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Modulation of Neurochemical Homeostasis and Enhancement of Brain Derived-neurotrophic Factor Associated with Reversal Effects of Geraniol in Mice Exposed to Ketamine-induced Schizophrenia-like Behavior

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Abstract: **Alterations of neurochemical homeostasis and brain derived neurotrophic factors are linked to schizophrenia-like features. It has been suggested that these schizophrenia-like alterations are reversible by naturally occurring psychotropic agents with neuroleptic property. Here, we investigated the antipsychotic property of geraniol, an acyclic monoterpene with neuroprotective and antioxidant functions, in the reversal study of ketamine-induced schizophrenia-like behavior. According to the reversal protocol, group 1 mice (n=5) received normal saline (10 mL/kg), mice in groups 2-5 received intraperitoneal injection of ketamine (20 mg/kg) for 14 days. From days 7-14 animals in groups 3-5 additionally received geraniol (25, 50 and 100 mg/kg, i.p.) and risperidone followed by behavioral assessments using novel object recognition test (NORT) and forced swim test (FST) respectively on day 15. Neurochemical assays such as dopamine, serotonin, acetylcholinesterase, glutamic acid decarboxylase (GAD) and brain derived neurotrophic factor (BDNF) were thereafter performed in the striatum, prefrontal-cortex and hippocampus with ELISA and standard biochemical procedures. Geraniol (25, 50 and 100 mg/kg) reverses ketamine-induced non-spatial memory impairment and behavioral despair in the NORT and FST respectively. The increased dopamine release in the striatum and hippocampus were significantly reversed by geraniol (100 mg/kg). Also, ketamine-induced increased serotonin and acetylcholinesterase levels were significantly reduced by geraniol. Notably, geraniol also dramatically increased the levels of GAD and BDNFin the different brain regions. We conclude that modulation of neurochemical homeostasis and enhancement of brain derived-neurotrophic factor are associated with the reversal effects of geraniol in mice exposed to ketamine-induced schizophrenia-like behavior.**

Keywords: **Ketamine, Neurochemical, Psychosi, Geraniol, Cognitive symptoms.**

1. INTRODUCTION

Schizophrenia is a complex neuropsychiatric disorder typified by multifaceted group of symptoms ranging from behavioral hyperactivity, social withdrawal and memory deficit (Bubeníková-Valešová et al., 2008; Xu et al., 2015; Ben-Azu et al., 2018a). Schizophrenia is globally recognized to contribute to the high level of mental disability and wastefulness of young

adults as it is often known to occur as a neurodevelopmental disease manifesting between the age of 18-30 (Kang-Yi et al., 2020). Importantly, the disease is reported to exhibit sex-dependent vulnerability factor with male counterparts widely known to be affected by the disease (Kang-Yi et al., 2020). Although the reason and pathological mechanisms for this trend remains largely unknown, the roles genetic and environmental interplay have been largely discussed as key players in the pathogenesis of the disease (Ben-Azu et al., 2018a; 2018c; Stilo et al., 2019). In recent decades, an increasingly growing body of research suggest that neurotransmitters such as dopamine (DA), 5-hydroxyltryptamine (5-HT), glutamate (GLU), gamma amino butyric acid (GABA), and acetylcholine (ACh) have surfaced as a popular model for studying schizophrenia (Bubeníková-Valešová et al., 2008; Ben-Azu*et al*., 2018a, 2018b, 2018c, 2018d, 2019, 2022). Pre-clinical studies have shown that acute exposure to psychotomimetics such as dopamine receptor agonist and non-competitive NMDA receptor glutamate antagonist such as ketamine causes stereotyped and hyperactive phenotypes (Omeiza et al., 2022a). These phenotypes correspond to the hallucinatory and delusional behavior seen in the clinical presentations of schizophrenia patients (Krystal et al., 1999; Xu et al., 2015). Also, various subanesthetic ketamine doses intoxication have been shown to induce behavioral despair and cognitive shutdown in rodents (Chatterjee et al., 2011; Nikiforuk et al., 2012; Ben-Azu et al., 2018c, 2022), which corresponded to the psychotic episodes and depressive-like phenotype as well as the learning and memory impairments clinically associated with the disease (Abel et al., 2003; Morgan et al., 2006; Linn et al., 2007; Xu et al., 2015).

Quite apart from the neurotransmitters implicated in schizophrenia, another important biomarker is the brain derived neurotrophic factor (BDNF), which has been linked to the pathophysiology of the disease (Nurjono et al., 2006; Bora, 2019). BDNF is a neurotrophin with roles in neurodevelopment, synaptic plasticity and long-term potentiation (Camuso et al., 2021; Ben-Azu et al., 2018d). Derangement in BDNF at the protein and gene levels may play a part to altered brain development, neural networks, and memory formation, and it may explain, at least in part, some of the morphological and neurochemical irregularities observed in the brains of schizophrenia patients and animals (Ben-Azu et al., 2018d; Mehterov et al., 2022). For instance, BDNF has been shown to play a significant role in the adult brain in maintaining the proper functions of several neurotransmitter neurons (Colucci-D'Amato et al., 2020; Gao et al., 2022) including those implicated in SCZ (ACh, DA, Glu, GABA, 5-HT, and so on). Thus, neurochemical and BDNF-related pathways have remained important targets for the treatment of SCZ in reversing the phenotypes induced by psychotomimetics in SCZ models. However, numerous studies have shown that neurochemical and BDNF dysregulation by ketamine are reversible by clinically used antipsychotic drugs especially the second-generation antipsychotic drugs such as clozapine, risperidone but inconsistently attenuated by the first-generation antipsychotic drugs (Ben-Azu et al., 2018a, 2018n, 2019). Of note, several reports have thus shown the possible beneficial role of naturally occurring agents with numerous positive impacts documented in the last decade (Ben-Azu et al., 2018a, 2019; Ishola et al., 2021; Omeiza et al., 2022a, 2022b).

Geraniol which is chemically referred to as 3,7-dimethylocta-trans-2,6-dien-1-ol, is a monoterpene of plant origin. It is widely distributed in many vegetable plants and fruits such as lemongrass, ginger, palmosoral, cilantro, rose, nutmeg, and orange (Babukumar et al., 2017; Lei et al., 2019). Diverse pharmacological studies revealed that geraniol possesses a strong antioxidant (Prasad et al., 2017),anti-microbial (Sato et al., 2007; Rudrakanjana et al., 2022), anti-inflammatory (MurbachTeles Andrade et al., 2014),anticancer (Duncan et al., 2004), and anti-ulcer (de Carvalho et al., 2014) properties. Moreover, geraniol is also adjudged to demonstrate neuroprotective functions (Farokhcheh et al., 2021). For example, geraniol gained international recognition as a nutritional food additive and serve as supplement in a variety of neurological conditions. It has been shown to demonstrate antiparkinsonic-like activity against different models of Parkinson's disease (Rekha et al., 2013; Rekha et al., 2018),and remarkably abolishes related behavioral cognitive deficits induced by senescent-promoting compounds such as D-galactose (Rajendran et al., 2022) and lipopolysaccharide (Jiang et al., 2017). Moreover, one reason that stems the genesis of the hypothesis of this study was based on the ability of geraniol to elicitdepressive-like features on brain functions (Katty et al., 2018) and anticonvulsant-like activity (Lins et al., 2014) in mice. Interestingly, the mechanisms associated with these clinical effects have been uncovered to be related to enhancement of GABA system (Lins et al., 2014). However, no study exists on the effect of geraniol on schizophrenia given the role played by GABAergic system in the pathogenesis of the disease. Given this background, we thus set out to investigate the ability of geraniol to reverse already existing schizophrenia via mechanisms linked to normalization of neurochemical dysregulation and enhancement of GABAergic signaling in the reversal treatment of ketamine induced schizophrenia in mice.

2. METHODS AND MATERIALS

2.1. Experimental animals

Male Swiss mice weighing 20-25 g were used in this study. Animals were housed in an air temperature-controlled environment (23 ± 2 ˚C) with a 12-hour light:12-hour dark cycle, relative humidity 40-70%, and access to food and water *ad libitum*at the Laboratory Animal Centre of the University of Port Harcourt's animal house in Nigeria. All procedures in this study followed the National Institutes of Health Guide for the Care and Use of Laboratory Animals (Publication No. 85-23, revised 1985) and the University's animal ethical law. Ethical approval was obtained with ethical number (UPH/CEREMAD/REC/MM83/037)

2.2. Drugs and chemicals

Ketamine hydrochloride (Rotex Medica, Germany), geraniol, risperidone adrenaline, neurotransmitters (dopamine, glutamate, serotonin) Enzyme-linked immunosorbent assay (ELISA) kits (Abnova, Germany), were all used in the study.

2.3. Drug preparations and treatments

Normal saline was used to dissolve geraniol (GER), and risperidone (RIS) (typical antipsychotic agent). Ketamine (KET) was also diluted with normal saline. Doses of geraniol (25, 50 and 100 mg/kg, i.p.), and RIS (0.5 mg/kg), KET (20 mg/kg), used in this study were chosen based on the findings from preliminary investigations (Medeiroset al., 2018; Monte et al., 2013; Ben-Azu et al., 2018a).

2.4. Experimental design

2.4.1. Reversal effects of geraniol on ketamine-induced schizophrenia-like behaviors, and neurochemical alterations in mice

The reversal effects of geraniol on KET-induced SCZ-like behaviors, neurochemical, and neurotrophic, alterations were investigated as previously described in three different divided studies (da Silver et al., 2017; Ben-Azu et al., 2018a). In this protocol, sub-chronic treatment of psychotic episodes was induced. Mice were grouped into 7 groups (n = 7). Group 1 received normal saline (10 mL/kg, i.p.), while groups 2-7 received one daily injection of KET (20 mg/kg, i.p.) for 14 days. Thereafter, from the 8^{th} to 14^{th} day of treatment, group 2 was treated with normal saline (10 mL/kg, i.p.) as negative control, group 3-5 was treated geraniol (25, 50 and 100 mg/kg, i.p.), groups 6 RIS (0.5 mg/kg, i.p.) additionally once daily with a 30 min interval between treatments.

Behavioral studies consisting of KET-enhanced immobility in forced swim test paradigm (representing negative symptoms) (Ben-Azu et al., 2018d)based reduction in immobility time as previously described was thereafter investigated after 24h. Tests for spatial and non-spatial working memory impairments based on discrimination index (DI) using novel object recognition test (NORT), as previously described (Zhu *et al*., 2014).

2.5. Preparation of brain tissues for biochemical assays

Following behavioral assays, mice (n = 5) in the respective groups were sacrificed under cervical dislocation and the brains were rapidly removed. The whole brains were weighed and dissected into specific brain regions (striatum, prefrontal cortex, and hippocampus)on a cold ice tray at 4ºC, homogenized with 1 mL of 10% w/v phosphate buffer (0.1M, PH 7.4) respectively, centrifuged and various portions for the different biochemical assays were set apart.

2.5.1. Determination of brain neurochemicals

Regional brain DA and 5-HT levels of the striatum, prefrontal cortex, and hippocampus were estimated in mouse brain using ELISA kits (Abnova, Germany) according to the manufacturer's instructions. All reagents, standard solutions and samples were brought to room temperature before use. In the assay of glutamic acid decarboxylase (GAD) levels, its assay was performed as previously described (Yu *et al*. 2011). Acetylcholinesterase (AChE) enzyme activity, a marker for cholinergic neurotransmission, was measured in the striatum, prefrontal cortex and hippocampus by the Ellman's assay (Ellman *et al.*, 1961) as described by Eduviere *et al.* (2016).

2.5.2. Determination of brain derived-neurotrophic factor (BDNF) levels

Regional brain BDNF levels of the striatum, prefrontal cortex and hippocampus were determined in mouse brain using ELISA kits (Abnova, Germany) according to the manufacturer's instructions.

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2.6. Statistical analysis

Values were expressed as means ± S.E.M using GraphPad Prism 5 software (San Diego, CA, USA). One-way analysis of variance (ANOVA) was used to analyze the result of behavioral tests and neurochemicals. A set point value of $P < 0.05$ was taken as statistically significant

3. RESULTS

3.1 Geraniol reverses ketamine-enhanced immobility in forced swim test in mice

As shown in Fig. 1, intraperitoneal injection of KET (20 mg/kg) significantly (p <0.05) increased the duration of immobility in the FST in comparison with saline-treated group, which suggests behavioral despair, as shown in Fig. 1. On the other hand, 50 mg/kg ($p < 0.05$) and 100 mg/kg ($p < 0.01$) of geraniol as well as RIS (0.5 mg/kg, i.p.) ($p < 0.01$) profoundly [$F(5,36) = 6.954$, $p< 0.0001$] reversed the behavioural despair induced by KET in FST in mice relative to KET treatment alone (Fig. 1).

Fig. 1: Geraniol reverses ketamine-enhanced immobility in forced swim test in mice. Bars represent the mean ± S.E.M of 7 animals / group. #p< 0.05 compared to saline group, and *p< 0.05, **p< 0.01compared to KET group (one-way ANOVA followed by Bonferroni *post-hoc* test). **KET** = Ketamine, **RIS** = Risperidone

3.2 Geraniol reverses ketamine-induced non-spatial working memory impairment in mice

The effect of geraniol on KET-induced deficit in non-spatial working memory based on DI in the NORT in the reversal treatment protocol is shown in Fig 2. Intraperitoneal injection of KET (20 mg/kg) markedly ($p < 0.01$) reduced non-spatial working memory function relative to saline-treated group. Treatments with geraniol (100 mg/kg) and RIS significantly ($p < 0.01$) [$F(4,30) = 4.870$, $p = 0.0017$] reversed KET-induced non-spatial memory impairment (Fig. 2).

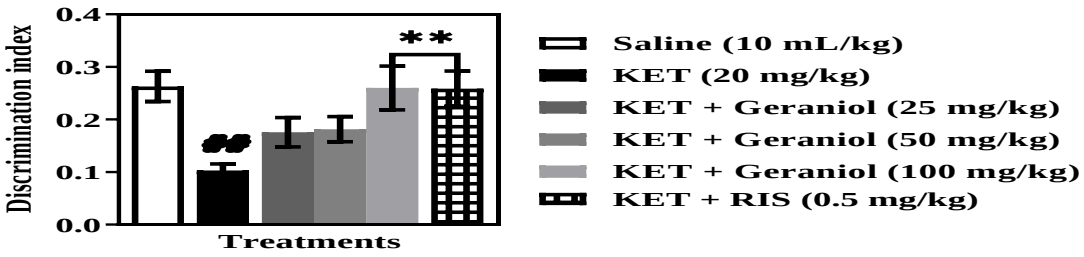

Fig. 2: Geraniol reverses ketamine-induced non-spatial working memory impairment in mice. Bars represent the mean ± S.E.M of 7 animals / group. #p< 0.05, ##p< 0.01 compared to saline group and *p< 0.05, **p< 0.01, ***p< 0.001 compared to KET group (one-way ANOVA followed by Bonferroni *post-hoc* test). **KET** = Ketamine, **RIS** = Risperidone

3.3. Geraniol reverses ketamine-induced alterations in dopamine concentrations in mice brains

As illustrated in Fig 3A-B, KET (20 mg/kg, i.p.) induced a significant increase in dopamine concentrations in the striatum, prefrontal cortex and hippocampus (p< 0.001) when compared with saline group. In the striatum and prefrontal cortex, geraniol (100 mg/kg, i.p.) and RIS (0.5 mg/kg, i.p.) significantly (p< 0.001) reversed KET-induced increase in dopamine concentration when compared with KET-treated group (Fig 3A). However, in the hippocampus, only RIS (0.5 mg/kg, i.p.) (p< 0.001) reversed the effect of KET as indicated by reduced dopamine level in comparison with KET control group (Fig. 3A).

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Intraperitoneal injection of KET (20 mg/kg) increased serotonin levels in the striatum and prefrontal cortex ($p< 0.001$) when compared with saline group (Fig. 3B). Chronic treatment with KET did not produce any significant change in 5-HT level in the hippocampus relative to saline group. Meanwhile, treatment with geraniol (100 mg/kg, i.p.) reduced KET-induced increase in 5-HT concentration in the striatum and prefrontal cortex when compared with KET group. Similarly, treatment with the standard antipsychotic agent, RIS (0.5 mg/kg, i.p.) decreased 5-HT levels in the striatum and prefrontal cortex in comparison with KET control (Fig. 3B).

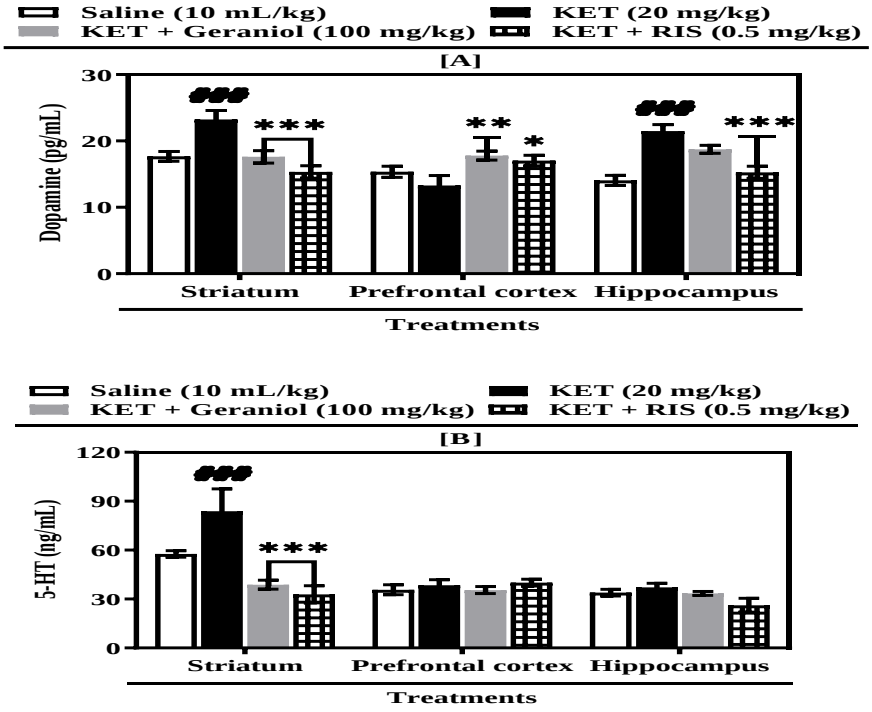

Fig 3: Geraniol reverses ketamine-induced alterations in dopamine (A) and serotonin (B) concentrations in the striatum, prefrontal cortex and hippocampus of mice brains. Bars represent the mean ± S.E.M of 7 animals / group. $^{###}p < 0.001$, compared to saline group and *$p< 0.05$, **$p< 0.01$, ***$p< 0.001$ compared to KET group (two-way ANOVA followed by Bonferroni *post hoc* test). **KET** = Ketamine, **RIS** = Risperidone

3.4 Geraniol enhances glutamic acid decarboxylase (GAD) concentrations in mice brains treated with ketamine

The effects of geraniol on KET-induced changes on GAD concentration in the striatum, prefrontal cortex and hippocampus of mice brains in the preventive and reversal treatments with ketamine are shown in Fig. 4. Intraperitoneal injection KET (20 mg/kg) significantly ($p< 0.001$) reduced GAD concentration in the striatum, prefrontal cortex and hippocampus in the preventive treatment (Fig. 5). Geraniol (100 mg/kg, i.p.) and RIS (0.5 mg, i.p.) ($p< 0.001$) significantly increased GAD concentrations in the striatum when compared with KET group. In the prefrontal cortex, geraniol (100 mg/kg, i.p.) ($p< 0.001$) and RIS (0.5 mg, i.p.) ($p< 0.05$) increased GAD levels in a specific manner. Although geraniol (100 mg/kg, i.p.) did not show any significant effect in the hippocampus, risperidone (0.5 mg/kg, i.p.) produced a significant increase in GAD level when compared with KET group (Fig. 4).

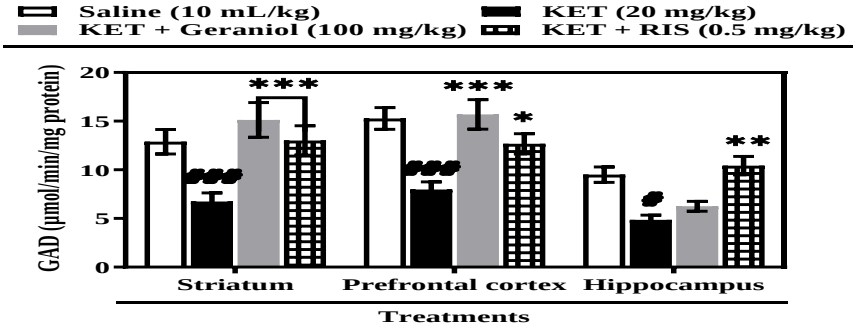

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Fig. 4: Geraniol enhances glutamic acid decarboxylase (GAD) concentrations in mice brains treated with ketamine. Bars represent the mean ± S.E.M of 7 animals / group. $^{\#}p< 0.05$, $^{\#\#\#}p < 0.001$ compared to saline group; *p< 0.05, **p< 0.01, ***p< 0.001 compared to KET group (two-way ANOVA followed by Bonferroni *post hoc* test). **KET** = Ketamine, **RIS** = Risperidone

3.5. Effects of geraniol on acetylcholinesterase (AChE) activity in mice brains treated with ketamine

Ketamine (20 mg/kg, i.p.) significantly increased AChE activity in the prefrontal cortex (p< 0.01) and hippocampus (p< 0.001) but not in the striatum, which were reversed (p< 0.001) by geraniol (25, 50 and 100 mg/kg, i.p.) and RIS (0.5 mg/kg, i.p.) (Fig. 6). In the striatum, geraniol (100 mg/kg, i.p.) (p< 0.05) and RIS (0.5 mg/kg, i.p.) (p< 0.001) reduced AChE activity when compared to KET group (Fig. 5).

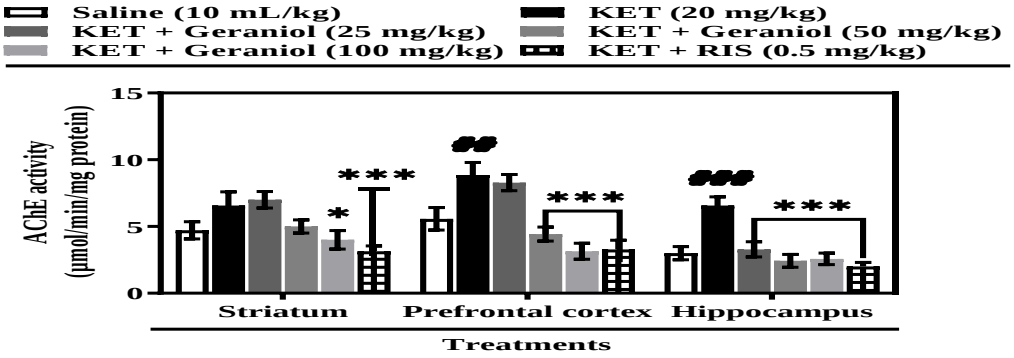

Fig 5: Effects of geraniol on acetylcholinesterase (AChE) activity in mice brains treated with ketamine. Bars represent the mean ± S.E.M of 7 animals / group. $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$ compared to saline group; *p< 0.05, ***p< 0.001 compared to KET group (two-way ANOVA followed by Bonferroni *post hoc* test). KET = Ketamine, RIS = Risperidone

3.6. Geraniol up-regulates BDNF concentrations in ketamine-treated mice

As shown in Fig 7, KET (20 mg/kg) profoundly decreased BDNF concentration in the striatum (p< 0.05), prefrontal cortex (p< 0.01) and hippocampus (p< 0.01) (Fig. 6). In the striatum, geraniol (100 mg/kg, i.p.) (p< 0.01) and RIS (0.5 mg/kg, i.p.) (p< 0.01) significantly increased BDNF concentrations when compared with KET group. However, unlike risperidone (0.5 mg/kg, i.p.), geraniol (100 mg/kg, i.p.) did not produce any significant increase in BDNF level in the prefrontal cortex compared with KET group. Moreover, in the hippocampus, geraniol (100 mg/kg, i.p.) and RIS (p< 0.05) increased BDNF levels when compared with KET treatment alone (Fig. 6).

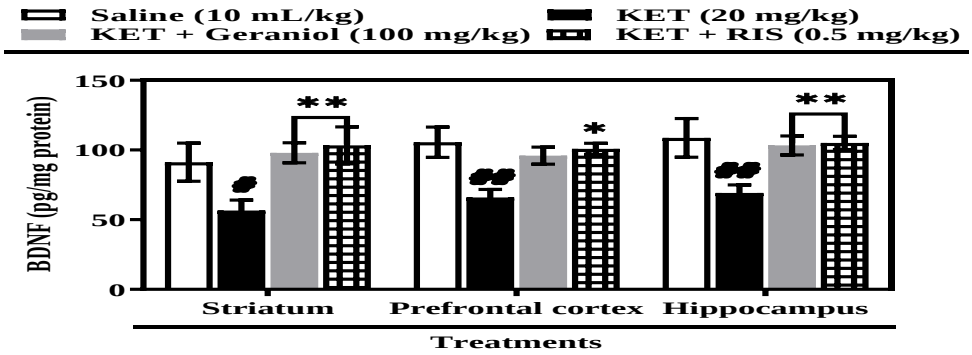

Fig.6: Geraniol up-regulates BDNF concentrations in ketamine-treated mice. Bars represent the mean ± S.E.M of 7 animals / group.$^{\#\#}p < 0.01$ compared to saline group; *p< 0.05, **p< 0.01 compared to KET group (two-way ANOVA followed by Bonferroni *post hoc* test). **KET** = Ketamine, **RIS** = Risperidone

4. DISCUSSION

In this study, we investigated the effects of geraniol on ketamine-induced schizophrenia-like behavior using a reversal approach. Here, we found that geraniol reversed ketamine-induced cognitive impairment and behavioral despair in mice.

Accordingly, the increased dopamine release in the striatum and hippocampus were significantly reversed by geraniol. Also, ketamine-induced increased serotonin level, which was particularly linked to behavioral despair, was attenuated by geraniol. Moreover, the increased AChE activity that is usually associated with cognitive decline in schizophrenia condition was significantly reduced by geraniol. Notably, geraniol also dramatically increased the levels of GAD, the neurochemical enzyme responsible for the synthesis of GABA, and BDNF, a popular brain trophic factor, in the different brain regions.

It is well known that ketamine-induced schizophrenia-like behavior induces neurobehavioral features in mice that are like clinical human psychosis (Krystal *et al*., 1994; Becker et al., 2003; Ben-Azu et al., 2018c; Haafet al., 2018; Omeiza et al., 2022; Ben-Azu et al., 2022).The behavioral phenotypes induced by ketamine are associated with alterations in neurochemical activities such as dopamine, serotonin, GABA and acetylcholine (ACh) especially in the striatum, prefrontal cortex, and hippocampus (Chatterjee et al., 2012; Yadav et al., 2017; Ben-azu et al., 2018a; 2018d). However, the brain insults caused by ketamine are reversible by antipsychotic drugs popularly used in clinical settings. Interestingly, we found that geraniol, a naturally occurring acyclic monoterpene with neuroprotective and antioxidant functions (Lins et al., 2014; Jiang et al., 2017; Katty et al., 2018; Rekha et al., 2018; Farokhcheh et al., 2021) reverses ketamine-induced schizophrenia. Ketamine is a non-competitive NMDA receptor antagonist popularly known to negatively influence the homeostasis of dopaminergic neurotransmission in the mesolimbic and cortical brain regions. Of interest is the role of ketamine in the dysregulation of dopamine in the striatum and some selected cortical brain areas such as the prefrontal cortex and hippocampus. Given the prominent role of dopamine in the regulation of cortical-dependent working memory, ketamine-induced perturbation of dopamine concentration in this area is primarily associated with distortion of spatial and non-spatial working memory functions (Ben-Azu et al., 2018a). Also, ketamine causes blockade of glutamatergic neurotransmission, which leads to induction ofexcessive dopaminergic neurotransmission in the striatal brain regions due to inhibition of GABAergic system thereby leading to behavioral disinhibition (Chatterjee et al., 2012; Ben-Azu et al., 2018a). These alterations at the cortical and sub-cortical levels have been linked tothe pathological basis of positive and cognitive symptoms of the disease (Coyle et al., 2012; Kokkinou et al., 2021). However, treatment with geraniol reversed these alterations as evidenced by reduced dopaminergic activities in these brain areas. Also, administration of geraniol significantly lowered the dopamine levels which was associated with improved cognitive functions as well the depressive phenotype demonstrated herein. Furthermore, ketamine-induced cognitive impairment has also been attributed to increased AChE, a cortical metabolic degradative enzyme of ACh. In this study, we also confirmed that ketamine-induced schizophrenia is associated with altered cholinergic system, which is in conformity with previous studies (Oshodi et al., 2021; Ben-Azu et al., 2022; Atef et al., 2022). Therefore, the finding that geraniol inhibits ketamine-induced increased AChE activity, is a confirmation of its ability to attenuate the cognitive deficit associated with schizophrenia.

In addition to inducing dopaminergic alteration, ketamine has also been shown to alter other neurotransmitters signaling pathways such as serotonin and GABA (Silver et al., 2009; Lopes-Aguiar *et al*., 2020). Serotonergic system is a very popular neurotransmitter that is notably linked to the complex groups of symptoms of schizophrenia, particularly the cognitive impairment and behavioral despair (Monte et al., 2013; Ben-Azu et al., 2018a, 2018c). Ketamine-induced serotonergic system in schizophrenia disease is strongly interconnected to hyperactivation of 5-HT_{2A} pathway in the frontal-parietal cortex, an important brain responsible for the control of executive functioning (Adams et al., 2008). Although several mechanisms have been attributed to serotonin-dependent clinical effect of antipsychotic drugs, one interesting and explicable advantage that is common with the second-generation antipsychotic drugs over the first-generation is based on inhibition of 5-HT_{2A}receptors in cortical brain regions (Nemeroff, 2005; Gareri et al., 2014, 2019; Ibrahim et al., 2022).In addition to this, is the ability of the second-generation antipsychotic drugs to enhance GABAergic signaling, an important mechanism that has been adjudged to normalize the executive function and oscillatory-dependent activity of the cortical brain region (Ben-Azu et al., 2018d). Previous studies have shown that altered GABAergic system typified by decreased GAD concentrations in the cortical as well as the sub-cortical brain regions play important role in the pathogenesis of behavioral disinhibition associated with schizophrenia. GAD is an important biogenic enzyme responsible for the synthesis of the primary inhibitory neurotransmitter, GABA. Herein, we also found that ketamine-induced schizophrenia-like behavioris also associated with GAD depletion (Ben-Azu et al., 2018d).Thus, in this study, the ability of geraniol to reverse ketamine-induced dysregulation of serotonin and GAD depletion in the cortical and subcortical brain regions suggests it possesses the capacity to ameliorate the debilitating negative and cognitive symptoms of this disease.

Additionally, schizophrenia-like disease is previously reported to be associated with depletion of BDNF levels, an essential neurotrophic factor responsible for the regulation of neuronal development, maturation, and plays also an important role in

synaptic plasticity and cognitive functions (Angelucci et al., 2005, 2007; Zuccato et al., 2009; Silakarma and Sudewi, 2019). BDNF is also known to promote induction of GAD synthesis in different brains such as cortical areas, regulate neurochemical homeostasis as well as protects against glutamate-mediated excitotoxicity (Maqsood and Stone, 2016). In this study, we additionally confirmed that ketamine-induced schizophrenia is related to low level of BDNF, which is in line with previous findings (Ben-Azu et al., 2018d). On the other hand, treatment with geraniol as well the standard drug used in this study, risperidone significantly reversed the ketamine-induced depletion of BDNF in the striatum and hippocampus when compared with ketamine group. Interestingly, some reports had earlier shown that geraniol possesses the ability to reverse neurological disorder via up-regulation of BNDF-dependent signaling and functions (Atef et al., 2022).

5. CONCLUSION

Our findings suggest that modulation of neurochemical activities and enhancement of brain derived-neurotrophic factor are associated with the reversal effects of geraniol in mice exposed to ketamine-induced schizophrenia-like behavior.

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