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# ETHANOL STEM BARK EXTRACT OF *BLIGHIA SAPIDA* (*SAPINDACEAE*) REVERSE KETAMINE INDUCED SCHIZOPHRENIA LIKE PHENOTYPES AND OXIDATIVE STRESS IN MICE

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## ABSTRACT

This study evaluated the effect of ethanol extract of *Blighia sapida* (EEBS) stem bark in the reversal of ketamine-induced schizophrenia-like features and oxidative stress in mice. Thirty-five (35) animals were randomly divided into groups (n=5). Animals received ketamine (20 mg/kg per day intraperitoneally or saline for 14 days and ethanol extract of *Blighia sapida* (10 mg/kg, 20 mg/kg, 40 mg/kg, and 80 mg/kg), risperidone (0.5 mg/kg i.p) or vehicle treatment from days 8 to 14. Twenty-Four (24) hours after the last treatment, behaviour related to positive (locomotor activity) and cognitive (Y-maze) of schizophrenia were assessed. Thereafter, oxidative markers, nitrite levels, glutathione synthase and malondialdehyde concentrations were measured using spectrophotometric technique. Ethanol extract of *Blighia Sapida* in a dose dependent manner and risperidone significantly ($p<0.05$) reversed ketamine induced alteration in behaviour paradigms as assessed in open field test and Y-maze tests. 80mg/kg showed the highest significant reduction in locomotor activity counts/ 5minutes with mean value 373.8 ± 14.38 compare with ketamine (20mg/kg i.p) alone with mean value 584.2 ± 16.23 in open field test, while 40, and 80 mg/kg significantly ($p<0.05$) reversed ketamine induced cognitive dysfunction as measured by with mean values of 75. 68 ± 1.563 % and 79.70 ± 2.381 % respectively compare with ketamine alone with mean percentage alternation 56.53 ± 1.248 % in Y-maze test. Assessment of oxidative parameters in ketamine induced oxidative stress in mice brain showed risperidone and varied doses of EEBS significantly ($p>0.05$) decreased nitrite level, increased glutathione synthase (GSH) activity and decreased malondialdehyde (MDA) level compared to the group that received Ketamine alone for the 14 days of treatment (KET). The results provides basis for further evaluation of neuroprotective properties of *Blighia sapida* and suggest antioxidant system as its probable mechanism of action.

**Keywords**: *Blighia sapida*, Stem bark, Schizophrenia, Oxidative stress, Mice.

## INTRODUCTION

Schizophrenia is a cluster of disorders characterized by fundamental disturbances of thinking, perception and emotions. Behavioural manifestations of schizophrenia are categorized as positive or negative and, a sufferer usually exhibits a mixture of the two symptoms (Reena et al. 2011, Ben-Azu et al. 2018a, 2022). The negative symptoms of schizophrenia may include: lethargy, apathy, reduction in speech, social withdrawal whereas, positive symptoms usually manifest as hallucinations, delusions, tangentiality, pressure of speech, inappropriate dressing. However, the cognitive symptoms are known to manifest as learning and memory impairment (McCutcheon et al. 2023). The typical classes of antipsychotics such as chlorpromazine, haloperidol is effective against the positive symptoms, however significantly associated with extra-pyramidal side effects such as tardive dyskinesia and akathisia. The atypical class notably, clozapine and risperidone were originally believed to be effective in ameliorating the positive and negative symptoms and, are better tolerated with respect to extra-pyramidal adverse effects but they exhibit significant cardiovascular risk (**Chatterjee, 2012).** While the disease is associated with several underlying pathological factors consistently linked to disruption of neurochemical imbalances such as dopamine, glutamate, serotonin, and gamma aminobutyric acid (GABA), the role of glutamatergic receptor such as N-methyl-D-aspartate (NMDA) receptor notably linked to oxidative stress has been strongly implicated in the pathogenesis of the disease (Monte et al. 2013; Ben-Azu et al. 2018a, 2018b, 2023).

Ketamine, a short acting dissociative anaesthetic agent, and non-competitive NMDA receptor antagonist, is known to induce the positive, negative symptoms, and cognitive deficits in humans (Hallak et al., 2011) and in preclinical animal models (Monte et al. 2013; Ben-Azu et al. 2018a, 2018b, Usman et al. 2019) at sub anaesthetic dose (20mg/kg). Single or repeated ketamine administration induces changes in systems involving glutamate, dopamine, serotonin and gamma aminobutyric acid (GABA), neurotransmitters implicated in schizophrenia pathophysiology (Lindefors et al. 1997), eliciting oxidative stress and subsequent altered endogeneous antioxidant systems (Ben-Azu et al., 2018a, 2018b, 2023). Oxidative stress which is a state of an imbalance in the generation of free and antioxidant systems might overwhelm neurotransmitter metabolism, leading to dopamine auto-oxidation and impaired glutaminergic neurotransmission, as evident in hyperdopaminergic state in schizophrenia, whereas excess dopamine activity result in increased oxidative damage (Ben-Azu et al. 2018a, 2018b, 2023). Glutamate causes excitotoxic damage by binding to non-NMDA receptors, increasing calcium input, enhancing the neuronal nitric oxide species (NOS) activity and increase nitric oxide NO production (Nakao et al. 2003). Sustained oxidative stress decreased glutathione synthase (GSH) activity and increased levels of malondialdehyde MDA, which correlates with clinical symptoms and cognitive deficits in schizophrenia (Dadheech et al. 2008). This suggests that oxidative mechanism may be involved in the pathophysiology of schizophrenia (Akyol et al. 2004).

*Blighia Sapida*, commonly known as *Ackee* is a soap berry plant of the family *Sapindaceae.* It is a perennial herbaceous plant that is prominently found in Western Tropical Africa. *It* is a medicinal plant used in traditional medicine among many ethnic nationalities in Africa (Olusegun and Olutomi, 2013). Various parts of *Blighia Sapida* plants, alone or in combination, have been reportedly used for the treatment of psychosis, cancer, gonorrhea, stomach ache, hernia, backache, diarrhoea and constipation (Owonubi, 2006). *Blighia sapida* stem bark contains phytochemicals such as flavonoids, polyphenols, and carotenoids (Sofowora, 2006, Bachtela and Israni-Wingerb, 2020). These compounds possess antioxidant properties that may contribute to neuroprotective effects in the brain (Olusegun and Olutomi, 2013). Ethanol extract of the plant stem bark had previously been reported to possess antipsychotic properties in apomorphine induced stereotypy behaviour in mice (Usman et al. 2019).

## MATERIALS AND METHODS

### Plant Material

The bark of the stem of *Blighia sapida (sapindaecae)* was collected during the raining season from Igboora farm settlement in Afijio, Oyo state, and identified at the Forestry Research Institute of Nigeria (FRIN), Ibadan with voucher number 110254.

### Preparations of *Blighia sapida* stem bark extract

The ethanol extract of *Blighia sapida* (EEBS) was prepared using cold extraction. The stem bark was air – dried for 4 weeks, and was pulverized with an electric crusher. A 200 g of pulverized stem bark was soaked in 70% ethanol and left for 48 hours. After which, it was filtered on absorbent cotton and on Whatman 3 mm paper. The volume of the filtrate was concentrated using Rotary evaporator at 40.

$$\text{MDA (units/mg protein)} = \frac{\text{Absorbance x volume of mixture}}{E_{532nm} \text{ x volume of sample x mg protein}}$$

### Statistical Analysis

Data were expressed as Mean ± S.E.M and were analyzed using one–way analysis of variance (ANOVA) and post hoc tests (Student's Newman-Keuls) for the multiple comparisons where appropriate using GraphPad InStat® Biostatistics software. The level of significant was set at p< 0.05.

## RESULTS

### Effect of ethanol extract of *Blighia sapida* in the reversal of ketamine-induced hyper-locomotion

Animals that received varied doses of EEBS (10, 20, 40, 80 mg/kg i.p) and risperidone (0.5mg/kg *i.p*) showed significant (P<0.05) decrease in activity counts/5minutes respectively, compare with the negative control (KET) that received ketamine (20mg/kg i.p) alone. (Table .1).

**Table 1: Effect of EEBS on reversal treatment of chronic ketamine-induced hyperlocomotion**

| S/N | Treatment and Dose | Locomotor Activity (count/5minute) |
|---|---|---|
| 1 | VEHICLE 10 mL/kg | 382.4 ±14.21 |
| 2 | KET 20 mg/kg i.p | 584.2 ±16.21 |
| 3 | KET + EEBS 10mg/kg i.p | 461.4 ± 26.13 |
| 4 | KET + EEBS 20mg/kg i.p | 496.6 ±13.99 |
| 5 | KET + EEBS 40mg/kg i.p | 422.0 ± 30.78 |
| 6 | KET + EEBS 80mg/kg i.p | 373. 8 ± 14.38 |
| 7 | KET + RISP 0.5 mg/kg i.p | 401.8 ± 40.93 |

Values represent the Mean ± SEM (n=5). One way ANOVA, significant [$F$ (6, 28) = 8.228, $P$< 0.0001] differences between various treatment groups for number of activity counts for 5 minutes.

$^{\#}p$< 0.05 as compared to vehicle group, $^{*}$ $p$< 0.05 as compared with ketamine group.

**KET** = Ketamine, **RISP** = Risperidone, **EEBS** = Ethanol extract of *Blighia Sapida* Stem Bark

**Effect of ethanol extract of *Blighia sapida* in the reversal of ketamine-induced cognitive dysfunction**

EEBS (40 and 80 mg/kg i.p) and Risperidone (0.5 mg/kg, i.p) significantly (P<0.05) showed increased percentage alternation compared with ketamine (20mg/kg i.p) alone. EEBS at dose 10 and 20mg/kg showed no significant increase in percentage (%) alternations compared with the negative control group (Table. 2).

**Table.2: Effect of EEBS on reversal treatment of ketamine-induced cognitive dysfunction**

| S/N | Treatment and Dose | Percentage Alternation (%) |
|---|---|---|
| 1 | VEHICLE 10 mL/kg | 77.75 ± 2.861 |
| 2 | KET 20 mg/kg i.p | 56.53 ±1.248$^{\#}$ |
| 3 | KET + EEBS 10mg/kg i.p | 60.79 ±3.250 |
| 4 | KET + EEBS 20mg/kg i.p | 64.75 ±2.615 |
| 5 | KET + EEBS 40mg/kg i.p | 75.68 ± 1.563$^{*}$ |
| 6 | KET + EEBS 80mg/kg i.p | 79.70 ±2.381$^{*}$ |
| 7 | KET + RISP 0.5 mg/kg i.p | 80.33 ± 3.223$^{*}$ |

Value represents the Mean ± S.E.M (n=5). One way ANOVA revealed that there is significant [$F$ (6, 29) = 7.961, $P$< 0.0001] difference between various treatment groups.
$^{\#}p$< 0.05 as compared to vehicle group, $^{*}p$< 0.05 as compared with ketamine group.

**KET** = Ketamine, **RISP** = Risperidone, **EEBS** = Ethanol extract of *Blighia sapida* Stem Bark

**Effects of ethanol extract of *Blighia sapida* on Nitrite level in the reversal of ketamine induced oxidative stress**

Animals in extract treated groups KET + EEBS that received doses of EEBS (10, 20, 40, 80 mg/kg i.p) and KET + RISP (positive control) animals that received risperidone (0.5mg/kg i.p) showed significantly (P<0.05) decreased nitrite level compared with negative control animals (Fig.1).

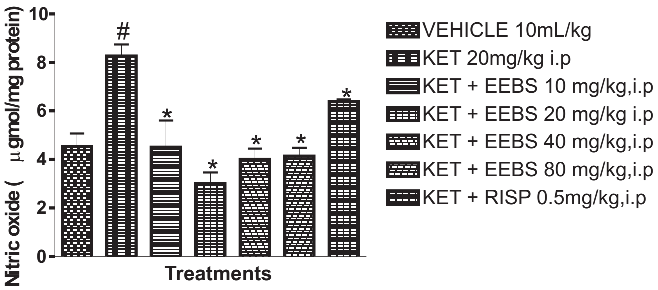


**Fig. 1: Effects of EEBS on Nitrite level in mice brain.**

Value represents the Mean±SEM (n=5). One way ANOVA shows that there is significant [F (6, 28) = 9.587, P <0.0001] difference between various treatments groups when compared with negative control group that received ketamine (20mg/kg i.p) alone.
$^{\#}p$<0.05 when ketamine group was compared to vehicle.* $p$<0.05 as compare with ketamine group.
**KET**= Ketamine, **RISP**=Risperidone, **EEBS**= Ethanol extract of *Blighia sapida* Stem Bark

**Effects of ethanol extract of *Blighia sapida* on glutathione synthase (GSH) activity in the reversal of ketamine induced oxidative stress**

KET + EEBS animals that received EEBS (20, 40, 80 mg/kg i.p respectively) and positive control animals that were given risperidone

(0.5mg/kg i.p) significantly (P<0.05) showed increased GSH level compare with the negative control (KET 20mg/kg i.p) that received ketamine (20mg/kg i.p) (Fig.2).

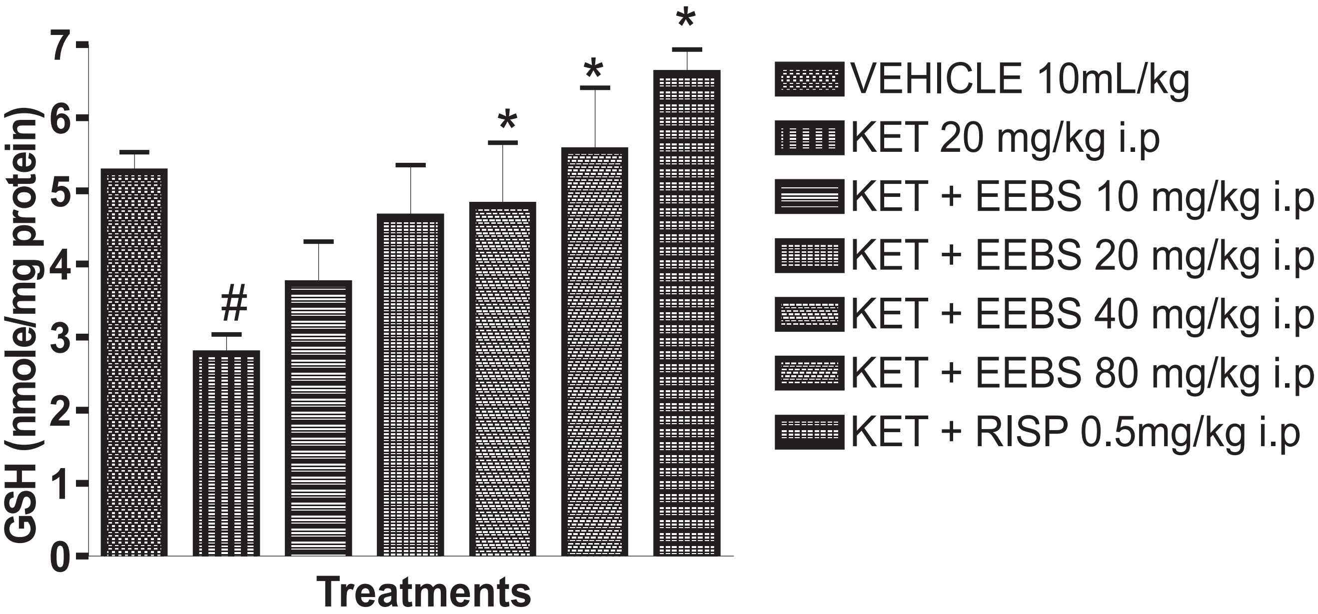


**Fig.2: Effects of EEBS on glutathione synthase (GSH) activity in mice brain.**

Value represents the Mean ± SEM (n=5).One way ANOVA shows that there is significant [F (6, 41) =8.275, P < 0.0001] difference between various treatments groups when compared with negative control group that received ketamine (20 mg/kg) alone.

#*p*< 0.05 as compared with vehicle.* *p*< 0.05 as compare with ketamine group.

**KET**= Ketamine, **RISP**=Risperidone, **EEBS=** Ethanol extract of *Blighia sapida* Stem Bark

**Effects of ethanol extract of *Blighia sapida* on Malondialdehyde (MDA) concentration in the reversal of ketamine induced oxidative stress.**

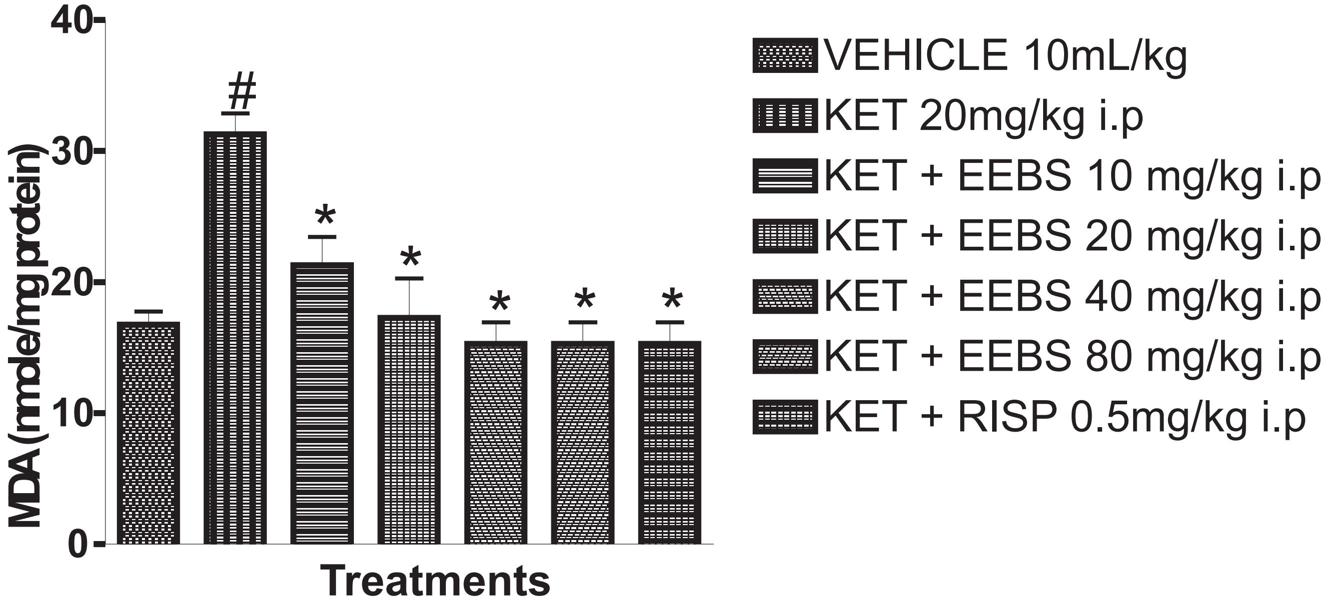


**Fig.3: Effects of EEBS on Malondialdehyde (MDA) conentration in mice brain.**

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Value represents the Mean ± SEM (n=5). One way ANOVA shows that there is significant [F (6, 41) =8.275, P < 0.0001] difference between various treatments groups when compared with negative control group that received ketamine (20 mg/kg) alone.

$^{\#}p < 0.05$ as compared with vehicle. * $p < 0.05$ as compare with ketamine group.

**KET**= Ketamine, **RISP**=Risperidone, **EEBS**= Ethanol extract of *Blighia sapida* Stem Bark

## DISCUSSION

Pharmacological experiments have demonstrated that sub anaesthetic doses of ketamine induce schizophrenia-like symptoms in humans (hyperactivity) as well as behavioural activation in experimental animals i.e hyper locomotion and alterations in working memory and cognition that resemble those observed in schizophrenia patients (Becker and Grecksch, 2004). Stimulation of schizophrenic-like behaviour in mice by ketamine has been partially associated with its direct antagonistic effect on NMDA receptors and indirect dopamine agonist activity. Open field and Y-maze tests have been used previously to evaluate the effects of antipsychotic drugs (e.g., haloperidol, olanzapine and clozapine) on locomotor activity and cognitive function in rodents (Ben Azu et al., 2016). Present study showed that risperidone and EEBS (10,20,40,80 mg/kg) significantly reduced activity counts / 5minute compared with negative control in a spontaneous activity cage (open field test), a measure of locomotor activity in mice, suggesting EEBS may have indirect effect on dopaminergic transmission via glutamatergic NMDA receptor, which is same for most psychotropic drugs. Phytochemicals present in *Blighia sapida* exhibit anti-oxidant, anti-inflammatory and neuroprotective properties that may modulate neurotransmitter levels, particularly dopamine and glutamate, which are implicated in schizophrenia (Phani Kumar et al., 2015, Anupama and Sunilkumar, 2019, Bachtela and Israni-Wingerb, 2020). EEBS (80mg/kg i.p) and risperidone (0.5mg/kg i.p) treated mice showed reduced activity counts compare with untreated mice (vehicles), this confirmed the sedative effect of EEBS and probable anti-psychotic-like effect (Usman et al., 2019), also EEBS (40, 80 mg/kg i.p) treated mice significantly showed increased percentage alternation in ketamine induced cognitive dysfunction compare with the negative control mice. This may be attributed to the activities of phytochemicals like flavonoids, phenolics, and saponins compounds in EEBS that may influence synaptic plasticity and regulate neutrophic factors, contributing to improved cognitive function, as seen in effects of atypical antipsychotic drugs.

Oxidative stress plays a key component in schizophrenia pathophysiology, constituting a central point where other factors of vulnerability meet and their interactions could play a decisive role in the severity of symptoms of the disease (Padurariu et al., 2010, Ben-Azu et al., 2022). Oxidative stress, increased plasma levels of MDA, a product of lipid peroxidation, decreased glutathione peroxidase, an enzyme that reduces lipid hydroperoxides, and free hydrogen peroxides, and other markers of oxidative stress (Sarandol et al. 2007).

In context of this study, animals in negative control group showed increased nitrite level, high MDA levels and decreased GSH compared with the vehicle group. Extract treated animals (EBSS 80 mg/kg i.p) showed significantly decreased nitrite levels compared to negative control animals. The effect of the highest dose of EEBS (80mg/kg i.p) administered to KET + EEBS 80mg/kg i.p animals is similar to that of risperidone (0.5mg/kg) treated animals (positive control). Ability of phytochemicals contained in EEBS such as flavonoids, polyphenols, and carotenoids to chelate or bind to biometals, preventing them from participating in reactions that produce reactive oxygen species could be a significant factor responsible for reduced Nitrite level in schizophrenia.

Specifically, EEBS treatments significantly increased GSH levels in the animals similarly with risperidone which is consistent with previous studies that demonstrated that risperidone treatment increased GSH levels (Monte et al., 2013, Ben-Azu et al., 2018b, 2018c, 2023). GSH is a water soluble tripeptide antioxidant enzyme consisting of cysteine, glycine, and glutamic acid. It is known to serve as a neuroprotective antioxidant agent to that reduces lipid hydroperoxides and to a great extent its enhancement reverses oxidative damage in the brain of rats treated with ketamine (Stojkovic et al., 2012, Aoyama, 2021). Complementarily to this, like risperidone, EEBS treated animals showed reduced MDA level compared with ketamine control animals, suggesting reduced lipid peroxidation in neuronal cells. Previous studies have shown that phytochemicals contained in *Blighia sapida*, possesses anti-oxidant effects that may help to neutralize free radicals generation and consequently reduce oxidative stress, which is particularly implicated in the pathogenesis of schizophrenia. Some of these phytochemicals have been documented to elicit beneficial effects (Phani-Kumar et al., 2015) in protecting neurons, by mitigating oxidative stress, inflammation and other disease exacerbating mechanisms.

## CONCLUSION

In conclusion, the findings from this study showed that ethanol extract of *Blighia sapida* stem bark reverses ketamine-induced schizophrenic-like phenotypes such as hyperlocomotion and cognitive impairment, through mechanisms associated with oxidative stress inhibition in mice brains.

## CONFLICT OF INTEREST

The authors declared no conflict of interest.

## ETHICAL STATEMENT

The institutional Animal Care and Use Research Ethics Committee, ACUREC, (University of Ibadan, Ibadan, Nigeria) approved this animal study and its experimental procedures, which was performed in accordance with the university, Animal Care and Use Research Ethics Committee guidelines 2014.The animals were handled according to the National Institute of Health (NIH 2011) guidelines for care and use of laboratory animals.

## REFERENCES

Akyol O, Zoroglu SS, Armutc F, Sahin S, Gurel A. (2004). Nitric oxide as a physiological factor in neuropsychiatric disorder. In Vivo; 18(3): 377-390.

Aline C, Padurariu M, Irina D, Stefanescu C, Dobrin R. *(2013).* Oxidative stress in schizophrenia-focusing on the main markers. *Psychiatria Danubina; 23 (3): 237-245.*

Anupama R, Sunilkumar T. (2019). Phytochemical analysis and nutraceutical studies on aril of *Blighia sapida* K.D Koenig. J. Pharmacog. & Phytochem; 8(4):34-40. E-ISSN: 2278-4136.

Aoyama K. (2021). Glutathione in the brain. Int. J. Mol. Sci; 9: 5010. doi: 10.3390/ijms22095010. PMID: PMC8125908.

Bachtela N, Israni-Wingerb K. (2020). Focus: Plant-based Medicine and Pharmacology. Yale J. Biol. Med; 93(2): 227–228. PMCID: PMC7309659.

Becker A, Grecksch G. (2004). Ketamine-induced changes in rat behaviour: a possible animal model of schizophrenia. Test of predictive validity. Prog. Neuropsychopharmacol Biol. Psychiatry; 28:1267–77.

Ben-Azu B, Aderibigbe OA, Ajayi MA, Iwalewa EO. (2016). Neuroprotective effects of the ethanol stem bark extracts of *Terminalia ivoresis* in ketamine –induced schizophrenia –like behaviours and oxidative damage in mice. Pharm. Biol; 54(12):2871-2879. doi:10.1080/13880209.2016.1190382.

Ben-Azu B, Adebayo OG, Jarikre TA, Oyovwi MO, Omogbiya IA, Eduviere AT, 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. Metab. Brain Dis; 37: 2807–2826. https://doi.org/10.1007/s11011-022-01075-5.

Ben-Azu B, Aderibigbe AO, Ajayi AM, Eneni AE, Umukoro S, Iwalewa EO. (2018). Involvement of GABAergic, BDNF and Nox-2 mechanisms in the prevention and reversal of ketamine-induced schizophrenia-like behavior by morin in mice. Brain Research Bulletin; 139; 292-306, ISSN 0361-9230, https://doi.org/10.1016/j.brainresbull.2018.03.006.

Ben-Azu B, Aderibigbe AO, Omogbiya IA, Ajayi AM, Owoeye O, Olonode ET, et al., (2018). Probable mechanisms involved in the antipsychotic-like activity of morin in mice. Biomed. Pharmacother; 105: 1079-1090. ISSN 0753-3322. https://doi.org/10.1016/j.biopha.2018.06.057.

Ben-Azu B, Del Re EC, Vander-Zwaag J, Carrier M, Keshavan M, Khakpour M, et al., (2023). Emerging epigenetic dynamics in gut-microglia brain axis: experimental and clinical implications for accelerated brain aging in schizophrenia. Front. Cell. Neurosci; 17:1139357, doi: 10.3389/fncel.2023.113935.

Ben-Azu B, Nwoke EE, Aderibigbe AO, Omogbiya IA, Ajayi AM, Olonode ET, et al., (2018). Possible neuroprotective mechanisms of action involved in the neurobehavioral property of naringin in mice. Biomed. Pharmacother; 109:536-546. doi: 10.1016/j.biopha.2018.10.055. PMID: 30399589.

Ben-Azu B, Uruaka CI, Ajayi AM, Jarikre TA, Nwangwa KE, Chilaka KC, et al., (2023). Reversal and Preventive Pleiotropic Mechanisms Involved in the Antipsychotic-Like Effect of Taurine, an Essential β-Amino Acid in Ketamine-Induced Experimental Schizophrenia in Mice. Neurochem. Res; 48:816-829. 10.1007/s11064-022-03808-5.

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.

Chindo BA, Adzu B, Yahaya TA, Karniyus GS. (2012). Ketamine-enhanced immobility in forced swim test: A possible animal model for the negative symptoms of schizophrenia. *Prog. Neuropsychopharmacol Biol Psychiatry*; 38: 310–316.

*Dadheech G, Mishra S, Gautam S, Sharma P. (2008). Evaluation of antioxidant deficit in schizophrenia. Indian J. Psychiatry; 50:16-20.*

Hallak JE, Maia-De-Oliveira JP, Abrao J, Evora PB. (*2013).* Rapid improvement of acute schizophrenia symptoms after intravenous sodium nitroprusside: A randomized, double-blind, placebo-controlled trial. *JAMA Psychiatry;* 70: 668–676.

Lindefors N, Barati SO, Connor WT. (1997). Differential effects of single and repeated ketamine administration on dopamine, serotonin and GABA transmission in rat medial prefrontal cortex. Brain Res; 759:205–12.

McCutcheon RA, Keefe RE, McGuire PK. (2023). Cognitive impairment in schizophrenia: aetiology, pathophysiology, and treatment. Mol. Psychiatry; 28:1902–1918. https://doi.org/10.1038/s41380-023-01949-9.

Monte, AS, De Souza GC, McIntyre RS, Soczynska JK, dos Santos JV, Cordeiro RC, et al., ( 2013). Prevention and reversal of ketamine-induced schizophrenia related behavior by minocycline in mice: Possible involvement of antioxidant and nitrergic pathways. J. Psychopharmacol.; 27(11): 1032-1043. doi:10.1177/0269881113503506.

Nakao S, Nagata A, Miyamoto E, Masuzawa M, Murayama T, Shingu K.( 2003). Inhibitory effect of propofol on ketamine induced c-Fos expression in the rat posterior cingulated and retrosplenial cortices is mediated by GABAA receptor activation. Acta Anaesthesiol Scand; 47: 284-90.

Olusegun OJ, Olutomi, OP. (2013). Chemical, Phytochemical and Antimicrobial Screening of Extracts of *Blighia sapida* for Agricultural and Medicinal Relevance. J. Nature and Science; 11(10):12-17.

*Owonubi OM. (1996). Some Pharmacological studies on Blighia Sapida. Med. Plant Res. Nigeria; 12: 187-195.*

*Padurariu M, Ciobica A, Hritcu L, Stoica B, Bild W, Stefanescu C. (2010). Changes of some oxidative stress markers in the serum of patients with mild cognitive impairment and Alzheimer's disease. Neurosci Lett; 469:6-10.*

Phani-Kumar G, Anilakumar KR, Naveen S. (2015). Phytochemicals Having Neuroprotective Properties from Dietary Sources and Medicinal Herbs. Phcog. J; 7(1); 1-17. doi:10.5530/pj.2015.7.1.

Reena K, Chatterjee M, Singhi S, Kaunda M, Ashwalayan V. (*2011).* Oxidative stress: a novel treatment target in psychiatric disorder. *Int. J. Pharm. Sci. Rev. and Res;* 9(030): 165-171.

Sarandol A, Sarandol E, Eker SS, Erdinc S, Vatansever E, Kirli S. (*2007).* Major depressive disorder is accompanied with oxidative stress: short-term antidepressant treatment does not alter oxidative-antioxidative systems. *Hum. Psychopharmacol;* 22:67–73. doi:10.1002/hup.829.

Sofowora EA. (2008). Medicinal Plants and medicines in Africa. University of Ife Press; 1-23.

Stojkovic T, Radonjic NV, Velimirovic M, Jevtic G, Popovic V, Doknic M, et al., (*2012).* Risperidone reverses phencyclidine induced decrease in glutathione levels and alterations of antioxidant defense in rat brain. *Prog. Neuropsychopharmacol. Biol. Psychiatry;* 39: 192–199.

Usman Y, Aderibigbe AO, Benneth BA, Fehintola FA. (2019). Antipsychotic effects of ethanol extract of *Blighia sapida* (*Sapindaecea*) stem bark in pharmacological models of psychosis in Swiss mice. *Afr. J. Med. Med. Sc*i; 48:151-160.