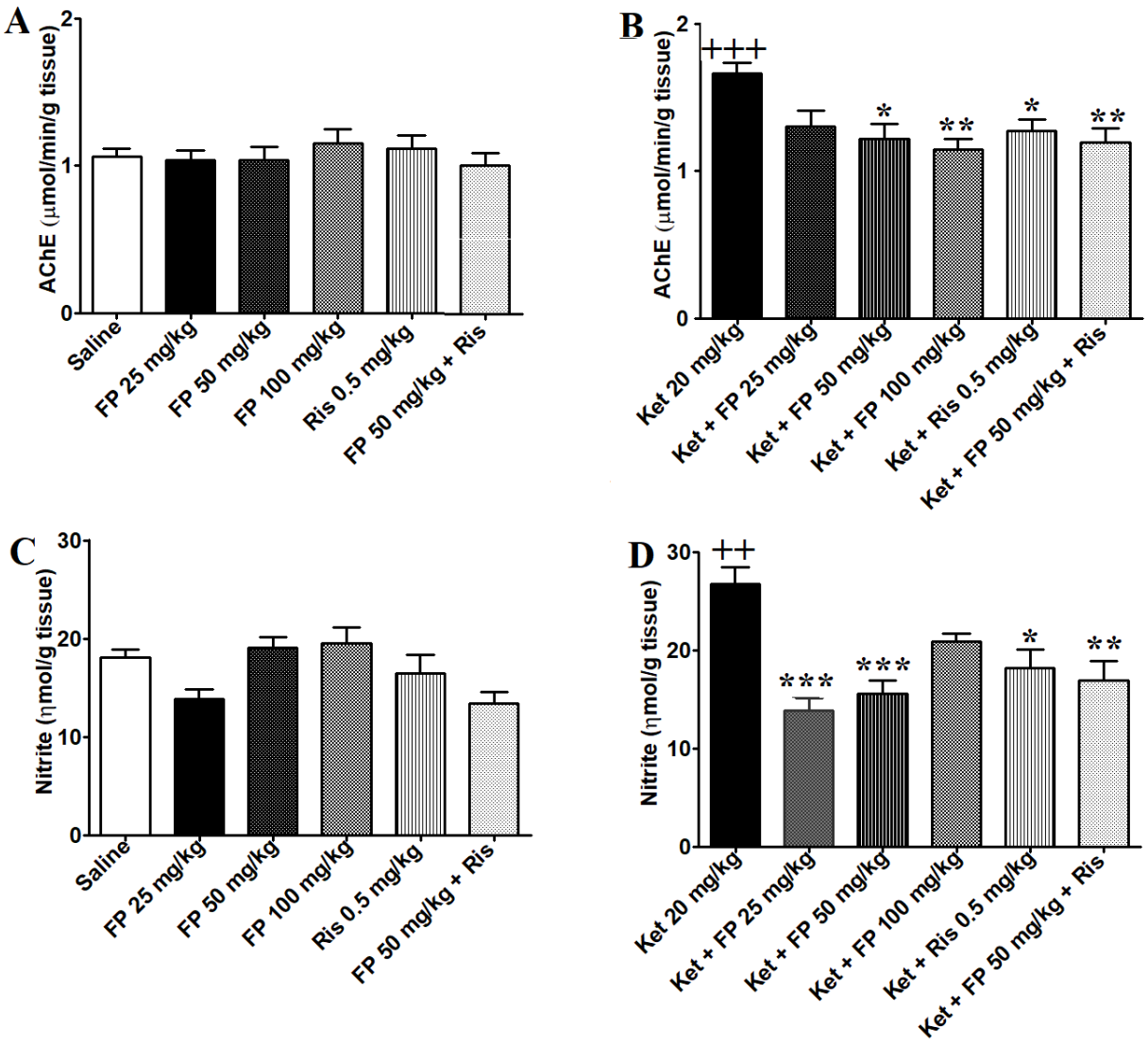


Figure 7: Effects FP on activity of acetylcholinesterase (AChE) in rats' brains (A) Controlled treated rats (F5, 23 = 0.4839, p = 0.7837) (B) ketamine treated rats {(F5, 26 = 5.636, p = 0.0019; +++p < 0.001 (Saline vs Ket 20 mg/kg); *p < 0.05 (Ket 20 mg/kg vs Ket + FP 50 mg/kg; Ket 20 mg/kg vs Ket + Ris 0.5 mg/kg; **p < 0.01 (Ket 20 mg/kg vs Ket + FP 100 mg/kg; Ket 20 mg/kg vs Ket + FP 50 mg/kg + Ris)}; and nitrite concentrations (C) Controlled treated rats (F5, 22 = 3.708, p = 0.0188); (D) ketamine-treated mice {(F5, 26 = 9.369, p < 0.0001; ++p < 0.01 (Saline vs Ket 20 mg/kg); *p < 0.05 (Ket 20 mg/kg vs Ket + Ris 0.5 mg/kg); **p < 0.01 (Ket 20 mg/kg vs Ket + FP 50 mg/kg + Ris); ***p < 0.001 (Ket 20 mg/kg vs Ket + FP 25 mg/kg; Ket 20 mg/kg vs Ket + FP 50 mg/kg)}.

Table 1: Binding affinities of major bioactive compounds from FP to some acknowledged target proteins for pharmacotherapy of schizophrenia

S/N	Protein	PDB ID	Compound/ligand	Binding Affinity (Kcal/mol)
1	Serotonin receptor 5HT1a	7E2Y	11-octadecanoic acid	-5.2
2	Serotonin receptor 5HT1a	7E2Y	Pentadecanoic acid	-3.9
3	Serotonin receptor 5HT1a	7E2Y	2, 3-dimethylphenylisothiocyanate	-4.4
4	Serotonin receptor 5HT2b	5TVN	11-octadecanoic acid	-4.5
5	Serotonin receptor 5HT2b	5TVN	Pentadecanoic acid	-4.4
6	Serotonin receptor 5HT2b	5TVN	2, 3-dimethylphenylisothiocyanate	-5.2
7	Serotonin receptor 5HT7	7XTC	11-octadecanoic acid	-5.7
8	Serotonin receptor 5HT7	7XTC	Penta decanoic acid	-4.9
9	Serotonin receptor 5HT7	7XTC	2, 3-dimethylphenylisothiocyanate	-4.7
10	Metabotropic glutamate receptor mGlu3	7WI6	11-octadecanoic acid	-2.8
11	Metabotropic glutamate receptor mGlu3	7WI6	Pentadecanoic acid	-3.7
12	Metabotropic glutamate receptor mGlu3	7WI6	2, 3-dimethylphenylisothiocyanate	-4.2
13	Metabotropic glutamate receptor mGlu5	6FFI	11-octadecanoic acid	-4.6
14	Metabotropic glutamate receptor mGlu5	6FFI	Pentadecanoic acid	-4.6
15	Metabotropic glutamate receptor mGlu5	6FFI	2, 3-dimethylphenylisothiocyanate	-4.3
16	Phosphodiesterase PDE10A	5XUI	11-octadecanoic acid	-4.3
17	Phosphodiesterase PDE10A	5XUI	Pentadecanoic acid	-4.0
18	Phosphodiesterase PDE10A	5XUI	2, 3-dimethylphenylisothiocyanate	-5.4
19	Dopamine receptor D_2	6VMS	11-octadecanoic acid	-4.8
20	Dopamine receptor D_2	6VMS	Pentadecanoic acid	-4.2
21	Dopamine receptor D_2	6VMS	2, 3-dimethylphenylisothiocyanate	-5.1

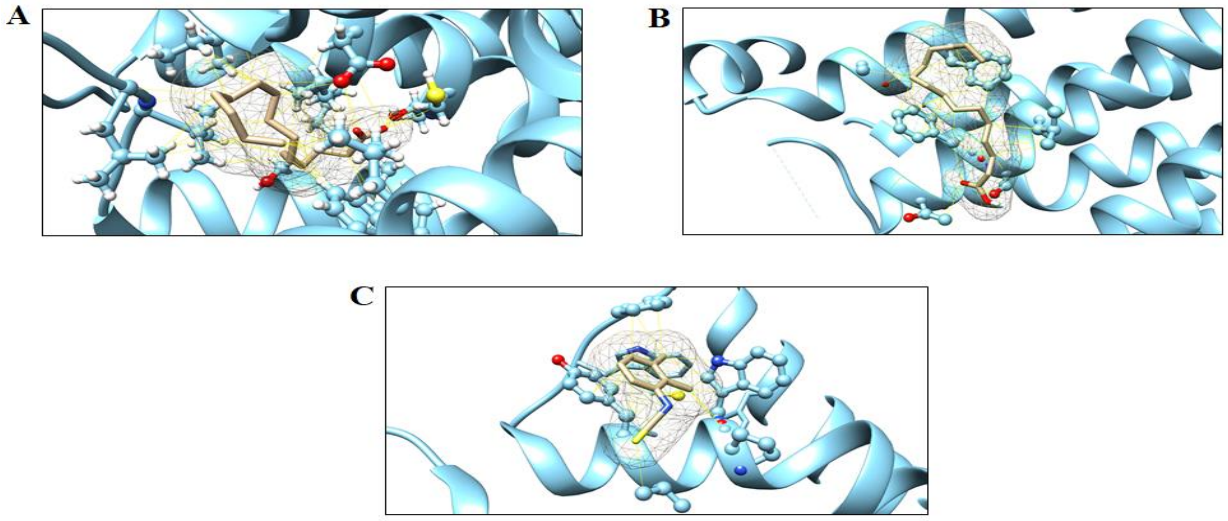


Figure 8: Molecular interactions between (A) Serotonin receptor $5HT_7$ and 11-octadecanoic acid, (B) Metabotropic glutamate receptor mGlu5 and pentadecanoic acid, (C) Dopamine (D_2) receptor and 2, 3-dimethylphenylisothiocyanate. The ligands are presented in brown stick, while the interacting atoms are presented in blue ball and stick presentations.

substantially ($^{+}p < 0.05$) elevated the levels of MDA in the brain in contrast to rats treated with saline. Co-administration of ketamine with FP, RIS and FP + RIS significantly ($F_{5, 20}$ =3.506, p = 0.0268; *p < 0.05) reduced the brain's levels of MDA (Figure 5D).

Effects of FP on the activities of Superoxide Dismutase (SOD) and Catalase (CAT) in rat brains

Repeated administration of FP significantly ($F_{5, 26}$ =17.55, p < 0.0001; *p < 0.05; ***p < 0.001) elevated activity of CAT in rats' brains in contrast to saline-treated rats (Fig. 6A). Injections of ketamine markedly ($^{+}p < 0.05$) decreased CAT activity in contrast to saline-treated rats. Co-administration of ketamine with FP, RIS and FP + RIS significantly ($F_{5, 22}$ = 18.11, p < 0.0001; **p < 0.01; ***p < 0.001) increased CAT activity related to rats that received only ketamine. Repeated administration of FP, RIS and FP + RIS significantly ($F_{5, 21}$ =9.801, p = 0.0002; **p < 0.01; ***p < 0.001) augmented SOD activity in contrast to saline-treated rats (Fig. 6C). Injections of ketamine significantly ($^{++}p < 0.01$) reduced brain activity of SOD compared to rats that were treated with physiological saline. Co-administration of ketamine with FP, RIS and FP + RIS substantially ($F_{5, 22}$ = 35.43, p < 0.0001; ***p < 0.001) elevated activity of SOD in rats' brain compared to rats that received only ketamine. Co-administration of ketamine and FP + RIS substantially ($^{\&\&}p < 0.01$) reduced the effects of FP 50 mg/kg without significant effects on RIS (Figure 6D).

Effects of FP on brain acetylcholinesterase (AChE) activities and nitric oxide (NO) concentrations in rats

Repeated administration of FP, RIS and FP + RIS had no significant ($F_{5, 23}$ = 0.4839, p = 0.7837) effects on AChE activity in rats' brains (Figure 7A). Treatment with only ketamine substantially ($^{+++}p < 0.001$) elevated the activity of AChE in rats' brains, in contrast to rats that received only saline. Administration of FP, RIS and FP +RIS significantly ($F_{5, 26}$ = 5.636, p = 0.0019; *p < 0.05; **p < 0.01) reduced activity of AChE in rats' brains compared to rats that received only ketamine. Treatment with RIS and FP + RIS significantly ($F_{5, 22}$ = 3.708, p = 0.0188) demonstrated effects on brain FP concentrations of NO. Repeated treatment with ketamine substantially ($^{++}p < 0.01$) elevated NO concentrations compared to rats treated with saline. Administration of FP, RIS and FP + RIS substantially ($F_{5, 26}$ = 9.369, p < 0.0001; *p < 0.05; **p < 0.01; ***p < 0.001) decreased NO concentrations in the brain compared to ketamine treated rats (Figure 7D).

Molecular Interactions

Table 1 shows a summary of the binding affinities of the major bioactive compounds from FP, including pentadecanoic acid, 2, 3-dimethylphenylisothiocyanate and 11-octadecenoic acid to acknowledged drug targets for the management of schizophrenia. These compounds demonstrated binding affinities ranging from -2.8 to -5.7 Kcal/mol on serotonin receptors, metabotropic glutamate receptors, phosphodiesterase, and dopamine receptor**s** with fairly strong molecular interactions. Molecular interactions of each of the three compounds with each of the receptors revealed numerous non-bonded interactions (Figure 8A, B & C). For instance, 11-octadecanoic acid formed one hydrogen bond with serotonin receptor 5HT7, involving the H30 hydrogen atom of the ligand and the OG1 atom of THR167. The 11-octadecanoic acid had contact with 70 atoms within the van der Waals interacting distance of -0.4 Å. Similarly, binding between metabotropic glutamate receptor mGlu5 and pentadecanoic acid is mediated by one hydrogen bond and 40 van der Waals interactions. No hydrogen bond was involved in Dopamine receptor D_2 interaction with 2, 3-dimethylphenylisothiocyanate; however, 23 Vander Waals were recoded. These interactions between these ligands and their respective receptors appear to be what is holding the ligands in their binding sites and are attributed to the strong binding affinities.

DISCUSSION

The present study revealed that extracts of *Ficus platyphylla* (FP) reversed ketamine-induced schizophrenic-like behaviors in rats via modulation of cholinergic, nitrergic and oxidative pathways. Twenty bioactive compounds were identified by GC–MS analysis of FP, with the main components being pentadecanoic acid, 2, 3-dimethylphenylisothiocyanate and 11-octadecenoic acid. *In silico* molecular dicking studies demonstrated binding affinities of these major bioactive compounds from FP to acknowledged macromolecular drug targets for the management of schizophrenia, including dopamine, serotonin and metabotropic glutamate receptors, and phosphodiesterase [55–59] with fairly strong molecular interactions.

Ketamine challenge is a suitable animal model for evaluating cognitive, negative and positive symptoms, age of onset, cholinergic, dopaminergic, GABAergic and nitrergic dysfunctions, oxidative stress, abnormal cortical alterations and functional dysconnectivity observed in schizophrenia [34, 60–61].

Ketamine induces schizophrenia-like behaviors, including hyperlocomotion, sensorimotor gating, and working memory deficiencies [62]. Repeated exposure to sub-anaesthetic doses of ketamine induces positive and negative phenotypes: working memory impairments, sensorimotor gating, and hyperlocomotion; prepulse inhibition (PPI) reduces acoustic startle responses' sensorimotor gating, impairment of working memory and increased ambulatory activity [33. 63–67], thus confirming that NMDA receptor dysfunction has a role in the development of schizophrenia. Moreover, Glutamate release at the prefrontal cortex (PFC) is increased by blocking the NMDA receptor [68], and pyramidal neurons become more excitable [69]. The capacity to restore PFC functions may offer potential treatment strategies in addition to behavior testing, as PFC dysfunction has been linked to behaviors associated with schizophrenia [70].

Ketamine inhibits gamma-aminobutyric acid (GABA) interneurons' NMDA receptors and reduces GABAergic

inhibitory tone [71–73], resulting in disinhibition of excitatory systems [68, 72, 74] and increased PFC's dopamine release, leading to psychotic disorders [33, 68, 74 – 78] and hyperlocomotion [74]. Ketamine-induced hyperlocomotion resulting from blocking GABAergic neurons' NMDA receptors in the subcortical and limbic areas of the brain is an acceptable model for screening new substances that may have antipsychotic effects in rodents [34, 61]. Hyperlocomotion connotes the positive symptoms of schizophrenia and is connected to augmented limbic striatal circuits' neural activity [79 – 80]. Compounds with antipsychotic properties attenuate ketamine-enhanced hyperlocomotion [34, 61]. In this study, FP, RIS and FP + RIS significantly reversed ketamine enhanced hyperlocomotion, suggesting antipsychotic-like activity in rats. The concomitant administration of both FP and RIS to ketamine treated rats significantly potentiated the effects of RIS on ketamine enhanced hyperlocomotion, indicating that FP might improve RIS's ability to treat positive symptoms of schizophrenia. In comparison to the saline-treated group, FP and RIS markedly reduced locomotor activity in the control rats.

Depressive symptoms, which have long been identified as a separate symptom domain of schizophrenia, and can arise at any point throughout illness, are frequently present in conjunction with the illness [81]. Depressive symptoms in schizophrenia may be psychological in nature, or they could be a fundamental symptom of the psychotic illness that eventually manifests as negative symptoms [81]. The brain mechanism underlying depression in schizophrenia is still fundamentally unknown. Studies have shown that neuroinflammation plays a part in schizophrenia and depression by impairing neuronal calcium activity in the thalamic nuclei and cortico-limbic circuit. [82–83]. Research on schizophrenia and depression in animals should yield important insights for clinical diagnosis and treatments [83]. The effects of FP on ketamine-enhanced depressed behavior, a negative sign of schizophrenia, were investigated using FST, an animal model for depression. Repeated application of ketamine in this study significantly enhanced immobility in FST. FP and RIS reduced the ketamine-treated rats' immobility period, which improved their depressive-like behaviour. Furthermore, in controlled rats that received FP and RIS, only significantly decreased immobility time in FST and oral administration of FP and RIS together markedly enhanced the effects of FP 50 mg/kg, indicating that RIS might improve FP's effectiveness in treating negative symptoms of schizophrenia.

Here, NORT was employed to evaluate how FP affected cognitive symptoms that are often associated with schizophrenic disorders. This test is used for evaluating various aspects of learning and memory, including working, both long-term and short-term memory, which are believed to be impaired in schizophrenia [41, 84]. Several studies have reported impairment of memory and learning after long-term ketamine infusions, including mechanisms linked to blockage of the α-7nACh receptor [85], an increase of AChE enzyme activity [80], and the release of proinflammatory cytokines [86 – 88]. In the present study, ketamine significantly decreased memory performance in NORT akin to previous studies [33, 34, 89]. Given that FP can correct ketamine-induced memory impairments, it suggests that it may be useful in treating cognitive abnormalities in psychotic patients.

Dysfunctions in central cholinergic, dopaminergic, glutaminergic and serotonergic pathways [80] as well as nitrergic and oxidative alterations are implicated in the pathogenesis of schizophrenia [90–91]. Studies have proven that ketamine escalates central synaptic cortical AChE enzymatic activity, reduces brain concentrations of ACh and cholinergic neurotransmissions culminating in ketamine-induced memory impairment [80]. FP reversed the elevated ketamine-induced AChE activity and enhanced cholinergic neurotransmissions to ameliorate memory deficit in this study.

Nitrergic and oxidative alterations are linked to the development of numerous neuropsychiatric disorders, including schizophrenia [33, 90]., Consequently, the suppression of oxidative stress and nitrergic pathways is are new therapeutic methodology for alleviation of neuronal damage ad altered signal processes in schizophrenic brains [92–93]. Nitric oxide (NO) is involved in the storage, absorption, and release of neurotransmitters and mediators, including acetylcholine, GABA, glutamate, glycine, noradrenaline and taurine, as well as peroxidation and reactive oxidative stress [94]. Investigations revealed substantial alterations in NO levels in brain structure and fluids of schizophrenic patients that culminate in neurodevelopmental changes associated with the disease, and antipsychotics can change the brain's NO metabolism by suppressing the activity of nNOS [93, 95]. Studies have demonstrated that nitric oxide levels are elevated in post-mortem brain tissue [96–98] and in plasma [91, 99] of schizophrenics, which substantiates the relationship between schizophrenia and NO synthase activity. In this investigation, a sub-aesthetic dosage of ketamine administered repeatedly increased the brain levels of nitrite in rats, which were reversed by FP and RIS co-administration. Our findings corroborate earlier studies demonstrating that treatments with clozapine and risperidone reversed the increased nitrite levels in mice's whole and specific brain regions [33, 34, 61]. There were no significant effects of FP and RIS on treatments in the control-treated rats,

One prevalent pathogenic route that underlies the pathophysiology of schizophrenia is oxidative stress. High oxygen consumption can lead to oxidative stress in the brain and elevated levels of polyunsaturated fatty acids in the membrane that is susceptible to lipid peroxidation, a low antioxidant defence system and activity that is redox regulated at glutamate and dopamine receptors [90, 100]. Lipid peroxidation, which results in neuronal degeneration and changes in neurotransmission, is caused by ROS and RNS molecules that alter D2 and N-methyl-D-aspartate (NMDA) receptors to modulate dopaminergic and glutamatergic neurotransmissions [33, 100–102], which makes them candidates for the treatment of negative and cognitive

symptoms associated with schizophrenia [84] believed to be connected with deceased antioxidant defense systems and increased oxidative stress [33]. To evaluate the effects of FP on the antioxidant defence status of the brain in rats treated with ketamine, we measured the levels of GSH and MDA as well as the activities of CAT and SOD. Continuous intraperitoneal injections of sub-anaesthetic doses of ketamine markedly elevated MDA, decreased GSH, and decreased CAT and SOD activity [61]. FP raised GSH levels as well as SOD and CAT activities, but MDA concentrations were reduced to ameliorate oxidative stress in ketamine treated rats, which supports the therapeutic benefits of FP in the management of schizophrenia.

CONCLUSION

The results showed that *Ficus platyphylla* modulates cholinergic, nitrergic, and oxidative pathways to correct schizophrenic-like symptoms in rats produced by ketamine. The major bioactive compounds in FP demonstrated binding affinities for recognized macromolecular drug targets for the management of schizophrenia including dopamine, serotonin and metabotropic glutamate receptors, and phosphodiestrase. These findings also suggest that co-administration of *Ficus platyphylla* extracts may improve risperidone's effectiveness in treating cognitive, negative, and positive symptoms of schizophrenia.

ABBREVIATIONS

Ach, Acetylcholine; AChE, Acetylcholinesterase; CAT, Catalase; CNS, Central nervous system; DTNB, 5, 5–dithiobis-(2-nitrobenzoic acid); FP, *Ficus platyphylla;* Forced swim test (FST); GABA, γ–aminobutyric acid; GC-MS; Gas Chromatography-Mass Spectrometry; GSH, Glutathione; GSS, Glutathione-S-synthase; HPLC, High Performance Liquid Chromatography; *KET*, Ketamine; MDA, Malondialdehyde; NO, Nitric oxide; NOS, Nitric oxide synthase; NMDA, N-methyl D-aspatate; NORT, Novel object recognition test; OFT, Open-field test; PFC, Prefrontal cortex; PPI, Prepulse inhibition; RIS, Risperidone; RNS, Reactive nitrogen species; ROS, Reactive oxygen species; SOD, Superoxide dismutase; TBA, Thiobarbituric acid; TCA, Trichloroacetic acid.

ACKNOWLEDGMENT

The authors thank the staff of the Department of Pharmacology and Toxicology, Kaduna State University, for their technical support.

AUTHORS' CONTRIBUTION

BAC: conceptualized and designed experiments, carried out experiments, analyzed experimental data, and drafted the manuscript. **ZA***:* conducted experiments, **MAM***:* conducted experiments, **PMW**: carried out experiments and analyzed experimental data, **AM***:* participated in experiments, analyzed experimental data. **ZL**: carried out experiments and analyzed experimental data. **SA***:* supervised*,* reviewed, and revised the Manuscript and analyzed experimental data*.*

CONFLICT OF INTEREST

There were no possible conflicts of interest during the research process.

FUNDING

This research was financed by the Tertiary Education Trust Fund (TETFund) Nigeria (TETF/DR&D/CE/UNI/KADUNA/IBR/2022/VOL.1; Batch 5) and Kaduna State University (KASU).

REFERENCES

1. Chindo BA, Adzu B, Yahaya TY, Gamaniel KS. Ketamine enhanced immobility in forced swim test: A possible animal model for the negative symptoms of schizophrenia. Progress in Neuropsychopharmacology and Biological Psychiatry, 38, 2012a:310–316. https://doi.org/10.1016/j.pnpbp.2012.04.018
2. Hilker R, Helenius D, Fagerlund B, Skytthe A, Christensen K, Werge TM, Nordentoft M, Glenthøj B, Heritability of schizophrenia and schizophrenia spectrum based on the nationwide Danish Twin Register. Biological Psychiatry, 83(6), 2018:492–498. https://doi.org/10.1016/j.biopsych.2017.08.017
3. Mueser KT, McGurk SR. Schizophrenia. Lancet, 363, 2004:2063–2072. https://doi.org/10.1016/S0140-6736 (04)16458-1
4. Marde SR, Cannon TD. Schizophrenia. New England Journal of Medicine, 381(18), 2019: 1753–1761. https://doi.org/10.1056/NEJMra1808803
5. Harvey PD, Koren D, Reichenberg A, Bowie CR, Negative symptoms and cognitive deficits: what is the nature of their relationship? Schizophrenia Bulletin, 32, 2006: 250–258. d https://doi.org/10.1093/schbul/sbj011.
6. Heckers S. Neuropathology of Schizophrenia: Cortex, thalamus, basal Ganglia, and neurotransmitter-specific projection systems. Schizophrenia Bulletin, 23, 1997: 403 – 421. https://doi.org/10.1093/schbul/23.3.403
7. Goldman-Rakic PS, Selemon LD. Functional and anatomical aspects of prefrontal pathology in Schizophrenia. Schizophrenia Bulletin, 23, 1997: 437–458. https://doi.org/10.1093/schbul/23.3.437.
8. Crismon MI, Dorson PG. Schizophrenia. In: *Pharmacotherapy: A Pathophysiologic Approach* (Dipiro J. T., Talbert R. L., Yee G. C., Matzke G. R., Wells, B. G., and Posey, M. L., eds) 5th edition, McGraw-Hill Co. Inc. pp., 2002: 1219 – 1242.
9. Andreasen NC. Schizophrenia; The fundamental questions. Brain Research Reviews, 31, 2000: 106 – 112. https://doi.org/10.1016/s0165-0173.
10. Brown AS, Schaefer CA, Wyatt RJ. Maternal exposure to respiratory infections and adult schizophrenia spectrum disorders: A prospective

birth cohot study. Schizophrenia Bulletin, 26, 2000): 287 – 296. https://doi.org/10.1093/oxfordjournals.schbul.a033453

11. Seidman LJ, Buka SL, Goldstein JM. The relationship of prenatal and perinatal complications of cognitive functioning at age 7 in New England cohorts of the national collaborative prenatal project. Schizophrenia Bulletin, 26, 2000: 309 – 322. https://doi.org/10.1093/oxfordjournals.schbul.a033455
12. Clare AW. Psychological Medicine. In: Clinical Medicine for Medical Students and Doctors, 2nd edition (Kumar, P. G, and Clark, M. C., eds) Cambus Litho Ltd; East Kilbride, Scotland, 1991: 965 – 999.
13. Duncan GE, Sheitman BB, Lieberman JA. An integrated view of pathophysiological models of schizophrenia. Brain Research Reviews, 29, 1999: 250 – 264. https://doi.org/10.1016/s0165-0173(99)00002-8
14. Pillinger T, Osimo EF, Brugger S, Mondelli V, McCutcheon RA, Howes OD. A Meta-analysis of Immune Parameters, Variability, and Assessment of Modal Distribution in Psychosis and Test of the Immune Subgroup Hypothesis. Schizophrenia Bulletin, 45(5), 2019: 1120–1133. https://doi.org/10.1093/schbul/sby160.
15. Koga M, Serritella AV, Akira Sawa A, Thomas W, Sedlak TW, Implications for reactive oxygen species in schizophrenia pathogenesis. Schizophrenia Bulletin, 176(1), 2016: 52-71. https://doi.org/10.1016/j.schres.2015.06.022.
16. Howes O, McCutcheon R, Stone S. Glutamate and dopamine in schizophrenia: an update for the 21st century. Journal of Psychopharmacology, 29(2), 2015: 97–115. https://doi.org/10.1177/0269881114563634.
17. Frajerman A, Kebir O, Chaumette B, Tessier C, Lamazière A, Nuss P, Krebs MO. Membrane lipids in schizophrenia and early phases of psychosis: Potential biomarkers and therapeutic targets?. L'encephale, 46(3), 2020: 209–216.
18. Krebs MO, Bellon A, Mainguy G, Jay TM, Frieling H. One-Carbon Metabolism and Schizophrenia: Current Challenges and Future Directions. Trends in Molecular Medicine, 15, 2009: 562–570. https://doi.org/10.1016/j.molmed.2009.10.001
19. Velligan DI, Rao S. The epidemiology and global burden of schizophrenia. Journal of Clinical Psychiatry, 84(1), 2023: MS21078COM5. doi.org/10.4088/JCP.MS21078COM5
20. Stępnicki P, Kondej M, Kaczor AA. Current Concepts and Treatments of Schizophrenia. Molecules, 23, 2018: 2087, https://doi.org/10.3390/molecules23082087.
21. Li R, Ma X, Wang G, Yang J, C. Wang C. Why sex differences in schizophrenia? Journal of Translational Neuroscience (Beijing), 1(1), 2016: 37–42. PMCID: PMC5688947
22. Giordano GM, Bucci P, Mucci A, Pezzella P, Galderisi S. Gender differences in clinical and psychosocial features among persons with schizophrenia: a mini review. Frontiers Psychiatry, 2021 (12):789179. https://doi.org/10.3389/fpsyt.2021.789179
23. Charlson FJ, Ferrari AJ, Santomauro DF, Diminic S, Stockings E, Scott JG, McGrath JJ, Whiteford HA. Global epidemiology and burden of schizophrenia findings from the global burden of disease study 2016. Schizophrenia Bulletin, 44(6), 2018:1195–1203. https://doi.org/10.1093/schbul/sby058
24. Amos S, Akah PA, Enwerem N, Chindo BA, Hussaini IM, Wambebe C, Gamaniel K. Behavioural effect of *Pavetta crassipes*. Pharmacology Biochemistry and Behavior, 77(4), 2004: 751 – 759. https://doi.org/10.1016/j.pbb.2004.01.020
25. Saleem A, Qurat-ul-Ain, Akhtar MF. Alternative Therapy of Psychosis: Potential Phytochemicals and Drug Targets in the Management of Schizophrenia. Frontiers Pharmacology, 13, 2022:895668. https://doi.org/10.3389/fphar.2022.895668.
26. Chindo BA, Anuka J, Gamaniel KS. Toxicity screenings of *Ficus platyphylla* stem bark in rats. Pharmacologia, 3(10), 2012b:499 – 505.
27. Gamaniel KS, Amos S, Chindo B, Vongtau H, Olusola A, Abdulrahman EM, Odutola AA, Akah PA, Wambebe C. Behavioral effects of the methanolic extract of *Ficus platyphylla* bark in mice and rats. Nigerian Journal of Neuroscience, 3(1), 2000:17–23.
28. Chindo BA, Amos S, Odutola AA, Vongtau HO, Abah J, Wambebe C, Gamaniel KS. Central nervous system activity of the methanolic extract of *Ficus platyphylla* stem bark. Journal of Ethnopharmacology, 85, 2003:131–137. https://doi.org/10.1016/s0378-8741(02)00376-8
29. Chindo BA, Anuka JA, Lees G, Yaro AH, Adamu SS, Amos S, Wambebe C, Gamaniel KS. Psychopharmacological properties of the Saponin rich fraction of *Ficus .platyphylla* Stem Bark. International Journal of Biological and Chemical Sciences, 2(3), 2008: 239–248.
30. Chindo BA, Kahl E, Trzeczak D, Dehmel P, Becker A, Fendt M, Standardized extract of *Ficus platyphylla* reverses apomorphine-induced changes in prepulse inhibition and locomotor activity in rats. Behavioural Brain Research, 293, 2015:74–80. https://doi.org/10.1016/j.bbr.2015.06.044
31. Chindo BA, Ya'U J, Danjuma NM, Okhale SE, Gamaniel KS, Becker A. Behavioral and anticonvulsant effects of the standardized extract of *Ficus platyphylla* stem bark. Journal of

Ethnopharmacology, 154, 2014:351–360. DOI: 10.1016/j.jep.2014.03.061
32. Beschi DA, Appavoo MR, Irene Wilsy JI. GC-MS analysis, collected from Kavalkinaru area, Tirunelveli District, Tamil Nadu, India. European Journal of Molecular and Clinical Medicine, 8(11), 2021:4287–4292. ISSN 2515-8260.
33. Monte AS, Greicy CS, Roger SM, Joanna KS, Júnia VS, Rafaela CC, Bruna MM, Ribeiro DF, Silvânia MM. Prevention and reversal of ketamine-induced schizophrenia related behavior by minocycline in mice: possible involvement of antioxidant and nitrergic pathway. Journal of Psychopharmacology, 11, 2013:1032–1043.
34. Ben-Azu B, Omogbiya IA, Aderibigbe AO, Umukoro S, Ajayi AM, Iwalewa EO. Doxycycline prevents and reverses schizophrenic-like behaviors induced by ketamine in mice via modulation of oxidative, nitrergic and cholinergic pathways. Brain Research Bulletin, 139, 2018:114–124. https://doi.org/10.1016/j.brainresbull.2018.02.007
35. Brown RE, Corey SC, Moore AK. Differences in Measures of Exploration and Fear in MHC-Congenic C57BL/6J and B6-H-2k Mice. Behavioural Genetetics, 29, 1999:263–271. DOI:10.1023/a:1021694307672.
36. Lindholm JS, Autio H, Vesa L, Antila H, Lindemann L, Hoener MS, et al. The Antidepressant-like Effects of Glutamatergic Drugs Ketamine and AMPA Receptor Potentiator LY 451646 Are Preserved in Bdnf+/- Heterozygous Null Mice. Neuropharmacology, 62, 2012:391–397. doi:10.1016/j.neuropharm.2011.08.015.
37. Omogbiya IA, Umukoro S, Aderibigbe AO, Adewale GB. Jobelyn pretreatment ameliorates symptoms of psychosis in experimental models. Journal of Basic and Clinical Physiology and Pharmacology, 24, 2013:331–336. DOI: 10.1515/jbcpp-2012-0073
38. Porsolt RD, Anton G, Blavet N, Jalfre M. Behavioural Despair in Rats: a New Model Sensitive to Antidepressant Treatments. European Journal of Pharmacology, 47, 1978:379–391. DOI: 10.1016/00142999(78)90118-8
39. Kroczka B, Branski P, Palucha A, Pilc A, Nowak G. Antidepressant-like Properties of Zinc in Rodent Forced Swim Test. Brain Research Bulletin, 55, 2001:297–300. DOI: 10.1016/s03619230 (01)00473-7.
40. Kulkarni PD, Ghaisas MM, Chivate ND, Sankpal PS. Memory enhancing activity of *Cissampelos pariera* in mice. International Journal of Pharmacy and Pharmaceutical Sciences, 3(2), 2011:206–211.
41. Lueptow LM. Novel object recognition test for the investigation of learning and memory in mice. Journal of Visualized Experiments, 126, 2017: e55718. DOI: 10.3791/55718
42. Umukoro S, Eduviere AT. Methyl jasmonate attenuates memory dysfunction and decreases brain levels of biomarkers of neuroinflammation induced by lipopolysaccharide in mice. Brian Research Bulletin, 131, 2017:133–141. DOI: 10.1016/j.brainresbull.2017.04.002
43. Emokpae O, Ben-Azu B, Ajayi AM, Umukoro S. D-Ribose-L-cysteine attenuates lipopolysaccharide-induced memory deficits through inhibition of oxidative stress, release of proinflammatory cytokines, and nuclear factor-kappa B expression in mice. Naunyn Schmiedeberg's Archives of Pharmacology, 2020: https://doi.org/ 10.1007/s00210-019-01805-0.
44. Ajayi AM, Chidebe EO, Ben-Azu B, Umukoro S. Chrysophyllum albidum (African star apple) fruit-supplemented diet enhances cognitive functions and attenuates lipopolysaccharide-induced memory impairment, oxidative stress, and release of proinflammatory cytokines. Nutrire, 45, 2020: 20.
45. Misra HP, Fridovich I. The role of superoxide anion in the anti-oxidation of epinephrine and simple assay for superoxide dismutase. Journal of Biological Chemistry, 247(10), 1972:3170–3175. https://doi.org/10.1016/S0021-9258(19)45228-9
46. Sinha KA. Colorimetric assay of catalase. Analytical Biochemistry, 47, 1971:389–394. https://doi.org/10.1016/0003-2697(72)90132-7
47. Jollow DJ, Michell JR, Zampaglione N, Gillete J. Bromobenzene- induced liver necrosis. Protective role of glutathione an evidence for 3, 4 bromobenzene oxide as the hepatotoxic metabolite. Pharmacology, 11, 1974:151–169. https://doi.org/10.1159/000136485
48. Okhawa H, Ohishi N, Yagi E. Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction. Analytical Biochemistry, 95, 1979:351–358. DOI: 10.1016/0003-2697(79)90738-3
49. Green LC, Tannenbaum SR, Goldman P. Nitrate synthesis in the germ free and conventional rat. Science, 212, 1981:56–58. https://doi.org/10.1126/science.6451927.
50. Ellman GL, Courtney KD, Andres Jr V, Feather-Stone RM. A new and rapid colorimetric determination of acetylcholinesterase activity. Biochemical Pharmacology, 7, 1961:88–95. https://doi.org/10.1016/0006-2952(61)90145-9.
51. Adamu A, Shamsir MS, Wahab RA, Parvizpour S, Huyop F. Multi-template homology-based structural model of L-2-haloacid dehalogenase (DehL) from Rhizobium sp. RC1. Journal of Biomolecular Structure and Dynamics 35(15), 2017:3285–3296. https://doi.org/10.1080/07391102.2016.1254115.
52. James SA, Yam WK. 'Sub-structure-based screening and molecular docking studies of potential enteroviruses inhibitors.' Computational Biology and

Chemistry, 92, 2021:107499. https://doi.org/10.1016/j.compbiolchem.2021.107499
53. Morris GM, Huey R, Lindstrom W, Sanner MF, Belew RK, Goodsell DS, Olson AJ. AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility. Journal of Computational Chemistry, 30(16), 2009:2785–2791. https://doi.org/10.1002/jcc.21256.
54. Trott O, Olson AJ. AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. Journal of Computational Chemistry, 31(2), 2010:455-461. https://doi.org/10.1002/jcc.21334.
55. Conn PJ, Lindsley CW, Jones CK. Activation of metabotropic glutamate receptors as a novel approach for the treatment of schizophrenia. Trends in Pharmacological Sciences, 30(1), 2009:25–31. https://doi.org/10.1016/j.tips.2008.10.006.
56. Maksymetz J, Moran SP, Conn PJ. Targeting metabotropic glutamate receptors for novel treatments of schizophrenia. Molecular Brain, 10, 2017:15. https://doi.org/10.1186/s13041-017-0293-z
57. Kondej M, PStepnicki P, Kaczor AA. Multi-Target Approach for Drug Discovery against Schizophrenia. International Journal of Molecular Sciences, 19, 2018:3105. https://doi.org/10.3390/ijms19103105.
58. Tsegay EW, Demise DG, Hailu NA, Gufue ZH. Serotonin Type 6 and 7 Receptors as a Novel Therapeutic Target for the Treatment of Schizophrenia. Neuropsychiatric Disease and Treatment, 16, 2020:2499–2509. https://doi.org/10.2147/NDT.S263424
59. Wei FX, Gaurav1 A, Al-Nema M. *In silico* investigation on the probable macromolecular drug targets involved in the antischizophrenia activity of *Nardostachys jatamansi* Brazilian Journal of Pharmaceutical Sciences, 58, 2022:e191134. https://doi.org/10.1590/s2175-97902022e191134.
60. Frohlich J, Horn JDV. Reviewing the ketamine model for schizophrenia. Journal of Psychopharmacology, 28(4), 2014: 287–302. https://doi.org/10.1177/0269881113512909.
61. Ishola IO, Ben-Azu B, Adebayo OA, Ajayi AM, Omorodion IL, Edje KE, Adeyemi OO. Prevention and reversal of ketamine-induced experimental psychosis in mice by the neuroactive flavonoid, hesperidin: The role of oxidative and cholinergic mechanisms. Brain Research Bulletin, 177, 2021:239–251. DOI: 10.1016/j.brainresbull.2021.10.007.
62. Qin Z, Zhang L, Zasloff MA, Stewart AFR, HsiaoHuei HC. Ketamine's schizophrenia-like effects are prevented by targeting PTP1B. Neurobiology of Diseases, 155, 2021:105397. https://doi.org/10.1016/j.nbd.2021.105397.
63. Brody SA, Geyer MA, Large CH. Lamotrigine prevents ketamine but not amphetamine-induced deficits in prepulse inhibition in mice. Psychopharmacology 169, 2003:240–246. https://doi.org/10.1007/s00213-003-1421-2.
64. Kos T, Popik P, Pietraszek M, Schäfer D, Danysz W, Dravolina O, Blokhina E, Galankin T, Bespalov AY. Effect of 5-HT3 receptor antagonist MDL 72222 on behaviors induced by ketamine in rats and mice. European Neuropsychopharmacology, 16, 2006:297–310. Mhttps://doi.org/10.1016/j.euroneuro.2005.10.001
65. Braff DL, G.A Light GA, Swerdlow NR. Prepulse inhibition and P50 suppression are both deficient but not correlated in schizophrenia patients. Biological Psychiatry, 61, 2007:1204–1207. https://doi.org/10.1016/j.biopsych.2006.08.015
66. Vasconcelos GS, Ximenes NC, Soares de Sousa CN, Oliveira TQ, Lima LLL, de Lucena DF, Gama CS, Macêdo D, Vasconcelos SMM. Alpha-lipoic acid alone and combined with clozapine reverses schizophrenia-like symptoms induced by ketamine in mice: participation of antioxidant, nitrergic and neurotrophic mechanisms. Schizophrenia Research, 165, 2015:163–170. https://doi.org/10.1016/j.schres.2015.04.017.c
67. Mena A, Ruiz-Salas JC, Puentes A, Dorado I, Ruiz-Veguilla M, De la Casa LG, Reduced Prepulse inhibition as a biomarker of schizophrenia. Frontiers in Behavioral Neuroscience, 10, 2016:L 202. https://doi.org/10.3389/fnbeh.2016.00202.
68. Moghaddam B, Adams B, Verma A, Daly D. Activation of glutamatergic neurotransmission by ketamine: a novel step in the pathway from NMDA receptor blockade to dopaminergic and cognitive disruptions associated with the prefrontal cortex. Journal of Neuroscience, 17, 1997:2921–2927. https://doi.org/10.1523/JNEUROSCI.17-08-02921.1997.
69. Jackson ME, Homayoun H, Moghaddam B. NMDA receptor hypofunction produces concomitant firing rate potentiation and burst activity reduction in the prefrontal cortex. Proc. National Academic of Science USA, 101, 2004:8467–472.
70. Lewis DA. Cortical circuit dysfunction and cognitive deficits in schizophrenia implications for preemptive interventions. European Journal of Neuroscience, 35, 2012:1871–1878. https://doi.org/10.1111/j.1460-9568.2012.08156.x
71. Grunze HC, Rainnie DG, Hasselmo ME, Barkai E, Hearn EF, McCarley RW, Greene RW. NMDA-dependent modulation of CA1 local circuit inhibition. Journal of Neuroscience, 16, 1996:2034–2043. https://doi.org/10.1523/JNEUROSCI.16-06-02034.1996

72. Homayoun H, Moghaddam B. NMDA receptor hypofunction produces opposite effects on prefrontal cortex interneurons and pyramidal neurons. Journal of Neuroscience, 27, 2007:11496–11500. doi: 10.1523/JNEUROSCI.2213-07.2007.
73. Jeevakumar V, Kroener S. Ketamine administration during the second postnatal week alters synaptic properties of fast-spiking interneurons in the medial prefrontal cortex of adult mice. Cerebral Cortex, 26, 2016:1117–1129. DOI: 10.1093/cercor/bhu293.
74. Takahata R, Moghaddam B. Activation of glutamate neurotransmission in the prefrontal cortex sustains the motoric and dopaminergic effects of phencyclidine. Neuropsychopharmacology, 28, 2003:1117–1124.
75. Newcomer JW, Farber NB, Jevtovic-Todorovic V, Selke G, Melson AK, Hershey T, Craft S, Olney JW, Ketamine-induced NMDA receptor hypofunction as a model of memory impairment and psychosis. Neuropsychopharmacology, 20, 1999:106–118. https://doi.org/10.1016/S0893-133X(98)00067-0
76. Behrens MM, Ali SS, Dugan LL. Interleukin-6 mediates the increase in NADPH-oxidase in the ketamine model of schizophrenia. Journal of Neuroscience, 28, 2008:13957–13966. https://doi.org/10.1523/JNEUROSCI.4457-08.2008
77. Coyle JT, Basu A, Benneyworth M, Balu D, Konopaske G. Glutamatergic synaptic dysregulation in schizophrenia: therapeutic implications. Handbook of Experimental Pharmacology, 2012:267–295. https://doi.org/10.1007/978-3-642-25758-2_10
78. Grace AA. Dysregulation of the dopamine system in the pathophysiology of schizophrenia and depression. Nature Review Neuroscience, 17, 2016:524–532.
79. Irifune M, Shimizu T, Nomoto M. Ketamine-induced hyperlocomotion associated with alteration of presynaptic component of dopamine neurons in the nucleus accumbens of mice. Pharmacology Biochemistry and Behavior, 40, 1991:399–407. DOI: 10.1016/0091-3057(91)90571-i.
80. Chatterjee N, Rajkumar V, Surajit G, Gautam P. Neurochemical and molecular characterization of ketamine-induced experimental psychosis model in mice. Neuropharmacology, 63, 2012:1161–1171. DOI: 10.1016/j.neuropharm.2012.05.041.
81. Abdullah HM, Shahul HA, Hwang MY, Ferrando S. Comorbidity in Schizophrenia: Conceptual Issues and Clinical Management. Focus, 18(4), 2020:386–390. DOI: 10.1176/appi.focus.20200026.
82. Anticevic A, Schleifer C, Youngsun TC. Emotional and cognitive dysregulation in schizophrenia and depression: understanding common and distinct behavioral and neural mechanisms. Dialogues in Clinical Neuscience, 17, 2015:421–434. DOI: 10.31887/DCNS.2015.17.4/aanticevic.
83. Zhou C, Kong D, Zhu X, Wu W, Xue R, Li G, Xu Y, Liu S, Tian H, Zhuo C. Rethinking Schizophrenia and Depression Comorbidity as One Psychiatric Disorder Entity: Evidence From Mouse Model. Frontiers in Neuroscience, 14, 2020:115. https://doi.org/10.3389/fnins.2020.00115.
84. Meltzer H. Antipsychotic agents & lithium. In: Katzung, B.G., Masters, S.B., Trevor, A.J. (Eds.), Basic & Clinical Pharmacology, 12th ed. McGraw-Hill Companies, New York, NY, USA. (2010)
85. Coates KM, Flood P. Ketamine and its preservative, benzethonium chloride, both inhibit human recombinant $\alpha 7$ and $\alpha 4\beta 2$ neuronal nicotinic acetylcholine receptors in Xenopus oocytes. British Journal of Pharmacology, 134, 2001:871–879. DOI: 10.1038/sj.bjp.0704315.
86. Behrens MM, Sejnowski TJ. Does schizophrenia arise from oxidative dysregulation of parvalbumin interneurons in the developing cortex? Neuropharmacology, 57, 2009:193–200. DOI: 10.1016/j.neuropharm.2009.06.002
87. Lykhmus O, Mishra N, Koval L, Kalashnyk O, Gergalova G, Uspenska K, Komisarenko S, Soreq H, Skok M. Molecular mechanisms regulating LPS-induced inflammation in the brain. Front. Molecular Neuroscience, 9, 2016: 19.
88. da Silva AT, Maia AJ, Filho C, Monte AS, Isabelle de Góis QA, Cordeiro RC, de Jesus Souza MM, de Freitas LR, Freitas de LD, Maes M, Macêdo D. Reversal of schizophrenia-like symptoms and immune alterations in mice by immunomodulatory drugs. Journal of Psychiatric Research, 84, 2017:49–58.
89. Venâncioa CA, Magalhãesa AL, Summavielle T. Impaired spatial memory after ketamine administration in chronic low doses. Current. Neuropharmacology. 9, 2011: 251–255. DOI: 10.2174/157015911795016912.
90. Ng F, Berk M, Dean O, Bush AI. Oxidative stress in psychiatric disorders: evidence base and therapeutic implications. International Journal of Neuropsychopharmacology, 11, 2008:851–876. DOI: 10.1017/S1461145707008401
91. Zhang M, Zhao Z, He L, Wan C. A meta-analysis of oxidative stress markers in schizophrenia. Science China Life Sciences, 53, 2010:112–124. https://doi.org/10.1007/s11427-010-0013-8
92. Pazvantoglu O, Selek S, Okay IT. Oxidative mechanisms in schizophrenia and their relationship with illness subtype and symptom profile. Psychiatry and Clinical Neuroscience, 63, 2009:693–700. DOI: 10.1111/j.1440-1819.2009.02015.x
93. Zhang XY, Zhou DF, Shen YC, Zhang PY, Zhang WF, Liang J, Chen FC, Xiu MH, Kosten TA, Kosten TR.

Effects of risperidone and haloperidol on superoxide dismutase and nitric oxide in schizophrenia. Neuropharmacology, 62, 2012:1928–1934. DOI: 10.1016/j.neuropharm.2011.12.014

94. Nasyrova RF, Ivashchenko DV, Ivanov MV, Neznanov NG. Role of nitric oxide and related molecules in schizophrenia pathogenesis: biochemical, genetic and clinical Aspects. Front Physiology, 2015: 6:139. DOI: 10.3389/fphys.2015.00139
95. Nel A, Harvey BH. Haloperidol-induced dyskinesia is associated with striatal NO synthase suppression: reversal with olanzapine. Behavioural Pharmacology, 14, 2003:251–255. https://doi.org/10.1097/00008877-200305000-00010.
96. Yao JK, Leonard S, Reddy RD. Increased nitric oxide radicals in postmortem brain from patients with schizophrenia. Schizophrenia Bulletin, 30, 2004:923–934. https://doi.org/10.1093/oxfordjournals.schbul.a007142.
97. Lauer M, Johannes S, Fritzen S, Senitz D, Riederer P, Reif A. Morphological abnormalities in nitric-oxide-synthase-positive striatal interneurons of schizophrenic patients. Neuropsychobiology, 52, 2005:111–117. https://doi.org/10.1159/000087555.
98. Cui H, Nishiguchi N, Yanagi M, Fukutake M, Mouri K, Kitamura N et al., A putative cis-acting polymorphism in the NOS1 gene is associated with schizophrenia and NOS1 immunoreactivity in the postmortem brain. Schizophrenia Research, 121: 2010:172–178. https://doi.org/10.1016/j.schres.2010.05.003
99. Flatow J, Buckley P, Miller BJ. Meta-analysis of oxidative stress in schizophrenia. Biological Psychiatry, 74, 2013:400–409. https://doi.org/10.1016/j.biopsych.2013.03.018.
100. Bókkon I, Antal I. Schizophrenia: redox regulation and volume neurotransmission. Current Neuropharmacology, 9, 2011:289–300. https://doi.org/10.2174/157015911795596504.
101. Onaolapo OJ, Ademakinwa OO, Olalekan TO, Onaolapo AY. Ketamine-induced behavioural and brain oxidative changes in mice: an assessment of possible beneficial effects of zinc as mono- or adjunct therapy. Psychopharmacology (Berl) 234, 2017a:2707–2725. https://doi.org/10.1007/s00213-017-4666-x.
102. Onaolapo AY, Aina OA, Onaolapo OJ. Melatonin attenuates behavioural deficits and reduces brain oxidative stress in a rodent model of schizophrenia. Biomedicine and Pharmacotherapy, 92, 2017b:373–383. https://doi.org/10.1016/j.biopha.2017.05.094.