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Neuroprotective Effect of Jobelyn® on Ketamine-Induced Schizophrenia-Like Behaviors and Oxidative Damage in Mice Brain

Itivere Adrian Omogbiya[1*], Benneth Ben-Azu[1,2], Maxwell Oboh[1,2], Oruese Orovwigho[1], Tarela ME Daubry[3], Solomon Umukoro[4]

[1]Department of Pharmacology, Faculty of Allied Health Sciences, Delta State University, Abraka, Nigeria. [2]Delsu Joint Canada-Israel Neuroscience & Biopsychiatry Laboratory, Department of Pharmacology, Faculty of Allied Health Sciences, Delta State University, Abraka, Nigeria. [3]Department of Human Physiology, Faculty of Basic Medical Sciences, Delta State University, Abraka, Nigeria. [4]Department of Pharmacology and Therapeutics, Faculty of Basic Medical Sciences, University of Ibadan, Nigeria.

***Corresponding Author:** adrianomotive@gmail.com*
***Phone:** +2349056485691*
***ORCID:** https://orcid.org/0000-0002-2731-9287*

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ABSTRACT

Background and Purpose: Schizophrenia is a chronic, debilitating psychiatric disorder affecting many young adult populations worldwide. Evidence from studies of central changes in the oxidative defense system suggests the involvement of oxidative stress in the pathophysiology of schizophrenia. Jobelyn® (JB) is a commercial polyherbal formulation that has been documented to show beneficial effects on psychosis. Preliminary evidence from animal studies suggests that JB is efficacious in animal models of schizophrenia. This study investigated the effects of JB in the prevention and reversal of ketamine-induced schizophrenia-like behaviors and oxidative damage in mice.

Methods: In the reversal protocol, mice received ketamine (20 mg/kg, i.p.) or saline for 14 days, and JB (5, 10, or 50 mg/kg), risperidone (0.5 mg/kg, i.p.), or vehicle from days 8 to 14. In the prevention protocol, mice were pretreated with JB (5, 10, or 50 mg/kg daily), risperidone, or vehicle prior to ketamine. Behaviors related to positive (locomotor activity) and cognitive (Y-maze test) symptoms of schizophrenia were also assessed. Oxidative stress markers, including superoxide dismutase (SOD), catalase (CAT), glutathione (GSH), and thiobarbituric acid-reactive substances (TBARS) levels, were measured in the whole brain.

Results: JB and risperidone significantly ($P<0.05$) prevented and reversed ketamine-induced hyperlocomotion and memory impairment. Ketamine-induced reductions ($P<0.05$) in SOD, CAT, and GSH levels, alongside increased TBARS content, were ameliorated by JB ($P<0.05$). These data provide a rationale for evaluating JB as a novel antipsychotic agent and suggest that its mechanism of action includes a neuroprotective antioxidant mechanism.

Conclusion: Our findings showed that Jobelyn® prevented and reversed schizophrenia-like behavioral and oxidative alterations induced by ketamine.

INTRODUCTION

Schizophrenia is a chronic, debilitating psychiatric disorder affecting 1% of the world's population (GBD Mental Disorders Collaborators, 2022; Solmi *et al*., 2023). It is a major health challenge in modern medicine and one of the last frontiers of brain research (Correll *et al*., 2024). It is a relatively common, chronic, and frequently devastating neuropsychiatric disorder (Benvenutti *et al*., 2022; Okubo *et al*., 2024), and it imposes a disproportionately large economic burden in terms of hospitalization, chronic treatment and rehabilitation, and lost productivity. Schizophrenia is a clinical syndrome with peak onset in late adolescence or early adulthood, and its symptoms have long been reported to manifest across multiple domains of behavior (Robinson *et al.,* 1999). The full syndrome is characterized by positive symptoms (delusions and hallucinations), negative symptoms (impaired volition, affective flattening, social withdrawal), and cognitive symptoms (impaired memory and information processing) (Lewis and Lieberman, 2000; Zhu *et al.,* 2014).

Impaired interpersonal relations and cognitive function are increasingly recognized as core features of schizophrenia and are thought to be intrinsic to its pathogenesis (Elvevag and Goldberg, 2000). Cognitive impairments often precede the first psychotic episode (Erlenmeyer-Kimling *et al.,* 2000), are stable over time (Albus *et al.,* 2002; Reichenberg *et al.,* 2010), and strongly correlate with functional outcome (Green *et al.,* 2000; Green and Nuechterlein, 2004; Eneni *et al.* 2025). Existing therapies do not adequately address these aspects of the disease, in part reflecting the generalized nature of schizophrenic deficits, which span several neuropsychological domains (Heinrichs and Zakzanis, 1998). Although the pathophysiological mechanisms associated with this disease remain unclear, the dopamine (DA) hypothesis has dominated theories of schizophrenia for several decades (McCutcheon *et al*., 2020; Howes *et al*., 2024). However, focusing on the DA system has led to limited progress in understanding the pathophysiological processes in schizophrenia and, subsequently, to minimal development of novel therapeutics (Miyamoto *et al.,* 2012). In the past two decades, hypotheses of schizophrenia have progressed beyond the DA hypothesis. In a major paradigm shift regarding the etiology of schizophrenia, it has been proposed that numerous genetic and environmental risk factors converge on the N-methyl-D-aspartate receptor (NMDAR)-mediated glutamatergic system, resulting in NMDAR hypofunction in the limbic system during neurodevelopment (Krystal *et al.,* 1994; Okubo *et al*., 2024), and possibly oxidative alterations, based on the redox regulatory role of these NMDA receptors (Javitt *et al.,* 1998; Wood *et al.,* 2010, Eneni *et al.,* 2025).

In this context, relatively little progress has been made in developing new therapeutic targets for negative and cognitive symptoms, despite the presence of compensatory mechanisms for neuroprotective actions (Buckley and Stahl, 2007). The relative absence of genuinely novel psychotropic agents for the most severe and persistent psychiatric disorders is largely a consequence of the lack of sufficient disease models (Chatterjee *et al.,* 2012; Yee and Singer, 2013). A widely used animal model of schizophrenia involves the acute or repeated administration of phencyclidine and ketamine (Becker and Grecksch, 2004; Chatterjee *et al.,* 2012). Ketamine has been used clinically as a dissociative anesthetic since the 1960s and is regarded as a noncompetitive glutamate N-methyl-d-aspartic acid (NMDA) receptor antagonist (Martin and Lodge, 1985). Subanesthetic doses of NMDA receptor antagonists, such as ketamine (20–50 mg/kg), induce behavioral and neurochemical changes associated with symptoms of schizophrenia in humans and animals (Verma and Moghaddam, 1996; Lahti *et al.,* 2001; Nikiforuk *et al.,* 2013) and have been found to be associated with positive, negative, and cognitive symptoms (Chatterjee *et al.,* 2012) as well as oxidative alterations (Ben-Azu *et al*., 2019; Ebrahimi *et al*., 2023; Moghaddam *et al*., 2024).

Plants have offered mankind the first medicine, reserpine, clinically used for the treatment of psychotic disorders before the advent of chlorpromazine (Bleuler and Stoll, 1955). Currently, especially in developing countries such as Nigeria, most patients with psychosis still depend on medicinal plants for the management of the disease (Omogbiya *et al.,* 2013). One of the best approaches in the search for new medicines from plant sources (Omogbiya *et al.,* 2013).

Jobelyn® (JB), a unique polyherbal preparation used as an antianemic, immune booster, and energizer, is widely used by natives of Western Nigeria to treat neurological disorders, especially epilepsy in children (Okochi *et al.,* 2003; Oshiokoya *et al.,* 2008; Omogbiya *et al.,* 2021). JB is available as capsules and suspensions for the treatment of anemia and rheumatoid arthritis (Erah *et al.,* 2003). It is also used to combat stress and promote general well-being (Oshiokoya *et al.,* 2008; Omogbiya *et al.,* 2021). JB is rich in several phytochemicals, including proanthocyanidins, anthocyanidins, apigenidins, proapigenidins, apigenins, luteolins, naringenins, flavonoids, and polyphenols (Erah *et al.,* 2003; Okochi *et al.,* 2003; Adeleke *et al.,* 2025). Most of these compounds are present in the *Sorghum bicolor*, one of the herbal constituents of JB, and these phytochemicals have been found to exhibit a wide range of biological activities (Awika *et al.,* 2004; Heo *et al.,* 2004; Adeleke *et al.,* 2025). JB also contains other phytochemicals obtained from *Parquetina nigrescens* (Periplocaceae) and *Harungana madagascariensis* (Clusiaceae). Apigenin, luteolin, and naringenin have been shown to exert neuroprotective effects and reduce neuroinflammation, indicating their therapeutic efficacy in central nervous

system (CNS) disorders (Awika *et al.,* 2004; Heo *et al.,* 2004). Although previous studies have confirmed the antipsychotic property of JB (Omogbiya *et al.,* 2013), no studies have elucidated its possible neuroprotective effect in psychosis. Therefore, this study aimed to elucidate the mechanisms behind its potential neuroprotective effect and extend knowledge regarding JB's putative psychotropic properties by (1) investigating the possible effects of JB in the prevention and/or reversal of ketamine-induced schizophrenia-like behavior and (2) determining the effects of JB against ketamine-induced oxidative imbalance by measuring reduced glutathione (GSH), superoxide dismutase (SOD), catalase (CAT) levels, and lipid peroxidation, as indexed by malondialdehyde (MDA) content in mice, since oxidative damage has been implicated in the pathophysiology of schizophrenia (Wood *et al.,* 2009; Zhang *et al.,* 2010; Ben-Azu *et al.,* 2022).

MATERIALS AND METHODS

Animals

Adult male Swiss albino mice (*Mus musculus*) weighing 20-25 g used in this study were obtained from the Central Animal House, Faculty of Basic Medical Sciences, Delta State University, Abraka. The animals were housed five per plastic cage (42 × 30 × 27 cm) in a controlled environment at 25±1°C with a 12:12 light/dark cycle. They were fed standard rodent pellets and water *ad libitum* throughout the experimental period. They were acclimatized for at least a week prior to the commencement of the experiments. All procedures in this study were performed in compliance with the National Institutes of Health Guide for Care and Use of Laboratory Animals (Publication No. 85-23, revised 1985) and approved by the University of Ibadan Animal Care and Use Research Ethics Committee (UI-ACUREC/App/12/2016/01).

Drugs

The following drugs were used: ketamine hydrochloride (Sigma-Aldrich, St. Louis, USA), diluted in distilled water and administered intraperitoneally (i.p.); risperidone (RIS) (Sigma-Aldrich, St. Louis, USA), dissolved in distilled water and administered *per os* (p.o.); and JB, dissolved in distilled water. The doses (5, 10, or 50 mg/kg) of JB used in the present study were chosen according to the results of the preliminary study by Omogbiya *et al*. (2013). Appropriate vehicle groups were also assessed simultaneously *per os* at 10 mL/kg. Risperidone was used as a standard antipsychotic because the ketamine-induced model of schizophrenia has been shown to be more responsive to atypical antipsychotics (Becker and Grecksch, 2004).

Experimental Procedure

Briefly, in the prevention paradigm, the maintenance treatment phase of schizophrenia was simulated (Leucht *et al.,* 2003). Different groups of animals (n=5) were treated daily with vehicle, JB (5, 10, or 50 mg/kg, p.o.), or risperidone 0.5 mg/kg, p.o., for 14 days. Between the eighth and 14th days, these animals additionally received a daily dose of ketamine (20 mg/kg, i.p.) or vehicle 30 min after JB administration. In the reversal model, the acute treatment of psychotic episodes was simulated (Hatta *et al.,* 2009). Briefly, each animal group received a daily i.p. injection of either ketamine (20 mg/kg) or vehicle for 14 days. From the eighth day of treatment onwards, these animals additionally received daily oral administration of the vehicle JB (5, 10, and 50 mg/kg) or of risperidone (0.5 mg/kg), with a 30-min interval between treatments. Behavioral assessments of locomotor activity, evaluated using the open field test (OFT), and spatial recognition memory, evaluated using the Y-maze task (YMT), were conducted on the 14th day of treatment, 30 min after the last drug administration.

Behavioral Analysis

Open-Field Test (OFT)

Locomotor behavior was monitored using the open field apparatus. The apparatus consisted of a wooden box measuring 35 × 30 × 23 cm, with visible lines dividing the floor into 36 (20 cm × 20 cm) squares and a front glass wall (Omogbiya et al., 2013), and was placed in a soundproof room. The animals were placed in the rear-left square and allowed to explore. The duration of ambulation and the number of lines crossed were recorded for 5 min using a stopwatch. After each mouse session, the observation chamber was cleaned with 10% ethanol to remove olfactory cues.

Y-maze Test (YMT)

The effect of JB on spontaneous alternation performance, which serves as an index of spatial working memory, was assessed using the Y-maze test (YMT) to evaluate the cognitive impairment associated with schizophrenia, as described by Akanmu *et al*. (2007). Animals were gently placed individually in the Y-maze apparatus, which consisted of three identical arms (33 × 11 × 12 cm each) symmetrically separated at 120° (Dall'igna *et al.,* 2007). Specifically, each mouse was placed at the end of arm A and allowed to explore all three arms (labeled A, B, C) freely for 5 min, with the following parameters recorded: the number of arm visits and the sequence (alternation) of arm visits, assessed visually (Luszczki *et al.,* 2005). The percentage of alternation was calculated as the total number of alternations/(total arm entries − 2), as previously described (Yamada *et al.,* 1996; Dall'igna *et al.,* 2007). After each mouse session, the observation chamber was cleaned with 10% ethanol to remove olfactory cues.

Biochemical Assays

Following behavioral determinations, mice were sacrificed by decapitation under ether anesthesia and dissected. Thereafter, the whole brains were harvested, and each brain was homogenized with 5 mL of 10% w/v phosphate buffer (0.1 M, pH 7.4). Each brain tissue homogenate was centrifuged at 10,000 rpm for 10 min at 4°C. The pellet was discarded, and the supernatant was immediately divided into portions for oxidative stress measurements such as glutathione (GSH), catalase (CAT), superoxide dismutase (SOD), and thiobarbituric acid reactive substances (TBARS) levels (Misra and Fridovich, 1972; Ohkawa *et al*. 1979; Aksenov and Markesbery, 2001). Additionally, protein was measured using the Biuret reagent assay, with bovine serum albumin as the standard.

Superoxide Dismutase Assay

SOD activity was assessed using the method outlined by Misra and Fridovich (1972). This technique relies on detecting the inhibition of superoxide-driven adrenaline auto-oxidation in a spectrophotometer set at 480 nm. The specific activity of SOD was expressed as units per milligram of protein.

Catalase Assay

Catalase (CAT) activity was assayed by the method of Sinha (1972). Hydrogen peroxide (H_2O_2) disappearance was continuously monitored spectrophotometrically at 570 nm by measuring its absorbance in two cuvettes at 60- and 180-second intervals. Catalase activity was expressed as µmol of H2O2 decomposed per minute per mg of protein.

Glutathione (GSH) Assay

This assay was performed as described by Aksenov and Markesbery (2001) and is based on the reduction of 5,5'-dithiobis (2-nitrobenzoic acid) (DTNB) by thiols, which in turn become oxidized (disulfide), generating a yellow derivative, Trinitrobenzene (TNB), whose absorbance is measured spectrophotometrically at 412 nm. The amount of reduced glutathione in the sample was proportional to the absorbance at this wavelength. The concentration of reduced GSH in the brain tissues was expressed as nanomoles per milligram of tissue (nmol/mg protein).

Lipid Peroxidation Assay

Lipid peroxide formation was assessed by measuring thiobarbituric acid reactive substances (TBARS) using the method of Ohkawa *et al*. (1979). The samples were briefly mixed with 50 mM potassium phosphate monobasic buffer, pH 7.4. The homogenate (63 µL) was mixed with 100 µL of 35% perchloric acid, then the samples were centrifuged (5000 rpm/10 min). A quantity (150 µL) of the supernatant was collected and mixed with 50 µL of 1.2% thiobarbituric acid, then heated in a boiling water bath for 30 min. After cooling, lipid peroxidation was determined by the absorbance at 535 nm and expressed as nanomoles per milligram of tissue (nmol/mg protein) of malondialdehyde (MDA).

Statistical Analysis

The data are expressed as Mean ± S.E.M. The data were analyzed using one-way analysis of variance (ANOVA), followed by a post hoc test (Bonferroni) where appropriate, with GraphPad InStat® Biostatistics software (GraphPad Software, Inc., La Jolla, USA, version 5.0). A level of $P<0.05$ was considered statistically significant for all tests.

RESULTS

Prevention and Reversal of Ketamine-Induced Hyperlocomotion by JB

In the prevention protocol [F (5, 24) = 38.48, $P<0.0001$] (Figure 1A) and the reversal protocol [F (5, 24) = 49.66, $P<0.0001$] (Figure 1B), ketamine administration significantly increased the number of line crossings (hyperlocomotion) in the OFT and reduced the ambulation time in seconds for groups treated with ketamine alone as compared to vehicle-treated groups. This was observed in both the prevention [F (5, 24) = 51.17, $P<0.0001$] (Figure 2A) and reversal protocols [F (5, 24) = 43.49, $P<0.0001$] (Figure 2B) when compared to animals treated with the vehicle (10 mL/kg, p.o.). In the prevention protocol, administration of JB (5 and 10 mg/kg, p.o.) and risperidone (0.5 mg/kg, p.o.) prevented ($P<0.05$) ketamine-induced hyperlocomotion and reduced ambulation time, except for JB (50 mg/kg), which was not significant. In the reversal protocol, JB (5, 10, and 50 mg/kg) and risperidone (0.5 mg/kg, p.o.) significantly ($P<0.05$) reversed ketamine-induced hyperlocomotion, as indicated by decreased line crossings and increased ambulation time.

Prevention and Reversal of the Ketamine-Induced Memory Impairment by JB

In the assessment of spatial working memory performance (Figures 3A and 3B), animals treated with ketamine showed a significant reduction in the percentage of correct alternations in the Y-maze during both the preventive [F (5, 24) = 8.215, $P<0.0001$] and reversal [F (5, 24) = 24.32, $P<0.0001$] protocols, compared to the vehicle group (10 mL/kg, p.o.). In both protocols, administration of JB (5, 10, and 50 mg/kg, p.o.) and risperidone (0.5 mg/kg, p.o.) significantly ($P<0.05$) prevented and reversed the ketamine-induced impairment in the percentage of correct alternations.

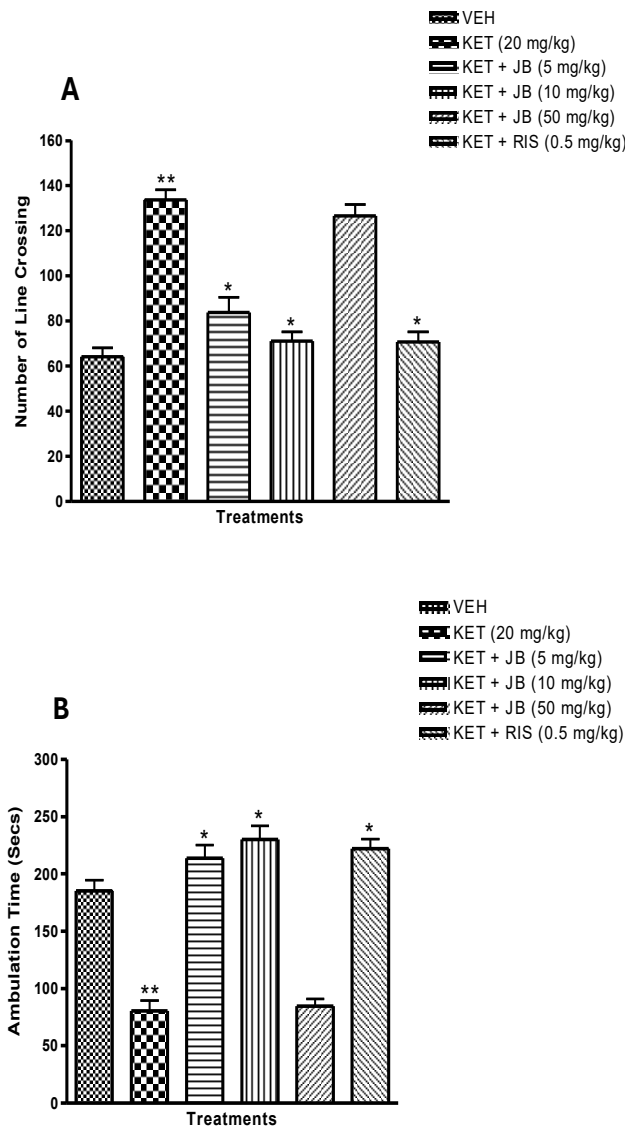

Figure 1: Preventive effect of JB administration (x14 days) on ketamine-induced (x7 days) hyperactivity in mice. A: number of line crossings; B: ambulation time. Value represents the mean ± S.E.M of 5 animals/group. ***P*<0.05 compared with the vehicle group; **P*<0.05 with the ketamine group. One-way ANOVA plus Bonferroni post hoc test. VEH = Vehicle, KET = Ketamine, RIS = Risperidone, JB = Jobelyn®.

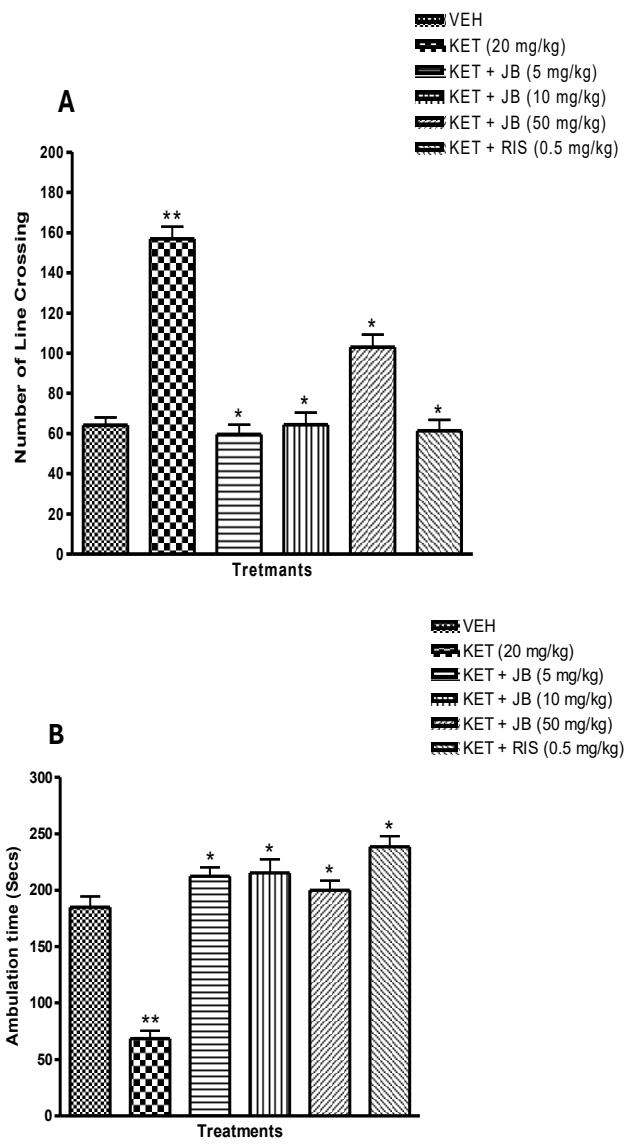

Figure 2: Reversal effect of JB (x7 days) on following 14 days of ketamine-induced hyperactivity in mice. A: number of line crossings; B ambulation time. Value represents the mean ± S.E.M of 5 animals/group. ***P*<0.05 compared with the vehicle group; **P*<0.05 with the ketamine group. One-way ANOVA plus Bonferroni post hoc test. VEH = Vehicle, KET = Ketamine, RIS = Risperidone, JB = Jobelyn®.

Prevention and Reversal of the Ketamine-Induced Memory Impairment by JB

In the assessment of spatial working memory performance (Figures 3A and 3B), animals treated with ketamine showed a significant reduction in the percentage of correct alternations in the Y-maze during both the preventive [F (5, 24) = 8.215, *P*<0.0001] and reversal [F (5, 24) = 24.32, *P*<0.0001] protocols, compared to the vehicle group (10 mL/kg, p.o.). In both protocols, administration of JB (5, 10, and 50 mg/kg, p.o.) and risperidone (0.5 mg/kg, p.o.) significantly (*P*<0.05) prevented and reversed the ketamine-induced impairment in the percentage of correct alternations.

Prevention of Ketamine-induced Brain Oxidative Stress by JB

We also assessed JB's impact on whole-brain biochemical markers of oxidative stress. In preventive treatment, ketamine significantly reduced SOD activity [F(5, 24) = 43.08, *P*<0.0001] compared to the vehicle group (Figure 4A). Pretreatment with JB (5, 10, and 50 mg/kg, p.o.) and risperidone (0.05 mg/kg, p.o.) significantly (*P*<0.05) prevented the ketamine-induced decrease in SOD activity. Ketamine also markedly decreased CAT activity and GSH levels in the entire brain [F(5, 24) = 23.04, *P*<0.0001] (CAT) and [F(5, 24) = 44.01, *P*<0.0001] (GSH) (Figure 4B and 4C) compared to the vehicle group. Similarly, pretreatment with JB (5, 10, and 50 mg/kg, p.o.) and

risperidone (0.05 mg/kg, p.o.) significantly (P<0.05) mitigated the reductions in CAT activity and GSH levels caused by ketamine. Lastly, in preventive treatment, ketamine increased lipid peroxidation, as measured by MDA levels, in the whole brain [F(5, 24) = 95.34, P<0.0001] {Figure 4D}, reflecting decreased endogenous antioxidant levels compared to the vehicle group. Pretreatment with JB (5, 10, and 50 mg/kg, p.o.) and risperidone (0.5 mg/kg, p.o.) significantly (P<0.05) prevented the ketamine-induced rise in lipid peroxidation, as indicated by lower MDA levels in the neurochemical assay.

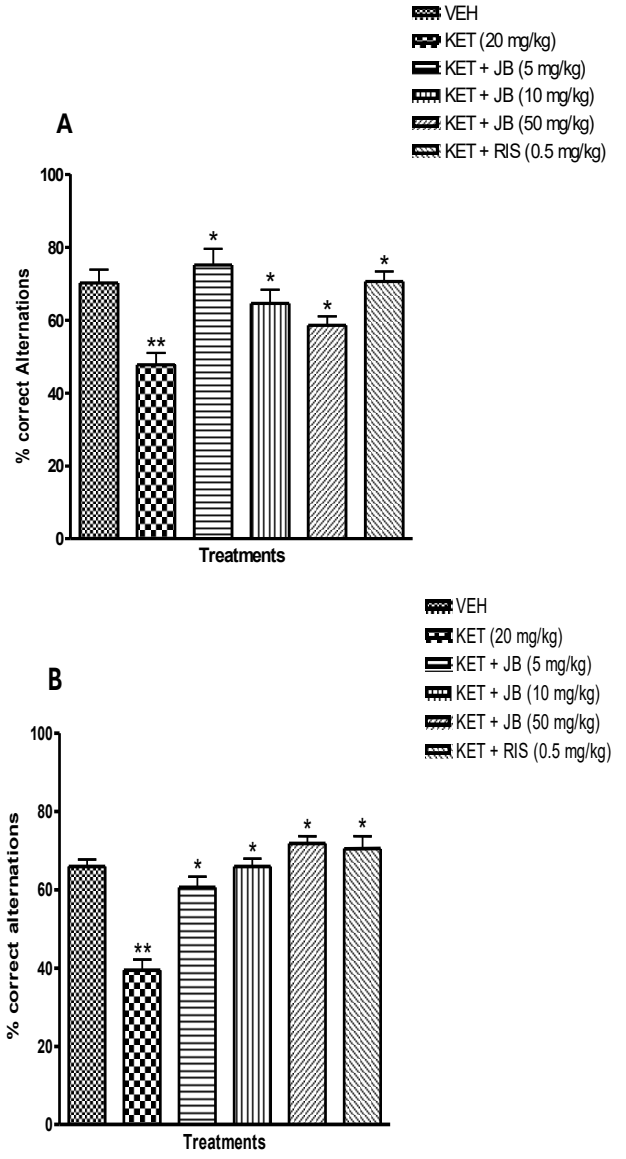

Figure 3: Effect of JB on ketamine-induced memory impairment as measured by alternation in mice. A: preventive effect of JB (x 14 days); B: reversal effect after 7 days administration of ketamine. Value represents the mean ± S.E.M of 5 animals/group. **P<0.05 compared with the vehicle group; *P<0.05 with the ketamine group. One-way ANOVA plus Bonferroni post hoc test. VEH = Vehicle, KET = Ketamine, RIS = Risperidone, JB = Jobelyn®.

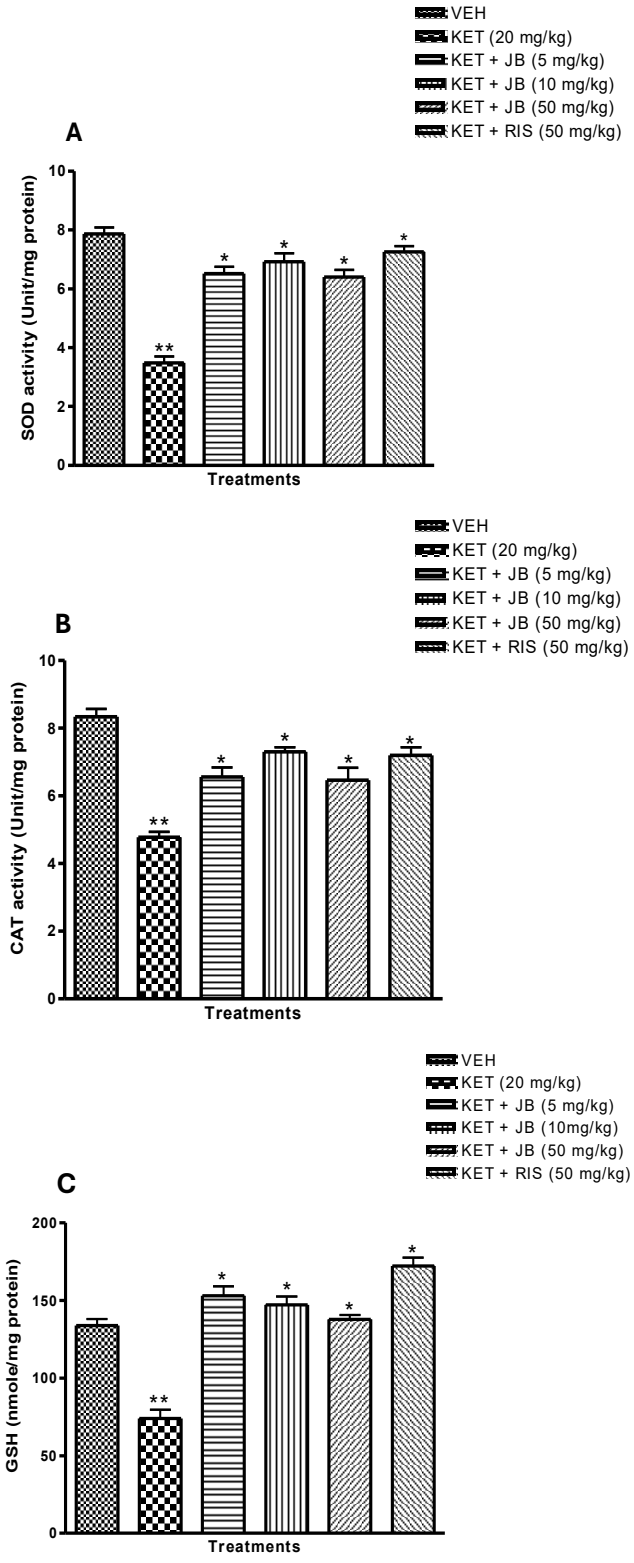

Figure 4: Preventive effect of JB administration (x14 days) on ketamine-induced (x days) changes in activities/levels of oxidative stress markers in mice brain. A: superoxide dismutase (SOD); B: catalase (CAT); C: glutathione (GSH); D: malondialdehyde (MDA). Value represents the mean ± S.E.M of 5 animals/group. **P<0.05 compared with the vehicle group; *P<0.05 with the ketamine group. One-way ANOVA plus Bonferroni post hoc test. VEH = Vehicle, KET = Ketamine, RIS = Risperidone, JB = Jobelyn®.

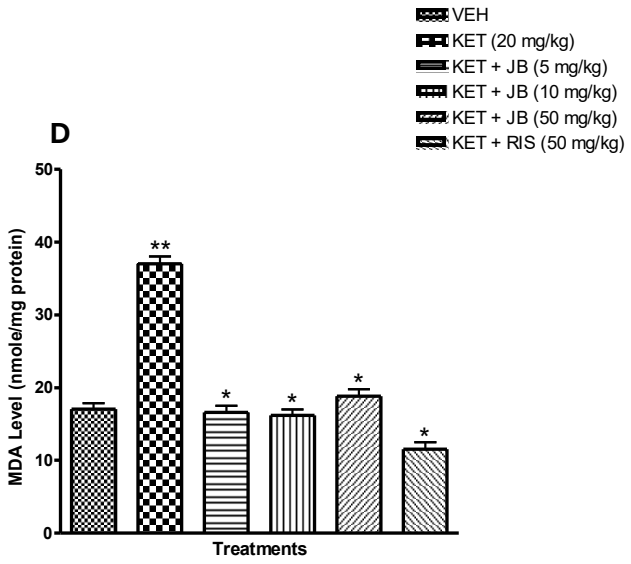

Figure 4 (Cont'd): Preventive effect of JB administration (x14 days) on ketamine-induced (x days) changes in activities/levels of oxidative stress markers in mice brain. A: superoxide dismutase (SOD); B: catalase (CAT); C: glutathione (GSH); D: malondialdehyde (MDA). Value represents the mean ± S.E.M of 5 animals/group. ***P*<0.05 compared with the vehicle group; *-*P*<0.05 with the ketamine group. One-way ANOVA plus Bonferroni post hoc test. VEH = Vehicle, KET = Ketamine, RIS = Risperidone, JB = Jobelyn®.

Reversal of Ketamine-induced Brain Oxidative Stress by JB

In the reversal treatment, SOD and CAT activities followed the same pattern and were significantly decreased by ketamine administration [F (5, 24) = 55.92, *P*<0.0001] (SOD activity) and [F (5, 24) = 25.86, *P*<0.0001] (CAT activity) (Figure 5A and 5B), compared with the vehicle-treated group. Administration of JB (5, 10, and 50 mg/kg, p.o.) and risperidone significantly reversed (*P*<0.05) the decrease in SOD and CAT activities in the whole brain compared with the group treated with ketamine only. As observed in the prevention treatment, ketamine administration also significantly decreased the GSH concentration [F (5, 24) = 34.98, *P*<0.0001] (Figure 5C) compared with the vehicle-treated group (10 mL/kg, p.o.). Treatment with JB (5, 10, and 50 mg/kg, p.o.) and risperidone (0.05 mg/kg, p.o.) significantly reversed (*P*<0.05) the decrease in GSH concentration in the whole brain compared with the group treated with ketamine only. As observed in the prevention protocol, ketamine administration also significantly increased lipid peroxidation, as indicated by an increase in MDA content [F (5, 24) = 34.56, *P*<0.0001] following the neurochemical assay (Figure 5D). However, in the same context, treatment with JB (5, 10, and 50 mg/kg, p.o.) and risperidone (0.5 mg/kg, p.o.) significantly reversed (decreased) ketamine-induced lipid peroxidation (*P*<0.05), as evidenced by a decrease in MDA content.

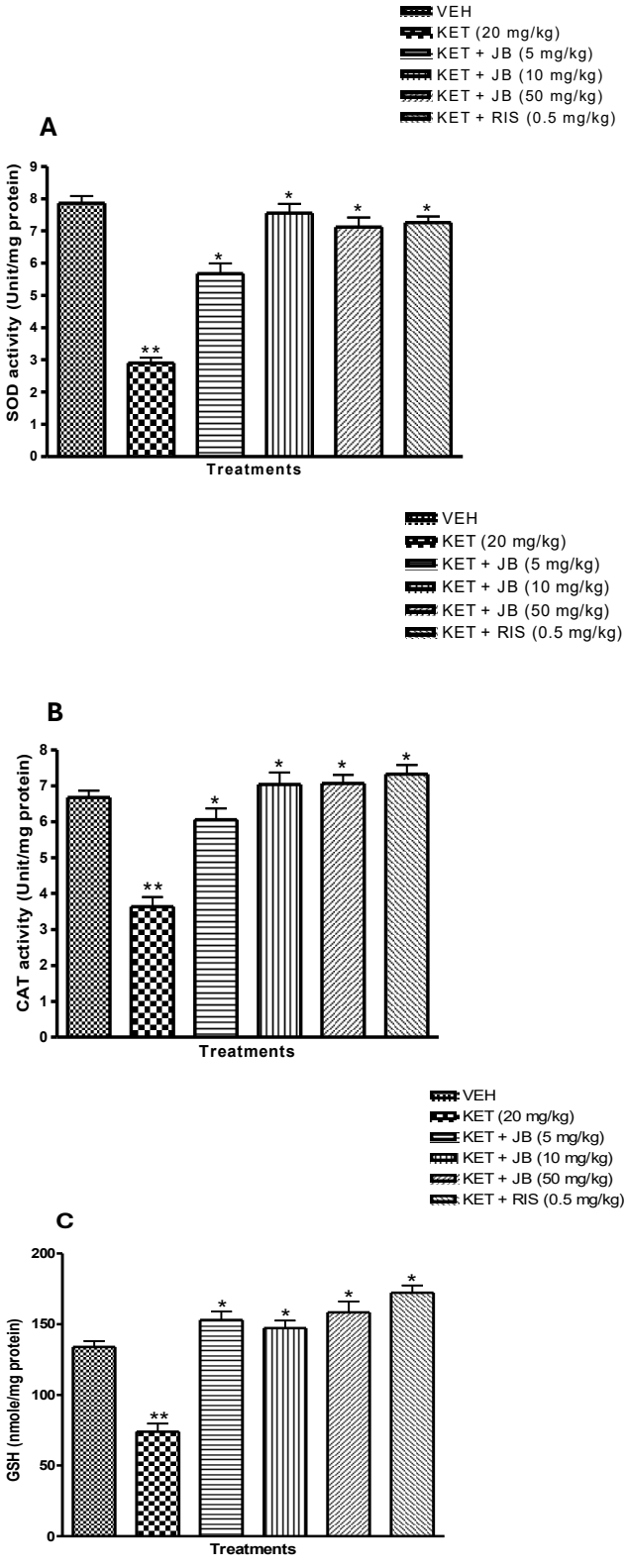

Figure 5: Reversal effect of JB (x7 days) on 14 days ketamine-induced changes in activities/levels of oxidative stress markers in mice brain. A: superoxide dismutase (SOD); B: catalase (CAT); C: glutathione (GSH); D: malondialdehyde (MDA). Value represents the mean ± S.E.M of 5 animals/group. ***P*<0.05 compared with the vehicle group; **P*<0.05 with the ketamine group. One-way ANOVA plus Bonferroni post hoc test. VEH = Vehicle, KET = Ketamine, RIS = Risperidone, JB = Jobelyn®.

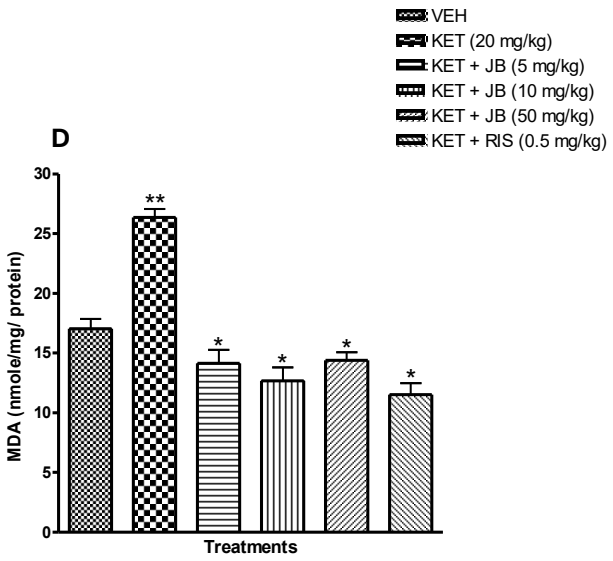

Figure 5 (Cont'd): Reversal effect of JB (x7 days) on 14 days ketamine-induced changes in activities/levels of oxidative stress markers in mice brain. A: superoxide dismutase (SOD); B: catalase (CAT); C: glutathione (GSH); D: malondialdehyde (MDA). Value represents the mean ± S.E.M of 5 animals/group. $^{**}P<0.05$ compared with the vehicle group; $^{*}P<0.05$ with the ketamine group. One-way ANOVA plus Bonferroni post hoc test. VEH = Vehicle, KET = Ketamine, RIS = Risperidone, JB = Jobelyn®.

DISCUSSION

Animal models used to study schizophrenia include both models of positive, negative, and cognitive symptoms and models of oxidative damage (Zhang *et al.,* 2010). This study investigated the antipsychotic effect of JB and the underlying mechanisms. Therefore, our data suggest that JB may have a novel therapeutic effect in the management of different phases of schizophrenia.

Schizophrenia is a heterogeneous chronic mental disease characterized by severe behavioral perturbations, including breakdown of thought processes and deficits in typical emotional responses (GBD Mental Disorders Collaborators, 2022; Howes *et al*., 2024). The symptoms and etiology of neuropsychiatric disorders like schizophrenia have been strongly linked to abnormalities in neurotransmitters such as dopamine, serotonin (5-HT), and gamma-aminobutyric acid (GABA), as well as to various systems involved in their transmission (McCutcheon *et al*., 2020). Recently implicated are low levels of antioxidants in the brain that counteract reduction-oxidation (redox) reactions (Fraguas *et al*., 2017; Palaniyappan *et al*., 2021; Pillinger *et al*., 2022). Studies have demonstrated that subanesthetic doses of ketamine induce schizophrenia-like symptoms in humans, as well as behavioral activation (Lahti *et al.,* 1995), and oxidative alterations in experimental animals (Behrens *et al.,* 2009).

Ketamine has been shown to act through noncompetitive blockade of NMDA glutamate receptors (NMDARs) (Krystal *et al.,* 1994). Indeed, the positive and negative symptoms, as well as cognitive impairments, induced by ketamine (Hou *et al.,* 2013) have been partially attributed to the blockade of NMDARs. Administration of ketamine thereby indirectly increases dopamine availability by decreasing activity in the glutamate-dopamine pathway (Geyer and Maghaddam, 2002). This is because NMDAR stimulation inhibits mesolimbic dopamine release but facilitates mesocortical dopamine release (Krystal *et al.,* 1994). Sub-anesthetic doses of ketamine produce several excitatory effects after systemic administration, and these effects result either from disinhibitory actions or from disruption of the negative feedback regulation of excitatory amino acid-secreting neurons (Duncan *et al.,* 1998). The disinhibition of GABAergic neurons in limbic and subcortical brain regions leads to increased neuronal activity in limbic-striatal circuits via increased glutamate and dopamine release; these neurochemical events are associated with positive symptoms of schizophrenia (Lorrain *et al.,* 2003; Chatterjee *et al.,* 2012). The blockade of NMDARs in the prefrontal cortex (PFC) reduces dopamine release, which may, in part, help explain the cognitive symptoms of the disorder (Seamans and Yang, 2004; Neill *et al.,* 2010). This hypothesis underlies the lower density of glutamatergic receptors and high number of dopaminergic neurons in the brains of schizophrenic patients (Tsai *et al.,* 1998). However, chronic administration of subanesthetic doses of ketamine induces an array of classical symptoms in mice and, at the same time, is susceptible to blockade by antipsychotic agents (Hirsch and Steinert, 2019; Javitt and Zukins, 2012).

In line with this view, our study found that JB (5 to 10 mg/kg demonstrated a significant preventive effect, except for JB (50 mg/kg). The study also showed that JB significantly reversed ketamine-induced behavioral deficits in locomotion. The ability of JB to attenuate ketamine-induced hyperlocomotion may suggest the presence of phytochemical constituents with tranquilizing activity, with results comparable to those of risperidone, an atypical antipsychotic agent. In line with this evidence, JB has been tested for its antipsychotic property in a phase II clinical trial as an add-on therapy to a typical antipsychotic agent (Clinical trial, 2014; Adebesin *et al*., 2024). Previous studies by Omogbiya *et al*. (2013) demonstrated that acute administration of JB (5 and 10 mg/kg, p.o.) attenuated the behavioral alterations (stereotypy) induced by apomorphine (1 mg/kg, i.p.), a dopamine agonist, reduced the hyperlocomotion and stereotypy induced by amphetamine (1 and 10 mg/kg, i.p.), and antagonized the lethality induced by the same amphetamine (10 mg/kg, i.p.) (an indirect dopamine agonist) in the same study. In the same context, one of our present findings elsewhere shows that JB also

ameliorated ketamine-induced psychosis (ketamine-induced hyperlocomotion (acute study) and ketamine-enhanced immobility in the forced swim test). The antagonism of these behavioral alterations and protection from lethality due to hypersecretion of dopamine induced by these dopamine agonists and the NMDAR antagonist, respectively, clearly shows the antidopaminergic and glutamatergic modulatory properties of JB in its therapeutic effect on psychosis, thus further justifying its potential against the positive and negative symptoms of schizophrenia

Notably, this study also showed that JB significantly prevented and reversed ketamine-induced cognitive dysfunction (learning and memory) in the Y-maze test (YMT), an index of cognitive function, suggesting an effect of JB against ketamine-induced deficits in working memory. The above-mentioned changes in neurotransmitter systems are associated with behavioral changes reported following long-term administration of NMDA receptor antagonists. Impairment of cognitive functions and information processing following chronic NMDA receptor antagonist (e.g., ketamine) has been reported in several studies across different animal species (Mandillo *et al.,* 2003). Consistent with these observations, this study also found that ketamine impaired cognitive function in the negative control groups treated with ketamine alone during the 14-day treatment protocol following the YMT evaluation. Therefore, the finding that ketamine induces cognitive dysfunction in mice, a typical characteristic symptom of schizophrenia, further supports its relevance as an animal model predictive of antipsychotic activity (Mouri *et al.,* 2007). In this study, JB was able to prevent and reverse the decrease in percentage alternation (cognition) induced by ketamine, producing a cognition-enhancing effect comparable to that of risperidone in the experimental animals, thus suggesting the ability of JB to ameliorate the impaired working memory related to schizophrenia (Aultman and Moghaddam, 2001).

In this study, the beneficial effects of JB on ketamine-induced behavioral perturbations were associated with alterations in oxidative balance. Therefore, JB administration in this study restored GSH, SOD, and CAT levels and ameliorated ketamine-induced lipid peroxidation. Indeed, decreased endogenous antioxidant levels have been implicated in the pathophysiology of schizophrenia (Reddy *et al.,* 2003; Radonjić *et al.,* 2009). GSH is one of the most important tripeptides and a major non-enzymatic intracellular antioxidant (Zhang *et al.,* 2010). It is known to participate in the removal of free radicals such as peroxide, superoxide anions, and alkoxy radicals, in the maintenance of membrane protein thiols, and as a substrate for GPX and glutathione reductase. Ketamine-induced depletion of glutathione in the whole-brain supernatant in the present experiments was significantly prevented and restored with JB treatment. Increased GSH levels may result from enhanced synthesis or improved glutathione reductase activity in the presence of JB. Generally, SOD and GPX constitute a mutually supportive enzyme system of the first line of cellular defense against oxidative injury, decomposing oxygen and hydrogen peroxide before they interact to form more harmful hydroxyl radicals (Ranjekar *et al.,* 2003).

In this study, SOD and CAT activities were notably reduced in the group treated solely with ketamine. This reduction is primarily due to excessive production of superoxide anions in neuronal cells. A decline in SOD and CAT activities can result from increased breakdown of superoxide anions, leading to elevated hydrogen peroxide levels (Reddy *et al.,* 1991). When JB was administered alongside ketamine, it effectively prevented and reversed the decrease in these antioxidant enzymes in the brain, likely by scavenging oxidative free radicals. This free radical scavenging activity is probably mainly due to the phenolic compounds present in JB. Both previous studies and our current findings indicate that JB treatment significantly alleviates ketamine-induced oxidative stress by preserving endogenous neuronal antioxidants. This preservation may be a key factor in the observed reduction in ketamine-induced behavioral disturbances in this study.

Increased MDA formation, a marker of lipid peroxidation, was also observed in the ketamine-treated group (Rougemont *et al.,* 2002; Zhang *et al.,* 2010). In such instances of an abnormal increase in MDA levels, excessive free radical formation occurs, triggering neuronal membrane damage and augmenting the activation of membrane-bound enzymes (Wood *et al.,* 2009). It appears that lipid and neuronal damage are the primary causes of the marked increase in neuronal MDA content, which is an index of lipid peroxidation and the severity of schizophrenic symptoms (Pavlovic *et al.,* 2002; Pazvantoglue *et al.,* 2009). JB treatment prevented and reversed lipid peroxidation, resulting in decreased MDA formation in the whole-brain homogenate assayed. The decreased MDA formation in various treatment groups following JB prevention and reversal treatment confirms its antioxidant property.

The antioxidant activity of JB may be attributed to chemical groups such as phenolic, sulfhydryl, alkyl, and hydroxyl groups present in various phytochemical constituents, including flavonoids, apigenins, luteolins, naringenins, and polyphenols (Umukoro et al., 2025). Many of these constituents have been shown to readily cross the blood-brain barrier (BBB) and exert CNS activities, including neuroprotective, chemopreventive, and antioxidant effects (Aguirre-Hernandez *et al.,* 2010). Flavonoids are well recognized for their antioxidant, tranquilizing, and anxiolytic activities (Zijia *et al.,* 2009). It is known that most psychotic patients are in a dangerous state of

psychomotor excitement, thus requiring the use of drugs with tranquilizing or sedative properties (Hirsch and Steinert 2019; Baldessarini, 2001). Thus, from this study, it can be inferred that JB is able to prevent oxidative stress during possible inflammatory conditions by scavenging and/or neutralizing free radicals (such as superoxide anions and peroxides) and possibly down-regulating nitric oxide formation, known to participate in oxidative chain reactions (Halliwell, 2006; Wood *et al.,* 2009). The involvement of the proinflammatory pathway through interleukin-6 (IL-6) to nicotinamide adenine dinucleotide phosphate oxidase 2 [NADPH oxidase (Nox-2)] and the production of superoxide (Behrens *et al*., 2008), which in turn leads to an enduring decrease in inhibitory tone (inhibitory postsynaptic potential, IPSP) in the prefrontal cortex (Zhang *et al.,* 2008), via the loss of the inhibitory GABAergic phenotype of the parvalbumin-labeled interneurons, has been linked to the pathogenesis of schizophrenia through oxidative stress and inflammation. In other words, IL-6 has been found to be altered in schizophrenia (Behrens and Margarita, 2008). Importantly, the cognitive symptoms of this mental disorder have been linked to hyper-microglial activation and the resulting inflammatory response (Monji *et al.,* 2009). In this regard, JB's effects on these behavioral and oxidative alterations may, in part, result from its anti-inflammatory and immune-modulating properties (Benson *et al.,* 2013; Ayuba *et al.,* 2014, Adebesin et al., 2024; Adeleke et al., 2025), as well as from effects on glutamate neurotransmission, based on our recent findings from our laboratory, which show that this drug has the potential to modulate NMDAR transmission, although the actual mechanism of action is still under active investigation.

Furthermore, subchronic ketamine treatment induces oxidative stress, depleting putative non-enzymatic (GSH) and enzymatic (GPx and SOD) antioxidants and increasing superoxide anion levels in the brains of experimental animals (Ben-Azu *et al.,* 2022; Ebrahimi *et al.,* 2023). The antioxidant depletion observed in the ketamine-induced oxidative damage model was significantly prevented by JB treatment at 5, 10, and 50 mg/kg (p.o.). Therefore, the antioxidant activity of JB might be directly or indirectly associated with the maintenance or preservation of neuronal membrane integrity, which could help prevent alterations in neuronal marker enzymes such as SOD and CAT observed during oxidative stress. Keeping in mind the potential roles of proinflammatory cytokines and oxidative mechanisms in central nervous system disorders, such as schizophrenia, it is suggested that the antioxidant and antipsychotic properties of JB could provide a rationale for its use alongside standard antipsychotic drugs, or, if not, as a monotherapy regimen in clinical medicine for the management of psychosis.

CONCLUSION

Our findings show that Jobelyn® prevented and reversed schizophrenia-like behavioral and oxidative alterations induced by ketamine. These data provide a rationale for the design of clinical trials of Jobelyn® as an add-on therapy with atypical antipsychotics or a stand-alone antipsychotic agent targeting a wide array of schizophrenia syndromes.

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AUTHORS' CONTRIBUTION

All authors contributed adequately to the different phases of the study: conceptualization, execution, manuscript development, and text proofreading. IAO, BB, and SU conceptualized the study. IAO, BB, MO, TMD, and OO participated in the organization and execution of the experimental benchwork; BB analyzed the results. MO, OO, and TMD were involved in the final proofreading and organization of the text. IAO and BB interpreted the results and fine-tuned the manuscript's final draft.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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REFERENCES

Adebesin A, Omogbiya AI, Oluwole OG, Okubena O, Asomadu RO, Afolabi MOS, Makanjuola SBL, Ajonuma LC, Dosunmu AO, Otitoloju O, Umukoro S (2024). An evidence-based systematic review of pleiotropic potential health benefits of *Sorghum bicolor* supplement: A polyphenol-rich derivative of the leaf sheaths of sorghum plant. *Journal of Natural Remedies* 24:2320-3258. https://doi.org/10.18311/jnr/2024/33171

Adeleke PA, Okubena O. Okubena A, Ajayi AM, Okubena O, Jegede FB, Ijirighjo C, Otomewo LO, Adebesin A, Afolabi MOS, Umukoro S (2025). Anti-aging potentials of a polyphenol-rich supplement from African *Sorghum bicolor* leaf sheaths: A narrative review. *Mediterranean Journal of Pharmacy and Pharmaceutical Sciences* 5(4):58-77. https://doi.org/10.5281/zenodo.17742769.

Akanmu MA, Adeosu SO, Ilesanmi OR (2007). Neuropharmacological effects of oleamide in male and female mice. *Behavioural Brain Research* 182:88-94.

Aksenov MY, Markesbery WR (2001). Changes in thiol content and expression of glutathione redox system genes in the hippocampus and cerebellum in Alzheimer's disease. *Neuroscience Letters* 302:141-145.

Aultman JM, Moghaddam B (2001). Distinct contributions of glutamate and dopamine receptors to temporal aspects of rodent working memory using a clinically relevant task. *Psychopharmacology (Berl)* 153:353-364.

Awika JM, Rooney LW (2004). Sorghum phytochemicals and their potential impact on human health. *Phytochemistry* 65:1199-221.

Ayuba GI, Jensen GS, Benson KF, Okubena AM, Okubena O (2014). Clinical efficacy of a West African *Sorghum bicolor*-based traditional herbal preparation Jobelyn® shows increased hemoglobin and CD4+ T-lymphocyte counts in HIV-positive patients. *J Altern Complement Med.* 20(1):53-56.

Becker A, Grecksch G (2004). Ketamine-induced changes in rat behaviour: A possible animal model of schizophrenia. Test of predictive validity. *Progress in Neuropsychopharmacology and Biological Psychiatry* 28:1267-1277.

Ben-Azu B, Adebayo OG, Jarikre TA, Oyovwi MO, Edje KE, Omogbiya IA, Eduviere AT, Moke EM, Chijioke BS, Odili OS, et al (2022). Taurine, an essential β-amino acid insulates against ketamine-induced experimental psychosis by enhancement of cholinergic neurotransmission, inhibition of oxidative/nitrergic imbalances, and suppression of COX-2/iNOS immunoreactions in mice. *Metabolic Brain Disease* 37(8):2807-2826. DOI: 10.1007/s11011-022-01075-5.

Ben-Azu B, Aderibigbe AO, Ajayi AM, Eneni AO, Omogbiya IA, Owoeye O, Umukoro S, Iwalewa EO (2019). Morin decreases cortical pyramidal neuron degeneration via inhibition of neuroinflammation in mouse model of schizophrenia. *International Immunopharmacology* 70:338-353. DOI: 10.1016/j.intimp.2019.02.052.

Behrens MM, Ali SS, Dugan LL (2008). Interleukin-6 mediates the increase in NADPH oxidase in the ketamine model of schizophrenia. *Journal of Neuroscience* 28:13957-13966. DOI: 10.1523/JNEUROSCI.4457-08.2008.

Benson KF, Beaman J, Ou B, Okubena A, Okubena O, Jensen GS (2013). West African *Sorghum bicolor* leaf sheaths have anti-inflammatory and immune-modulating properties in vitro. *Journal of Medicinal Food* 16(3):230-238. DOI: 10.1089/jmf.2012.0214.

Benvenutti R, Gallas-Lopes M, Marcon M, Reschke CR, Herrmann AP, Piato A (2022). Glutamate NMDA receptor antagonists with relevance to schizophrenia: A review of zebrafish behavioral studies. *Current Neuropharmacology* 20(3):494-509. DOI: 10.2174/1570159X19666210215121428.

Bleuler M, Stoll WA (1955). Clinical use of reserpine in psychiatry: Comparison with chlorpromazine. *Annals of the New York Academy of Sciences* 61:167-73. DOI: 10.1111/j.1749-6632.1955.tb42463.x.

Chatterjee M, Verma R, Ganguly S, Palit G (2012). Neurochemical and molecular characterization of ketamine-induced experimental psychosis model in mice. *Neuropharmacology* 63:1161-1171.

Correll CU, Tusconi M, Carta MG, Dursun SM (2024). What remains to be discovered in schizophrenia therapeutics: Contributions by advancing the molecular mechanisms of drugs for psychosis and schizophrenia. *Biomolecules 14*(8):906. DOI: 10.3390/biom14080906.

Dall'igna OP, Fett P, Gomez MW, Souza S, Cunha R, Lara D (2007). Caffeine and adenosine A2a receptor antagonists prevent beta-amyloid (25-35)-induced cognitive deficits in mice. *Experimental Neurology* 203(1):241-245.

Duncan GE, Moy SS, Knapp DJ, Mueller RA, Breese GR (1998). Metabolic mapping of the rat brain after subanaesthetic doses of ketamine: Potential relevance to schizophrenia. *Brain Research* 787:181-190.

Ebrahimi F (2023). L-Carnitine prevents behavioral alterations in ketamine-induced schizophrenia in mice: Possible involvement of oxidative stress and inflammation pathways. *Journal of Toxicology* 2023:9093231. DOI: 10.1155/2023/9093231.

Elvevag B, Goldberg TE (2000). Cognitive impairment in schizophrenia is the core of the disorder. *Critical Reviews in Neurobiology* 14:1-21.

Eneni AO, Ben-Azu Benneth, Ajayi AM, Aderibibge AO (2025). Ketamine-induced behavioral perturbations, redox imbalances, and neurotransmitter deficits in mice: The preventive and reversal neuromodulatory potential of diosmin as an antipsychotic. *Brain Disorders* 18:100210.

Erah PO, Asonye CC, Okhamafe AO (2003). Response of *Trypanosoma brucei brucei*-induced anaemia to a commercial herbal preparation. *African Journal of Biotechnology* 2:307-311.

Fraguas D, Diaz-Caneja CM, Rodriguez-Quiroga A, Arango C, (2017). Oxidative stress and inflammation in first-episode psychosis: A systematic review and meta-analysis. *International Journal of Neuropsychopharmacology* 25(6):432-461. DOI: 10.1093/ijnp/pyab098.

Global Burden of Disease (GBD) Mental Disorders Collaborators (2022). Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Psychiatry* 9: 137-150. DOI: 10.1016/S2215-0366(21)00395-3.

Geyer MA, Moghaddam B (2002). Animal models relevant to schizophrenia disorders. *Neuropsychopharmacology: The Fifth Generation of Progress* 50:690-701.

Green MF, Nuechterlein KH (2004). The MATRICS initiative: Developing a consensus cognitive battery for clinical trials. *Schizophrenia Research* 72(1):1-3.

Green MF (1996). What are the functional consequences of neurocognitive deficits in schizophrenia? *American Journal of Psychiatry* 153:321-330.

Halliwell, B (2006). Oxidative stress and neurodegeneration: where are we now? *Journal of Neurochemistry* 97:1634-1658.

Hatta K, Sato K, Hamakawa H, Takebayashi H, Naoto K, Shinichiro O, Yasuhiko S, Nozomu A, Hiroyuki N, Chie U, Toshitaka K, Toyoaki K, Yutaka S (2009). Effectiveness of second-generation antipsychotics with acute-phase schizophrenia. *Schizophrenia Research* 113:49-55.

Heinrichs RW, Zakzanis KK (1998). Neurocognitive deficit in schizophrenia: A quantitative review of the evidence. *Neuropsychology* 12:426-445.

Heo HJ, Kim M, Lee J, Choi S, Cho H, Hong B, Kim H, Kim E, Shin D (2004). Naringenin from Citrus junos has an inhibitory effect on acetylcholinesterase and a mitigating effect on amnesia. *Dementia and Geriatric Cognitive Disorders* 17(3):151-157. DOI: 10.1159/000076349.

Hirsch S, Steinert T (2019). The use of rapid tranquilization in aggressive Behavior. *Deutsches Arzteblatt International* 116(26):445-452. DOI: 10.3238/arztebl.2019.0445

Hou Y, Zhang H, Xie G, Cao X, Zhao Y, Liu Y, Mao Z, Yang J, Wu C (2013). Neuronal injury, but not microglia activation, is associated with ketamine-induced experimental schizophrenic model in mice. *Progress in Neuro-psychopharmacol and Biological Psychiatry* 45:107-116. DOI: 10.1016/j.pnpbp.2013.04.006.

Howes OD, Bukala BR, Beck K (2024). Schizophrenia: From neurochemistry to circuits, symptoms and treatments. *Nature Reviews Neurology* 20: 22-35. DOI: 10.1038/s41582-023-00904-0.

Javitt DC, Zukin SR, Heresco-Levy U, Umbricht D (2012). Has an angel shown the way? Etiological and therapeutic implications of the PCP/NMDA model of schizophrenia. *Schizophrenia Bulletin* 38:958-966.

John R, Abolaji AO, Adedara AO, Ajayi AM, Aderibigbe AO, Umukoro S. (2022). Jobelyn® extends the life span and improves motor function in *Drosophila melanogaster* exposed to lipopolysaccharide via augmentation of antioxidant status. *Metabolic Brain Disease* 37:1031-1040. DOI: 10.1007/s11011-022-00919-4.

Krystal JH, Karper LP, Seibyl JP, Freeman, GK, Delaney, R, Bremner, JD, Heninger GR, Bowers MB Charney DS (1994). Subanaesthetic effects of the non-competitive NMDA antagonist, ketamine, in humans: Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Archive of General Psychiatry* 51:199-214.

Lahti AC, Koffel B, LaPorte D, Tamminga CA (1995). Subanesthetic doses of ketamine stimulate psychosis in schizophrenia. *Neuropsychopharmacology* 13:9-19.

Lahti AC, Weiler MA, Michaelidis TBA, Parwani A, Tamminga CA (2001). Effects of ketamine in normal and schizophrenic volunteers. *Neuropsychopharmacology* 25(4):455-467.

Leucht S, Barnes TR, Kissling W, Engel RR, Correll C, Kane JM (2003). Relapse prevention in schizophrenia with new-generation antipsychotics: A systematic review and exploratory meta-analysis of randomized, controlled trials. *American Journal of Psychiatry* 160:1209-1222.

Lewis DA, Lieberman JA (2000). Catching up on schizophrenia: Natural history and neurobiology. *Neuron* 28:325-334. DOI: 10.1016/s0896-6273(00)00111-2.

Lorrain DS, Baccei CS, Bristow LJ, Anderson JJ, Varney MA (2003). Effects of ketamine and N-methyl-D-aspartate on glutamate and dopamine release in the rat prefrontal cortex: Modulation by a group II selective metabotropic glutamate receptor agonist LY379268. *Neuroscience* 117:697-706.

Mandillo S, Rinaldi A, Oliverio A, Mele A (2003). Repeated administration of phencyclidine, amphetamine, and MK-801 selectively impairs spatial learning in mice: A possible model of psychomimetic drug-induced cognitive deficits. *Behavioural Pharmacology* 14:533-544.

Martin D, Lodge D (1985). Ketamine acts as a non-competitive N-methyl-D-aspartate antagonist on frog spinal cord in vitro. *Neuropharmacology* 24:999-1003.

McCutcheon RA, Krystal JH, Howes OD (2020) Dopamine and glutamate in schizophrenia: Biology, symptoms and treatment. *World Psychiatry* 19:15-33. DOI: 10.1002/wps.20693.

Misra HP, Fridovich I (1972). The role of superoxide anion in the autooxidation of epinephrine and a simple assay for superoxide dismutase. *Journal of Biological Chemistry* 247:3170-3175.

Miyamoto S, Miyake N, Jarskog LF, Fleischhacker WW, Lieberman JA (2012). Pharmacological treatment of schizophrenia: A critical review of the pharmacology and clinical effects of current and future therapeutic agents. *Molecular Psychiatry* 17:1206-1227.

Moghaddam AH, Estalkhi FM, Jelodar SK, Hasan TA, Farhadi-Pahnedari S, Karimian M (2024). Neuroprotective effects of alpha-pinene against behavioral deficits in ketamine-induced mice model of schizophrenia: focusing on oxidative stress status. *IBRO Neuroscience Reports* 16:278-287. DOI: 10.1016/j.ibneur.2023.12.012.

Monji A, Kato T, Kanba S (2009). Cytokines and schizophrenia: Microglia hypothesis of schizophrenia. *Psychiatry and Clinical Neurosciences* 63: 257-265. DOI: 10.1111/j.1440-1819.2009.01945.x.

Mouri A, Noda Y, Noda A, Nakamura T, Tokura T, Yura Y, Nitta A, Furukawa H, Nabeshima T (2007). Involvement of a dysfunctional dopamine-D1/N-methyl-D-aspartate-NR1 and Ca2+/calmodulin-dependent protein kinase II pathway in the impairment of latent learning in a model of schizophrenia induced by phencyclidine. *Molecular Pharmacology* 71:1598-1609.

Neill JC, Barnes S, Cook S, Cook S, Grayson B, Idris NF, Mclean SL, Snidgha S, Rajagopal L, Harte MK (2010). Animal models of cognitive dysfunction and negative symptoms of schizophrenia: Focus on NMDA receptor antagonism. *Pharmacology and Therapeutics* 128:419-432. DOI: 10.1016/j.pharmthera.2010.07.004.

Nikiforu A, Kos T, Fijał K, Hołuj M, Rafa D, Popik P (2013). Effects of the selective 5-HT7 receptor antagonist SB-269970 and amisulpride on ketamine-induced schizophrenia-like deficits in rats. PLoS ONE 8(6): e66695. DOI: 10.1371/journal.pone.0066695.

Novak G, Seeman MV (2022). Dopamine, psychosis, and symptom fluctuation: A narrative review. *Healthcare* 10(9):1713. DOI: 10.3390/healthcare10091713.

Ohkawa H, Ohishi N, Yagi K. (1979). Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction. *Analytical Biochemistry* 95:351-358. DOI: 10.1016/0003-2697(79)90738-3.

Okochi VI, Okpuzor J, Okubena MO, Awoyemi AK (2003). The influence of African herbal formula on the haematological parameters of trypanosome infected rats. *African Journal of Biotechnology* 2: 312-316.

Okubo R, Okada M, Motomura E (2024). Dysfunction of the NMDA receptor in the pathophysiology of schizophrenia and/or the pathomechanisms of treatment-resistant schizophrenia. *Biomolecules* 14(9):1128. DOI: 10.3390/biom14091128.

Omogbiya AI, Ben-Azu B, Eduviere AT, Eneni AO, Nwokoye PO, Ajayi AM, Umukoro S (2020). Monosodium glutamate induces memory and hepatic dysfunctions in mice: ameliorative role of Jobelyn® through the augmentation of cellular antioxidant defense machineries. *Toxicological Research* 37(3):323-335. DOI: 10.1007/s43188-020-00068-9.

Omogbiya IA, Umukoro S, Aderibigbe AO Bakre AG. (2013). Jobelyn® pretreatment ameliorates symptoms of psychosis in experimental models. *Journal of Basic and Clinical Physiology and Pharmacology* 24(4):331-336.

Oshikoya KA, Senbanjo IO, Njokanma OF, Soipe A (2008). Use of complementary and alternative medicines for children with chronic health conditions in Lagos, Nigeria. *BMC Complement and Alternative Med* 8:66. DOI: 10.1186/1472-6882-8-66.

Palaniyappan L, Sabesan P, Li X, Luo Q (2021). Schizophrenia increases variability of the central antioxidant system: A meta-analysis of variance from MRS studies of glutathione. *Frontiers in Psychiatry* 12: 796466. DOI: 10.3389/fpsyt.2021.796466.

Pavlovic D, Tamburic V, Stojanovic I (2002). Oxidative stress as marker of positive symptoms in schizophrenia. *Facta Universitatis* 9(2):157-161.

Pazvantoglu O, Selek S, Okay IT (2009). Oxidative mechanisms in schizophrenia and their relationship with illness subtype and symptom profile. *Psychiatry and Clinical Neurosciences* 63:693-700.

Pillinger T, McCutcheon RA, Vano L, Mizuno Y, Arumuham A, Hindley G, Beck K, Natesan S, Efthimiou O, Ciprani A, Howes OD (2022). Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. *The Lancet Psychiatry* 9(1): e1. DOI: 10.1016/S2215-0366(21)00362-X.

Radonjic NV, Knezevic ID, Vilimanovich U, Kravic-Stevovic T, Marina LV, Nikolic T, Todorovic V, Bumbasirevic V, Petronijevic ND (2009). Decreased glutathione levels and altered antioxidant defense in animal model of schizophrenia: long-term effects of perinatal phencyclidine administration. *Neuropharmacology* 58(3):739-745.

Rezaee N, Hone E, Sohrabi HR, Johnson S, Zhong L, Chatur P, Gunzburg S, Martins RN, Binosha Fernando WMAD (2024). Sorghum grain polyphenolic extracts demonstrate neuroprotective effects related to Alzheimer's disease in cellular assays. *Foods* 13(11):1716. DOI: 10.3390/foods13111716.

Robinson D, Woerner MG, Alvir JM, Bilder R, Goldman R, Geisler S, Koreen A, Sheitman B, Chakos M, Mayerhoff D, Lieberman JA (1999). Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. *Archives of General Psychiatry* 56:241-247.

Rougemont M, Do KQ, Castagne, V (2002). New model of glutathione deficit during development: Effect on lipid peroxidation in the rat brain. *Journal of Neuroscience Research* 70:774-783.

Seamans JK, Yang CR (2004). The principal features and mechanisms of dopamine modulation in the prefrontal cortex. *Progress in Neurobiology* 74:1-58.

Sinha AK (1972). Colorimetric assay of catalase. *Analytical Biochemistry* 47(2):389-394. DOI: 10.1016/0003-2697(72)90132-7.

Solmi M, Seitidis G, Mavridis D, Correll CU, Dragioti E, Guimond S, Tuominen L, Dargel A, Carvalho AF, Fornaro M, *et al* (2023). Incidence, prevalence, and global burden of schizophrenia - data, with critical appraisal, from the Global Burden of Disease (GBD) 2019. *Molecular Psychiatry* 28:5319-5327. DOI: 10.1038/s41380-023-02138-4.

Umukoro S, Ajayi AM, Ben-Azu B, Adeleke PA, Areelu J, Orji C, Okubena O (2023). Jobelyn® improves motor dysfunctions induced by haloperidol in mice via neuroprotective mechanisms relating to modulation of cAMP response-element binding protein and mitogen-activated protein kinase. *Metabolic Brain Disease* 38: 2269-2280. DOI: 10.1007/s11011-023-01253-z.

Umukoro S, Oluwole OG, Eduviere AT, Adrian OI, Ajayi AM (2015). Jobelyn® exhibited anti-inflammatory, antioxidant, and membrane-stabilizing activities in experimental models. *Journal of Basic and Clinical Physiology and Pharmacology* 26(5):501-508. DOI: 10.1515/jbcpp-2014-0113.

Verma A, Moghaddam B (1996). NMDA receptor antagonists impair prefrontal cortex function as assessed via spatial delayed alternation performance in rats: Modulation by dopamine. *Journal of Neuroscience* 16(1):373-379.

Wood SJ, Yucel M, Pantelis C Berk M (2009). Neurobiology of schizophrenia spectrum disorders: the role of oxidative stress. *Annals of Academic Medicine Singapore* 38:396-396.

Yee BK, Singer P (2013). A conceptual and practical guide to the behavioural evaluation of animal models of the symptomatology and therapy of schizophrenia. *Cell Tissue Research* 354(1):221-246. DOI: 10.1007/s00441-013-1611-0.

Zhang Y, Behrens MM, Lisman JE. (2008). Prolonged exposure to NMDAR antagonist suppresses inhibitory synaptic transmission in prefrontal cortex. *Journal of Neurophysiology* 100:959-965.

Zhang M, Zhao Z, He L, Wan C (2010). A meta-analysis of oxidative stress markers in schizophrenia. *Science China Life Sciences* 53:112-124.

Zhu F, Zheng Y, Ding Y-q, Liu Y, Zhang X, Wu R, Guo X, Zhao J (2014). Minocycline and risperidone prevent microglia activation and rescue behavioral deficits induced by neonatal intrahippocampal injection of lipopolysaccharide in rats. PLoS ONE 9(4):e93966. DOI: 10.1371/journal.pone.0093966.

Zijia Z, Liao L, Moore J, Wu T, Wang Z (2009). Antioxidant phenolic compounds from walnut kernels (*Juglans regia* L). *Food Chemistry* 113(1):160-165.