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Xylopia parviflora (A. Rich.) Benth. Ameliorates Ketamine-Induced Positive, Negative, and Cognitive Symptoms of Psychosis through Down-regulation of Neuro-oxidative Damage in Mice

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of article.

Abstract

Background: Ethno-botanical investigations on *Xylopia parviflora* (A. Rich.) Benth. revealed its application in the management of neurological disorders, including psychotic conditions.

Objective: To evaluate the neuroprotective effects of the hydroethanol leaf extract of *Xylopia parviflora* (XPE) on the positive, negative, and cognitive manifestations of psychosis in mouse models. .

Methods: Thirty mice were allocated into six groups (n=5). Treatments for each group are as follows: distilled water only (10 mL/kg; Grp A), distilled water + ketamine (50 mg/kg; Grp B), the extract (50, 100, and 200 mg/kg; Grps C-E), and haloperidol (5 mg/kg; Grp F). One hour subsequent to the administration of the extract and haloperidol, all groups were administered ketamine (50 mg/kg, i.p.) to induce psychosis. These treatment regimens were repeated over a period of 21 consecutive days. Twenty-four hours following the final treatment, the mice underwent forced swim (FST), open field (OFT), and object recognition tests (ORT), during which relevant parameters were monitored for a duration of five minutes. Thereafter, the animals were euthanized via cervical dislocation, and their brain tissues were harvested for antioxidant analyses.

Results: XPE (50-200 mg/kg) diminished the duration of immobility in the FST; enhanced the duration spent with the novel object and reduced the duration spent with the familiar object in the ORT; and diminished the frequency of section crossings in the OFT when compared with the distilled water + ketamine treated group. Furthermore, XPE increased antioxidant biomarkers in the brain.

Conclusion: XPE ameliorates ketamine-induced symptoms of psychosis through the attenuation of oxidative stress.

Keywords: *Xylopia parviflora;* Ketamine; Psychosis; Antipsychotic; Ethno-botanical

INTRODUCTION

Psychosis represents a multifaceted mental health disorder that influences a relatively small yet significant segment of the population (Maj *et al.,* 2021). Although the precise etiological factors remain incompletely elucidated, genetic predispositions, environmental influences, and neuro-developmental variables collectively play a role in its etiology. This condition is marked by a profound disconnection from objective reality (Shaw, 2014). Manifestations may include hallucinations, delusions, disorganized thought processes, and a compromised ability to recognize one's own psychological state. Psychosis may serve as a symptom of various mental health disorders, including schizophrenia, bipolar disorder, and major depressive disorders (Mandal *et al.,* 2022). Research has indicated that factors such as substance abuse, traumatic experiences, and medical conditions, including traumatic brain injuries, may precipitate psychotic episodes (Ahmed *et al.,* 2017). The lifetime prevalence of psychosis is heterogeneous across different studies, with estimates suggesting a range from 1% to 3% of the global populace (Moreno-Küstner *et al.,* 2018; Salazar de Pablo *et al.,* 2021). The onset of psychosis frequently occurs between the ages of 16 and 30, with empirical evidence indicating that males typically exhibit psychotic symptoms at an earlier age (late adolescence to early twenties) compared to females (mid-twenties to early thirties) (Selvendra *et al.,* 2022). Investigative studies suggest that estrogen may confer a protective effect, which may elucidate the later emergence of psychosis in women (Gogos *et al.,* 2015). Both genders appear to be affected by psychosis at approximately equivalent rates; however, males generally experience an earlier onset and exhibit more severe symptoms, whereas females may present with a greater prevalence of mood-related symptoms concomitant with psychosis (Gogos *et al.,* 2015). Psychotic disorders frequently co-occur with a myriad of other mental health disorders, including mood disorders (e.g., bipolar disorder), anxiety disorders, and substance use disorders (Lai *et al.,* 2015). These comorbid conditions can obfuscate diagnostic processes and therapeutic interventions. Research findings indicate that psychosis entails intricate interactions among diverse neurotransmitter systems, notably including dysregulation of dopamine, as well as the glutamatergic and serotonergic systems, alongside GABA, neuroinflammatory processes, and oxidative stress, all of which contribute to the initiation and progression of psychotic symptoms (Rawani *et al.,* 2024). These findings have informed the development of antipsychotic therapies, which aim to target these specific neurobiological pathways to mitigate psychotic manifestations. Oxidative stress, identified as a pivotal neurodevelopmental factor in the pathophysiology of psychosis, has been documented as contributing to neuronal injury, neurotransmitter dysregulation, and neuroinflammation (Mandal *et al.,* 2022; Rawani *et al.,* 2024). A comprehensive understanding of the role played by oxidative species in the etiology and progression of psychosis could yield valuable insights pertinent to the advancement of antipsychotic pharmacotherapies, specifically targeting these biological pathways to ameliorate the symptoms.

Xylopia parviflora (A. Rich) Benth. represents a tropical flora indigenous to the regions of West and Central Africa, classified within the Annonaceae family. The plant typically manifests as a diminutive arboreal structure or shrub, characterized by its slender, elongated foliage that is simple in nature and arranged alternately along the branches. The floral structures display a pale and yellowish pigmentation. The fruits of *Xylopia* species are frequently elongated and cylindrical, akin to diminutive capsules or pods. These fruits encompass seeds that are encased within the fleshy outer layer. Both the leaves and fruits of *Xylopia parviflora* are utilized in traditional medicinal practices (Dibacto *et al.,* 2022; Oladoja *et al.,* 2024). An ethnobotanical inquiry has disclosed the application of this plant in the management of central nervous system ailments, including psychosis (Dibacto *et al.,* 2022). Investigative studies underscore its antidiabetic attributes and neuroprotective capabilities, thereby positioning it as a significant resource in traditional healing and potential drug development (Dibacto *et al.,* 2022; Oladoja *et al.,* 2024). Oladoja *et al.* (2024) have documented the antidiabetic effect of *Xylopia parviflora* in laboratory rodent models. Based on an ethnobotanical investigation, traditional applications, and associated correlations, this research endeavor was undertaken to assess the neuroprotective effect of hydroethanol leaf extract of *Xylopia parviflora* in ketamine-induced positive, negative, and cognitive symptoms of psychosis, alongside its potential mechanisms underlying antipsychotic activity.

Methodology

Plant Materials

X. parviflora leaves were obtained from a rural area within Ibadan, Oyo State, Nigeria, during the month of March in the year 2024. A voucher specimen, catalogued as UIH 23,137, corresponding to the leaf specimen, was prepared by Dr. S. A. Odewo from the Forest Research Institute of Nigeria (FRIN), located in Ibadan, Oyo State, Nigeria. In addition, this specimen was appropriately deposited at the herbarium of the Forest Research Institute of Nigeria (FRIN) in Ibadan, Oyo State.

Drugs and Chemicals

Ketamine (JAWA International LTD, Lagos), Haloperidol (GRAMS Pharmaceuticals LTD, Lagos), Ethanol (Nosak Distilleries Limited, Lagos).

Preparation of Plant Extract

The freshly collected leaves of *Xylopia parviflora* underwent air-drying until a consistent weight was achieved, followed by grinding, weighing (750 g), and maceration in 1.5 L of hydroethanol (1:1) for a duration of seventy-two hours. Thereafter, the resultant extract was decanted and subjected to filtration using muslin cloth, followed by the utilization of Whatman filter paper. The extraction, decantation, and filtration processes were repeated for two additional cycles utilizing the obtained residues. The combined filtrates of the extract were subsequently evaporated to dryness at a temperature of 40°C under reduced pressure, yielding dark brown solids with a yield of 9.3%. The dehydrated extract was subsequently weighed and dissolved in distilled water to achieve the requisite working concentrations prior to administration to the experimental animals.

Experimental Animals

In this study, male and female Swiss mice, with an average weight ranging between 25-30 g, were employed. These animals were procured from the Faculty of Pharmacy Animal Center at Olabisi Onabanjo University in Sagamu, Ogun State. The animals were maintained under standardized environmental conditions (23-25°C; 12-hour light and dark cycle) and were granted unrestricted access to a standard rodent pellet diet and water. An acclimatization period of fourteen days was permitted prior to the commencement of the study.

Acute Toxicity Test

Five groups of Swiss mice, each comprising five mice (male and female), were subjected to food deprivation for approximately 12 hours preceding the experimental procedures. For the acute oral toxicity assessment, each group of mice was administered *X. parviflora* at oral doses of 250, 500, 1000, and 2000 mg/kg, respectively. The control group was given distilled water at a dose of 10 mL/kg. Two hours subsequent to treatment, the animals were monitored for behavioral manifestations and indicators of toxicity. Mortality was recorded within the first 24 hours, and those subjects that survived were observed for an additional 14 days to assess for any signs of delayed toxicity. The median lethal dose (LD_{50}) was calculated utilizing the Behrens-Karber methodology (Matsuo et al., 2002).

Neuro-Pharmacological Studies

Object recognition test

Mice were systematically allocated into six groups, each comprising five mice, and were administered different treatments including distilled water (10 mL/kg, baseline), distilled water + ketamine (50 mg/kg; negative control), extract (50 mg/kg, 100 mg/kg, and 200 mg/kg), and haloperidol (5 mg/kg/orally) serving as the standard reference group. Subsequently, one-hour post-administration of the extract and the standard drug, Ketamine (50 mg/kg, *i.p*.) was administered to all groups, except baseline group, to facilitate the induction of psychosis. The extract, haloperidol, and ketamine were consistently administered over a duration of 21 consecutive days. Following a 24-hour period after the completion of the 21-day treatment, the behavioral assessment was conducted. Initially, a green object was presented to the subjects for a recognition period of five minutes prior to the introduction of both the red and green objects. The time spent with each colored object was meticulously documented (Grayson et al., 2007; Antunes and Biala, 2012).

Open field test

A total of thirty mice were allocated into six groups, each consisting of five mice. Group A was administered normal saline (baseline), Group B received distilled water + ketamine (negative control) while Group C received 50 mg/kg of *X. parviflora*, Group D was given 100 mg/kg of *X. parviflora*, Group E was treated with 200 mg/kg of *X. parviflora*, and Group F was administered Haloperidol at a dose of 5 mg/kg. One hour subsequent to the administration of the extract, Ketamine (50 mg/kg, i.p.) was administered to induce psychosis. Both the extract and ketamine were administered over a continuous span of 21 days. The behavioral assessment was conducted on the 22nd day, precisely 24 hours following the administration of the final dose of ketamine. Each mouse was positioned at the center of the designated apparatus, and the frequency of sectional crossings was meticulously recorded (Powell and Miyakawa, 2006; Joshi *et al.,* 2012).

Forced swim test

The forced swim test serves as a behavioral indicator of despair (Noda *et al.,* 1995; Woźniak *et al.,* 2018). The methodology previously delineated in both the open field and object recognition tests was adhered to in this test. On the 22nd day, the assessment was executed. During the testing session, the duration of immobility was quantified and interpreted as a reflection of hopelessness or behavioral despair exhibited by the mice.

Antioxidant assay

Subsequent to the completion of these assessments, the mice were euthanized using ethyl ether; the brains were extracted, and the activities of antioxidant biomarkers, including Glutathione (GSH), Catalase (CAT), and Superoxide Dismutase (SOD) were subsequently evaluated.

Statistical analysis

The results derived from this investigation were articulated as mean ± S.E.M. (n=5). The data were subjected to analysis via One-way ANOVA (followed by Dunnet's post-hoc test) using Graph Pad Prism 6 software (Graph Pad Software Inc., CA, USA). Results were deemed statistically significant when $P<0.05$.

RESULTS

Acute toxicity study

In the acute oral toxicity assessment, the oral administration of *Xylopia parviflora* extract, up to a dose of 2 g/kg, did not manifest any indicators of toxicity or mortality within the timeframes of 24 hours to 14 days in the animals. The estimated oral LD_{50} of *Xylopia parviflora* was determined to be greater than 2 g/kg.

***Xylopia parviflora* Decreased Time Spent with Familiar Object and Increased Time Spent with New Object**

With regards to the object recognition assessment, the cohort subjected to treatment with distilled water and ketamine exhibited marked cognitive deficits, characterized by an extended duration spent with a familiar object ($P<0.01$) and a reduced duration with a novel object ($P<0.01$) in comparison to baseline measurements. Administration of *X. parviflora* at doses of 100-200 mg/kg resulted in a statistically significant increase ($P<0.01$, 0.001) in the duration spent with the novel object compared to the group treated with distilled water + ketamine. Furthermore, the extract at 50-200 mg/kg significantly reduced ($P<0.01$) the time spent by the animals with the familiar object in comparison to the distilled water + ketamine treated group (Table 1). The maximal effect of the extract was noted at 100 mg/kg, which is comparable to the effect observed with the standard treatment. The administration of Haloperidol at a dose of 5 mg/kg resulted in a statistically significant reduction ($P<0.01$) in the time spent with the familiar object and a notable increase in the time spent with the novel object by the mice when contrasted with the group treated with distilled water and ketamine (Table 1).

Table 1: Effect of Hydroethanol Leaf Extract of *Xylopia parviflora* on Object Recognition Test in Mice

Treatment	Dose (mg/kg)	Time spent with familiar object (Sec)	Time spent with new object (Sec)
Baseline (Distilled water)	(10 mL/kg)	0.033±0.008	1.180±0.160
Distilled water + Ketamine	50	0.276±0.053**	0.130±0.095**
X. parviflora + Ketamine	50	0.060±0.032[b]	0.170±0.094
X. parviflora + Ketamine	100	0.063±0.043[b]	1.453±0.247[c]
X. parviflora + Ketamine	200	0.046±0.014[b]	1.040±0.043[b]
Haloperidol + Ketamine	5	0.060±0.015[b]	1.147±0.053[b]

Values are mean ± S.E.M. (n=5). $^{**}P<0.01$ vs. Baseline; $^{b}P<0.001$, $^{c}P<0.001$ vs. Distilled water + Ketamine (One-way ANOVA followed by Tukey's multiple comparison test). **Ketamine (50 mg/kg)**

Xylopia parviflora Decreased the Number of Sectional Crossings

In the open field evaluation, subjects receiving distilled water combined with ketamine demonstrated a significant enhancement in hyperlocomotor activity, as evidenced by a heightened number of sectional crossings ($P<0.01$) relative to the baseline. Administration of *X. parviflora* at doses of 50 and 200 mg/kg led to a significant reduction in locomotor activity ($P<0.01$, 0.0001) in the mice, as evidenced by a decreased number of sectional crossings relative to the group treated with distilled water + ketamine (Table 2). The most pronounced effect of the extract was observed at a dose of 200 mg/kg ($P<0.0001$), which was comparable to the effect of the standard pharmacological agent (Table 2). The administration of Haloperidol at a dose of 5 mg/kg led to a significant reduction ($P<0.01$) in locomotor activity in the mice compared to the cohort treated with distilled water and ketamine (Table 2).

Table 2: Effect of Hydroethanol Leaf Extract of X*ylopia parviflora* on Locomotor Activity in Open Field Test in Mice

Treatment	Dose (mg/kg)	Number of Sectional crossing
Baseline (Distilled water)	(10 mL/kg)	62.00±4.041
Distilled water + Ketamine	50	108.3±12.17**
X. parviflora + Ketamine	50	63.67±4.807[b]
X. parviflora + Ketamine	100	87.33±0.881
X. parviflora + Ketamine	200	21.67±4.631[d]
Haloperidol + Ketamine	5	65.67±8.172[b]

Values are mean ± S.E.M. (n=5). $^{**}P<0.01$ vs. Baseline; $^{b}P<0.001$, $^{d}P<0.0001$ vs. Distilled water + Ketamine (One-way ANOVA followed by Tukey's multiple comparison test). Ketamine (50 mg/kg)

Xylopia parviflora Decreased the Duration of Immobility

Regarding the forced swim assessment, mice that were administered distilled water in conjunction with ketamine exhibited significant negative psychotic tendencies, as indicated by an increased duration of immobility ($P<0.001$) compared to baseline levels. The extract at doses of 50 and 200 mg/kg significantly decreased ($P<0.001$) the duration of immobility when compared to the distilled water + ketamine treated group (Table 3). The impact of the extract was found to be comparable to that of the standard treatment. Haloperidol at a dose of 5 mg/kg resulted in a significant decrease ($P<0.001$) in the duration of immobility in comparison to the group receiving distilled water and ketamine (Table 3).

Table 3: Effect of Hydroethanol Leaf Extract of X*ylopia parviflora* in Forced Swim Test in Mice

Treatment	Dose (mg/kg)	Duration of Immobility Test (min)
Baseline (Distilled water only)	(10 mL/kg)	2.317±0.095
Distilled water + ketamine	50	3.443±0.114***
X. parviflora + ketamine	50	2.160±0.070[c]
X. parviflora + ketamine	100	3.217±0.220
X. parviflora + ketamine	200	2.270±0.055[c]
Haloperidol + ketamine	5	2.183±0.183[c]

*Values are mean ± S.E.M. (n=5). ***P<0.001 vs. Baseline; [c]P<0.001 vs. Distilled water + Ketamine (One-way ANOVA followed by Tukey's multiple comparison test).* ***Ketamine (50 mg/kg)***

***Xylopia parviflora* Increased the levels of Antioxidants**

The brain tissue of mice subjected to distilled water and ketamine treatment displayed a significant reduction (P<0.05) in GSH levels and CAT activity (P<0.001) when evaluated against baseline measurements. *X. parviflora* at 50-200 mg/kg produced a significant increase in GSH (P<0.05, 0.001) compared to the distilled water + ketamine treated group. The extract at doses of 50 and 100 mg/kg elicited a significant increase (P<0.01) in catalase (CAT) activity compared to the distilled water + ketamine group (Table 4). Additionally, the extract exhibited a non-significant increase (P>0.05) in superoxide dismutase (SOD) activity in comparison to the distilled water + ketamine group. The standard pharmacological agent produced a significant enhancement in both glutathione (GSH) (P<0.0001) and CAT (P<0.001) levels (Table 4).

Table 4: Effect of Hydroethanol Leaf Extract of *X. parviflora* in the Brain Anti-oxidant Test in Mice

Treatment	Dose (mg/kg)	GSH (mM)	Catalase (µmol/min)	SOD (U mg^{-1} protein)
Baseline (Distilled water)	(10 mL/kg)	2.550+0.057	11.02+0.263	0.473+0.049
Distilled water + ketamine	50	1.113+0.239*	7.020+0.075***	0.586+0.129
X. parviflora + Ketamine	50	2.667+0.095[a]	9.833+0.266[b]	0.676+0.031
X. parviflora + Ketamine	100	2.407+0.326[a]	9.717+0.516[b]	0.566+0.129
X. parviflora + Ketamine	200	3.340+0.513[c]	7.280+0.710	0.666+0.112
Haloperidol + Ketamine	5	8.977+0.060[d]	10.69+0.083[c]	0.916+0.031

*Values are mean ± S.E.M. (n=5). [a]P<0.05, ***P<0.01 vs. Baseline; [b]P<0.001, [c]P<0.001 vs. Distilled water + Ketamine (One-way ANOVA followed by Tukey's multiple comparison test).* ***Ketamine (50 mg/kg)***

DISCUSSION

While antipsychotic medications are integral in the management of psychotic disorders, they are not without limitations, including inadequate symptom alleviation, considerable side effects (motor, metabolic, sexual, cognitive), and potential risks associated with prolonged use. These disadvantages

may contribute to poor medication adherence and diminished quality of life, underscoring the necessity for the development of novel, more efficacious treatments that exhibit fewer adverse effects. Moreover, the majority of these pharmacological agents exert their effects primarily through the modulation of neurotransmitter systems, without significantly impacting oxidative species. This investigation was conducted in light of ethnobotanical research and traditional uses of *X. parviflora* extract in treating mental health disorders such as psychosis, cognitive deficits, anxiety, and depression. In this study, validated pharmacological models were employed to assess the neuroprotective properties of the hydroethanol leaf extract of *X. parviflora* on ketamine-induced psychosis, with the objective of substantiating the claims made by practitioners of traditional medicine.

In the oral acute toxicity investigation, the administration of *Xylopia parviflora* at doses up to 2 g/kg via oral route did not manifest any indicators of toxicity or mortality within the time frame of 24 hours to 14 days in mouse subjects. It has been documented that an acute oral LD_{50} estimation exceeding 2000 mg/kg of the extract is deemed as safe and non-toxic (Ugwah-Oguejiofor *et al.,* 2019; Alelign *et al.,* 2020; VK *et al.*, 2021). The absence of atypical alterations in the general conduct of the animals, and mortality following acute oral LD_{50} estimates ranging from 2-5 g/kg of the extract is interpreted as harmless and safe (Nugroho *et al.,* 2020; Degu *et al.,* 2021). Consequently, it can be inferred that *Xylopia parviflora* is relatively safe.

The object recognition assessment constitutes a novel model developed to evaluate cognitive dysfunction in schizophrenia, as not all facets of memory domains exhibit significant enhancement through the administration of either typical or atypical neuroleptics (Lyon *et al.,* 2012; Rajagopal *et al.,* 2014). Within the confines of this study, mice receiving distilled water and ketamine demonstrated significant cognitive impairment, as evidenced by an increase in the time spent with the familiar object and a decrease in the time spent with the novel object, which suggests a decline in memory function. Meanwhile, *X. parviflora* administered at doses of 50-200 mg/kg significantly mitigated the cognitive deficits by prolonging the duration spent with novel objects and diminishing the time with the familiar objects. The maximal effect of the extract was noted at a dose of 100 mg/kg. Kumbol et al. (2018) attributed the antipsychotic-like effects of *Albizia zygia* to its capacity to alleviate ketamine-induced deficits in object recognition. Ben-Azu et al. (2018) documented the antipsychotic-like effect of morin through its ability to avert ketamine-induced impairments in object recognition. In light of the aforementioned findings, the attenuation of object recognition deficits by *X. parviflora* implies potential enhancements in memory function. Thus, it can be posited that *X. parviflora* demonstrates antipsychotic-like activity.

The open field test, which evaluates locomotor behavior, is an extensively employed model for the positive symptoms associated with psychosis (Yee and Singer, 2013; Ang et al., 2021). In the context of the open field test conducted, animals treated with distilled water and ketamine exhibited pronounced hyperlocomotor activity, as indicated by an increase in the number of sectional crossings, thereby suggesting characteristics associated with positive symptoms of psychosis. However, *X. parviflora* at doses of 50 and 200 mg/kg significantly diminished the locomotor activity of mice by reducing the frequency of sectional crossings. The peak effect of the extract was recorded at a dose of 200 mg/kg, which is comparable to that of the standard pharmacological agent. Sharma *et al.* (2016) and Akinpelu *et al.* (2018) reported the antipsychotic activity of medicinal plants, attributing it to hypo-locomotor activity on ketamine-induced hyper-locomotion model. The administration of phencyclidine has been shown to induce hyperactivity in locomotion among experimental animals, a condition that is ameliorated by antipsychotic medications (Sun *et al.,* 2009). Amoateng *et al.* (2017) reported the antipsychotic-like activity of medicinal plants based on a reduction in locomotor activity in a morphine-induced hyper-locomotion scenario. In consideration of these findings, the hypo-locomotor activity associated with *X. parviflora* suggests the presence of antipsychotic-like activity.

Numerous investigations have elucidated that the administration of NMDA receptor antagonists can, in addition to eliciting positive psychotic symptoms, precipitate negative psychotic symptoms, which can be assessed through the prolong immobility manifested in the forced swim test (Chindo *et al.,* 2012; Neves *et al.,* 2012). In the present study, the cohort treated with distilled water and ketamine displayed a significant increase in the duration of immobility, which suggests the presence of negative symptoms of psychosis. Meanwhile, the extract (50 & 200 mg/kg) markedly diminished the duration of immobility. Repeated administration of Ketamine, a NMDA receptor antagonist, exacerbates the duration of immobility in the forced swim test (Owolabi *et al.,* 2014). Kumbol *et al.* (2018) indicated that a plant extract exhibiting antipsychotic-like properties reduced the duration of Ketamine-induced immobility in the forced swim test. Chatterjee et al. (2012) documented the antipsychotic properties of *Panax quinquefolium* extract by demonstrating a reduction in the duration of Ketamine-induced exacerbated

immobility. Consistent with the aforementioned findings, the reduction in the duration of Ketamine-induced immobility by *X. parviflora* implies an improvement in the negative symptoms of psychosis. Consequently, it can be postulated that *X. parviflora* exhibits antipsychotic-like activity.

Oxidative stress has been recognized as a contributing factor in the onset of psychosis (Barron *et al.,* 2017; Fraguas *et al.,* 2017; Ventriglio *et al.,* 2021)). The application of natural products in mitigating the effect of psychosis, particularly those endowed with substantial antioxidant properties has been documented (Kumari *et al.,* 2011; Ajao *et al.,* 2018). In the present investigation, the brain tissue of mice administered with distilled water and ketamine demonstrated a significant decrease in GSH and CAT levels when compared to baseline measures, thereby indicating the presence of oxidative stress. However, *X. parviflora* demonstrated an enhancement in Catalase and superoxide dismutase activities. In light of this observation, it may be posited that *X. parviflora* possesses antipsychotic properties mediated through the generation of antioxidant biomarkers. Our findings align with the submissions of Nishiyama *et al.* (2010) and Dibacto *et al.* (2022), who previously undertook investigations regarding the aqueous and ethanolic extracts of *Xylopia parviflora* fruits. These studies revealed that these extracts possess substantial concentrations of polyphenols, alkaloids, proanthocyanins, and tannins, which have been associated with antioxidant properties and antinociceptive effects. Consequently, the probable mechanism underlying the antipsychotic properties of *Xylopia parviflora* may be associated with its capacity to inhibit the build-up of oxidative species in the brain environment, which has been implicated in the pathophysiology of psychosis.

CONCLUSION

The findings of this investigation indicate that the hydroethanol leaf extract of *X. parviflora* possesses antipsychotic-like properties, likely through the attenuation of oxidative stress in mouse models. This study further established the antipsychotic property of the extract against positive, negative, and cognitive symptoms of psychosis. Nevertheless, additional research is imperative to optimize their application and incorporate them into conventional treatment regimens for psychosis.

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