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Neurotoxicity, antipsychotic and antidepressant screening of the fruit of *Rosa moschata* in mice

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Abstract: Extract of *Rosa moschata* (RM) fruits was evaluated for the anti-schizophrenic and antidepressant activities. We first determined the neurotoxic effect of hydro-methanolic extract of RM using inverted-screen test. Further, the extract was tested in the ketamine-induced schizophrenia model and its antidepressant effect was assessed by tail suspension and forced swim test in mice. Different doses of extract were administered once/day to the animals for 14 consecutive days. Behavioral parameters were investigated 24h after last administration of drug/extract by performing Y-maze test, forced swim test and open field test. Results showed that TD_{50} of the extract was ~1000mg/Kg. Moreover, extract significantly increased % alternations in YMT, reduced immobility time in FST and enhanced locomotion in OFT compared to saline group. Similarly, RM extract decreased time of immobility in FST and TST significantly showed antidepressant effect. Thus, it was concluded that extract of RM has antipsychotic and antidepressant properties.

Keywords: *Rosa moschata*, schizophrenia, ketamine-induced antipsychotic model, psychosis, depression.

INTRODUCTION

Schizophrenia is a mental syndrome that affects 1% of the world population (Bhugra, 2005, Kiraz and Demir, 2021), exhibiting positive, negative and cognitive symptoms along with various comorbidities such as anxiety, depression, substance abuse and others. The positive symptoms of the disease include delusion as well as a hallucination. The negative symptoms may include a lack of interest, social isolation, paucity of speech and behavioral alterations. Similarly, the deficit in learning and attention are included in the cognitive symptoms of schizophrenia. All these symptoms affect the quality of life of the individual suffering from schizophrenia(Batinic, 2019). Depression is the most common comorbid disorder in schizophrenic patients and occurred in about 50% of the patients (Buckley *et al*., 2008;Etchecopar-Etchart *et al.*, 2021) however, it was also reported that in depressive conditions, psychotic-like symptoms exist. Thus, there is a common pathophysiological pathway between depression and schizophrenia. On the neurochemical basis, until today no specified etiology of this disorder has been found, however, many well-known hypotheses are associated with the etiology of schizophrenia such as the dopamine hypothesis(Howes and Shatalina, 2022), amphetamine hypothesis, endocannabinoid hypothesis (Fernandez-Espejo *et al.*, 2009;Little and D'Mello, 2022), GABAergic hypothesis, serotonergic hypothesis and NMDA receptor hypofunction hypothesis (Swanton, 2020;Eggers, 2023). Among all these hypotheses dopamine hypothesis and NMDA receptor hypofunction hypotheses have gained much popularity.

Various chemical-induced models, to mimic schizophrenia-like symptoms, have been used for this purpose and some have shown greater results such as the amphetamine-induced model, phencyclidine and ketamine-induced model and, endocannabinoid model of schizophrenia (Steeds*et al.,* 2015;Winship *et al.,* 2019). However, the ketamine-induced model is the most validated model for producing most of the symptoms of schizophrenia (Jones*et al.,* 2011). It induces behavioral alterations, hyperactivity and changes in cognitive performance and also produces biochemical and neurobiological alterations comparable to those found in schizophrenic brains (Narendran et al., 2005;Stone*et al.*, 2014;Sultana and Lee, 2020).

Current medication therapy for schizophrenia has little efficacy and a broad spectrum of adverse effects such as extrapyramidal syndrome, tardive dyskinesia and hyperprolactinemia of typical antipsychotics and weight gain in case of using atypical antipsychotics(Miyamoto *et al.,* 2012;Ohno*et al.*, 2019). In comparison, 1/3rdof patients are resistant to existing available therapy. There is also a significant need to explore new chemical components with increased potency and tolerability in the treatment of schizophrenia.

Since old age, medicinal plants have been a very effective way of acquiring different active constituents for the ailments of various diseases due to higher chemical diversity. In the present study, we investigated the effects

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of *Rosa moschata* against schizophrenia and depression in mice using animal models. *Rosa moschata* belongs to the family of *rosacea* having more than 120 species of this genus. The plant is a perennial climbing shrub. Traditionally this plant has been used in diarrhea, stomach disorders (Ali*et al.*, 2014), wound healing, eye disorders (Sharma and Devi, 2013) and relieving stress according to our recent experiments (Jamal *et al.*, 2019). The plant contain spalmitic acid, linolenic acid, margaric acid, vitamins A, C and E, flavonoids and essential oils (Honarvar*et al.*,2011). This plant has mind-soothing effects in traditional use and also the presence of strong antioxidants in their constituents, we investigate this plant for its antipsychotic activity along with antidepressant activity.

MATERIALS AND METHODS

Animals

Male albino mice (balb/c strain) weighing 25±2g were taken for the experiments with food and water *ad libitum.* Animals were brought to the behavioral room one hour before the tests for acclimatization. Tests were conducted in the light cycle of the 24-hour light/dark cycle, maintaining the temperature at 22±2ºC. All the procedures were performed according to the ethical guidelines of the institution. Ethical approval for use of animals has been obtained from Departmental ethical committee wide # AUST/Pharm/2016/124a.

Preparation of plant extract and drug used

Fully ripened fresh fruits of *Rosa moschata* were harvested in the months of October-November 2015fromLower Dir, Sayar Rashkhani Valley, Khyber Pakhtunkhwa, Pakistan. The plant has been identified by the esteemed botanist Prof. Dr. Jehandar Shah, University of Malakand, Pakistan. For the present study, the extract of *Rosa moschata* was provided by the same institution.

The extract of the plant was prepared according to the previous protocol (Ali*et al.* 2014).The fruit was shade air dried, cleaned and free from adulterants and ground twice to a fine powder. The powder was soaked in grade double-distilled methanol (80%) for around 15 days with intermittent stirring. The filtrate was vaporized by a rotary evaporator at 30-35°C under condensed pressure. The semi-solid extract was then placed in large Petri dishes and put in the open air at room temperature to make it concentrated (1300g). The extract was stored in a refrigerator at 2-8°C(Ali *et al.*, 2014).

Risperidone (RIS) was used as a positive control, while ketamine (KET), acquired from Global Pharmaceutical, Pakistan, was used to induce psychotic symptoms. All the chemicals and plant extract has been formulated in normal saline and administered not more than 1% of the total body weight of the animal.

Neurotoxicity

Inverted screen method

Acute neurotoxicity testing was performed by the inverted screen method (Coughenour *et al.*, 1977). It consists of a square mesh of 13cm on each side with a 0.06cm mesh size, supported by an iron grid and a lock on one side of the grid to block the screen from rotation. The test protocol is rather basic. A preparation trail was carried out one day before the testing of the compounds/extracts. Each animal was put on the screen on the day of testing and the screen rotates at 180º.

Rosa moschata extract was administered to different groups at different doses (500, 800 and 1000mg/Kg) 30 minutes before the procedure. The inverted screen procedure was performed after the time specified. Within the 60s, mice struggled to climb to the upright position of the inverted screen. The extract's TD50 was measured at a point where 50% of the animals did not climb upright to the screen.

Groups

In this experiment, ketamine was administered to each group for 14 consecutive days once/per day. During the 8th to 14th days along with ketamine administration, the extract was also administered after 30 minutes of the ketamine dose. Behavioral investigations were analyzed 24 h after the last dose as represented in fig. 1.

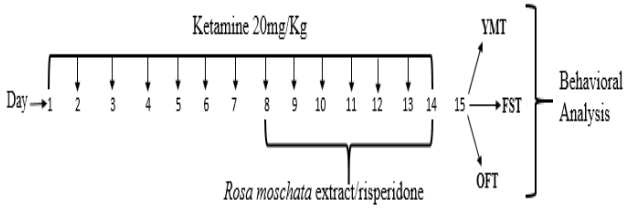

Fig. 1: Protocol of the antipsychotic experiment

For antipsychotic activity, animals were distributed into 6 (n = 8).a. Vehicle control (only vehicle was administered to these animals), b. Positive control (ketamine was administered to animals in this group), c. Standard drug control (Risperidone was administered to mice in this group following ketamine administration), d. Groups 4-6 (Different doses of the *Rosa moschata* extract were given to the animals in the respective groups). Ketamine (20mg/Kg) and RIS (0.5mg/Kg) were given to their respective group during the 8th to 14th days of the experiment. *Rosa moschata* at 3 different doses (50,100 and 150mg/Kg) were given to groups 4, 5 and 6 respectively during the 8th-14th days of the experiment.

Behavioral tests for antipsychotic activity

Y-Maze test

YMT is the most extensively used method for the assessment of cognitive performance in rodents(Kraeuter *et al.*, 2019). It was a Y-shaped stainless steel apparatus,

having 3 arms of the same size (36cm length, 20cm height and 6cm width). Arms were named "A", "B" and "C". During the experiment, each mouse was placed in arm "A" of the apparatusto search all the 3 arms for 5 minutes. The number of alternations of each animal was recorded. Entry inside all the arms of the maze on a consecutive occasion was considered as an alternation (Dall'Igna *et al.*, 2007). Percent alternations of each animal were measured by the following formula:

%Alternations= Total alternations/(total arm entries-2)

Forced Swim test (FST)

FST is mostly employed to determine behavioral despair in the animal model of schizophrenia(Chindo*et al.*, 2012). The apparatus consists of a plastic container (28cm in length, 12cm in diameter). The apparatus was filled with water up to 14cm in height of the container, maintaining the temperature at 25ºC. The animal was put inside the forcedswim apparatus for 6 minutes.The immobility of each animal in the last 5 minutes of the test was noted.

Open field test (OFT)

For the assessment of the locomotor activity of rodents, FST has been used(Kraeuter*et al.*, 2019). Square acrylic apparatus (78cm each side, 15cm wall height), was divided into 16 equal squares in such a way that in the periphery there were 12 squares while in the center there were 4 squares. Mice were placed in the mid of the apparatus in a noise-free environment and allowed to explore for 5 minutes. The locomotor activity of each animal was evaluated by the number of squares crossed during 5 minutes.

Antidepressant activity

Forced swimming test (FST)

Increased immobility by rodents is a sign of depression in FST. This test was performed according to the procedure of the Porsolt with minor modifications(Porsolt *et al.*, 1978;Moghaddam*et al.*, 2021). Thirty minutes before the test, each animal was administered vehicle (normal saline 0.9%), different doses of extract of the *Rosa moschata* (50, 100 and 150mg/Kg), or FLU (10mg/Kg). The animal was put in a container having a depth of 28cm with 12cm diameter, containing 14cm of water at 25ºC. The animal was left to swim for 6 minutes inside the container while recording the immobility. Data were analyzed in the last 4 minutes of the test period.

Tail suspension test (TST)

TST is the mostly used method for screening of antidepressant activity of unknown compounds(Sultana and Lee, 2020). Extract/vehicle or drug was given to the animal 30 minutes before the test. The animal was suspended by its tail 50cm above the ground for 6 minutes. The immobility of each animal was recorded in the last 4 minutes of the test period.

STATISTICAL ANALYSIS

Data were presented as mean ± SEM. Statistical analysis was performed using OriginLab (8.5 Version) software. In the ketamine-induced schizophrenia model, experimental data were compared with the ketamine-treated group and the results of ketamine group was compared with the vehicle-treated group, while in the depression model, the values were compared to the vehicle-treated group. Significance among different groups was acquired by using One-way ANOVA followed by *post hoc Tukey's* test. P value <0.05 was considered significant.

RESULTS

Neurotoxicity profile

The median neurotoxic dose (TD_{50}), the concentration of the extract that caused a neurological deficit in 50% of the animals in the inverted screen method, was 1000mg/Kg of the intraperitoneally administered extract of *Rosa moschata*.

The antipsychotic activity of Rosa moschata

Effect of Rosa moschata on reversal of increased locomotor activity induced by ketamine in OFT

The outcome of RM on reversal of hyperlocomotion induced by ketamine was analyzed through OFT. This test was applied to investigate hyperlocomotion in the ketamine-induced schizophrenia model in rodents. Chronic ketamine (20mg/Kg, Fig. 2) treatment for 14 days increased locomotor activity (hyperlocomotion) as compared to the vehicle-treated animals, by increasingthe number of squares crossed in OF significantly (Fig. 2; n=8). Bars showed that increased locomotor activity caused by treatment with ketamine was significantly ($p<0.05$) reverted by RM (50, 100 and 150mg/Kg) dose-dependently after treatment between days 8^{th}-14^{th} of the experiment. Results also showed that RIS 0.5mg/Kg significantly reverted hyperlocomotion in OFT.

Improvement in cognitive performance by using Rosa moschata in the Y-Maze test (YMT)

Fig. 3 showed that extract of RM improved the memory performance in ketamine-induced cognitive dysfunction in mice by increasing the percent alternations in YMT. It can be seen in the bar diagram that intraperitoneal KET (20mg/Kg) administration for 14 days, induced psychotic-like symptoms and reduced the percent alternations in YMT compared to the control group indicating that memory impairment was caused by ketamine. This cognitive deficit was improved significantly and dose-dependently by administration of R.M extract between days 8^{th}-14^{th} of the experiment. Extract of RM, 50, 100 and 150mg/Kg, significantly improved the ketamine-induced cognitive deficit in animals following treatment with the extract from day 8 to day 14 of the experiment

compared with the ketamine-treated group alone by increasing % alternations in YMT. The action of 150mg/Kg dose is comparable to the result of RIS (0.5mg/Kg p.o) that significantly reversed the ketamine-induced cognitive dysfunction by increasing % alternations in Y-maze.

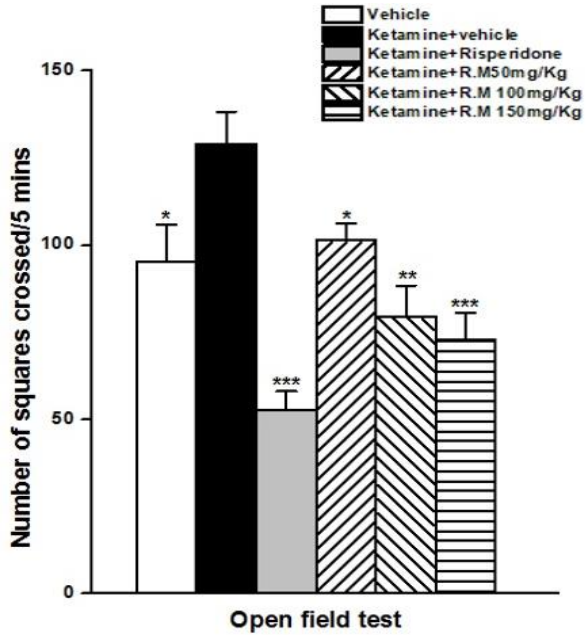

Fig. 2: R.M reversed the hyperlocomotor activity induced by ketamine

Rosa moschata dose-dependently reduced number of squares moved in the OF. Data are given as Mean ± SEM of 8 animals/group. One-way ANOVA shows that there is substantial difference exists between different treatment groups. * denotes p<0.05 as compared with KET group. *** denotes p<0.001.
RM = *Rosa moschata*, RIS = Risperidone, KET = Ketamine

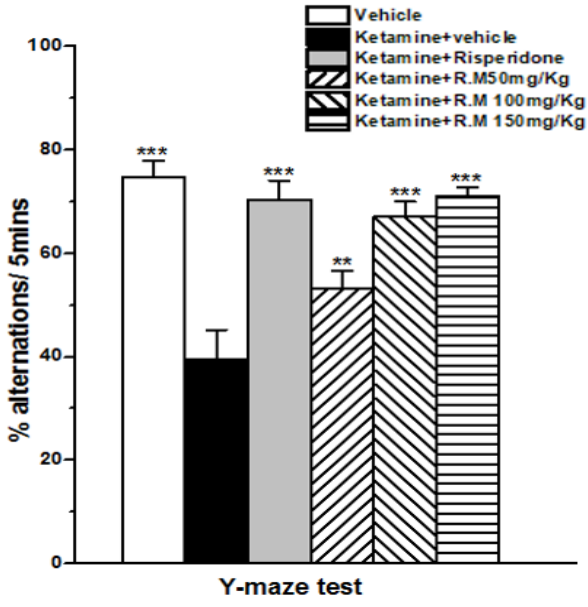

Fig. 3: Improvement in cognitive performance by *Rosa moschata* in Y-Maze

The figure shows that ketamine significantly and dose-dependently increased the percent alternations in the YMT. Values show the Mean ± SEM of 8 animals/group. One-way ANOVA exhibited that there are substantial differences exist between R.M groups (p<0.05) compared with KET group. *** denotes p<0.001. All the doses of R.M significantly improved the memory performance in mice in YMT.
RM = *Rosa moschata*, RIS=Risperidone, KET = Ketamine, YMT = Y maze test

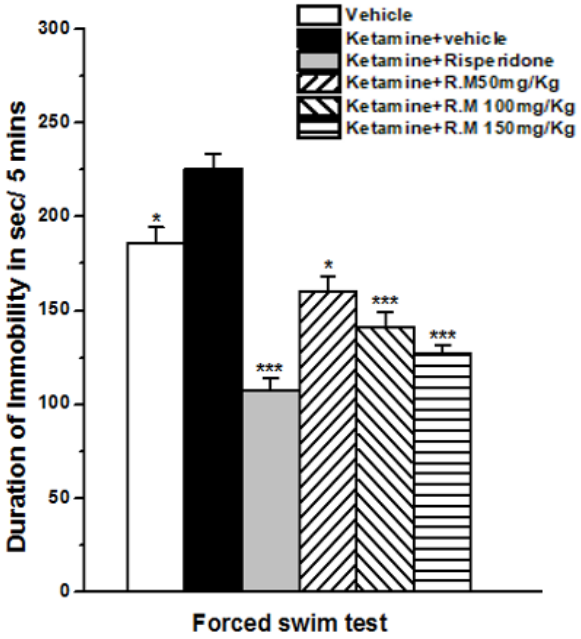

Fig. 4: *Rosa moschata* reduced the immobility time in ketamine-induced model in FST

Rosa moschata dose-dependently reduced the behavioral despair in the FST. Values are denoted as Mean ± SEM of 8 animals/group. One-way ANOVA indicated a significant difference in groups of RM (p<0.05), compared with KET group. *** denotes p<0.001.
RM = *Rosa moschata*, RIS=Risperidone, KET = Ketamine

As shown in the figure the maximum reversal (p<0.5) occurred with a dose of 150mg/Kg of RM (fig 3; n=8, P<0.05) following treatment from day 8 to 14, which was comparable to the reversal of hyperlocomotion by using RIS 0.5mg/Kg (fig 3, n=8).

Effect of RM on ketamine-induced immobility in FST

Fig. 4 clearly shows that RM ameliorates behavior despair in animals in the ketamine-induced model of schizophrenia. It was noted that KET (20mg/Kg) for 14 days of treatment increased the spell of immobility significantly (p<0.05) than the saline-treated group in FST. Moreover, RM (50, 100 and 150mg/kg), given from day 8 to day 14th of the treatment, significantly (p<0.05) and in a dose-dependent manner reversed the ketamine-induced enhanced immobility as compared with the result of the ketamine-treated group alone. Furthermore, an extract of R.M150mg/Kg showed optimum results compared to a known antipsychotic drug, RIS 0.5mg/Kg.

Antidepressant activity of Rosa moschata

Rosa moschata reduced the immobility time in FST

Fig. 5 shows the antidepressant effect of *Rosa moschata* in FST. One-way ANOVA analysis shows clearly that all three doses of RM (50, 100 and 150mg/Kg) significantly ($p<0.05$, n=8) and in a dose-dependent manner enhanced the mobility of mice in FST, thus showing antidepressant activity. The optimum antidepressant effect was shown in FST when a 150mg/Kg dose of R.M was given to mice, as compared with the effects shown by the vehicle-treated group (fig. 4, n=8; $p<0.05$). Similarly, FLU (10mg/kg) significantly ($p<0.05$) shortened the immobility duration in FST as compared to the vehicle-treated animals.

Rosa moschata reduced the immobility duration in TST

Fig. 6 shows that *Rosa moschata* significantly reduced the depression-like behavior in the TST. Fig. 6 reveals that RM significantly decreased the immobility spell in TST as compared with the result of vehicle-treated group (n=8, fig. 6, $p<0.5$). It is observed in the figure that the greater antidepressant effect of RM is seen at a dose of 150mg/Kg. The effect of 150mg/Kg extract as shown in the figure is comparable to the effect shown by fluoxetine 10mg/Kg. From the figure, it is depicted that RM dose-dependently reduces the immobility time in TST as compared with the vehicle-treated group. Similarly, FLU (10mg/Kg) shortened the immobility duration of mice in TST compared with the result of the negative control animals.

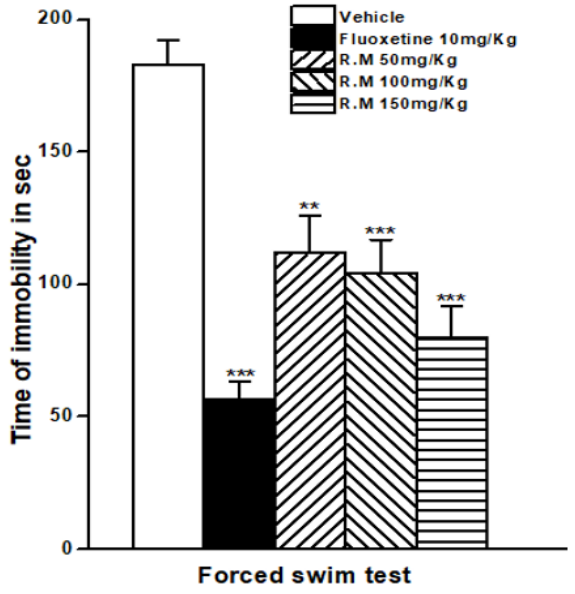

Fig. 5: *Rosa moschata* reduced the immobility time in FST

Rosa moschata reduced the behavior despair in the FST by increasing the swimming duration by the animals. Values show the Mean ± SEM of 8 animals in each group. One-way ANOVA shows that a significant difference present between R.M groups ($p < 0.05$) as compared with the vehicle group. *** denotes $p<0.001$.

R.M = *Rosa moschata*, RIS=Risperidone

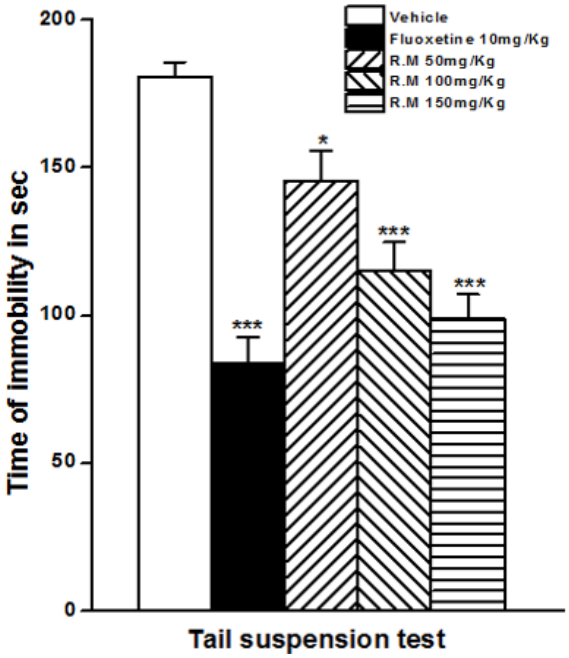

Fig. 6: *Rosa moschata* reduced the immobility duration in TST

Rosa moschata reduced the behavior despair in the TST.Values show the Mean ± SEM of 8 animals in each group. One-way ANOVA showed that significant differences exist between RM groups ($p < 0.05$) as compared with the vehicle group. *** denotes $p<0.001$.

RM = *Rosa moschata*, RIS = Risperidone

DISCUSSION

The current experiment was initiated by establishing a ketamine-induced working model in the lab that could elicit schizophrenia-like symptoms in mice. Previously, a dose of ketamine for inducing schizophrenia-like symptoms in mice was between 20-100mg/Kg. However, 20mg/Kg ketamine was selected for the experiment after the initial screening to induce schizophrenia in mice. In the current experiments, we analyzed that chronic administration of ketamine produced schizophrenia-like symptoms in mice that were reversed by hydromethanolic extract of *Rosa moschata*. It was also found that extract of R.M significantly reversed ketamine-induced schizophrenia-like symptoms in mice using OFT, FST and Y-maze test.

Although the mechanism by which ketamine-induced negative symptoms is not fully understood, however earlier studies have found the contribution of 5-HT_2 receptors to negative symptoms (Chatterjee *et al.*,2012; Mitazaki *et al.*, 2020). Therefore, it may be suggested that the extract of RM may be involved in the regulation of 5-HT receptors in the alleviation of negative symptoms of schizophrenia. It has been suggested that ketamine-induced increased immobility in FST might be mediated via the blockade of 5-HT_2 receptors by using risperidone

(Chindo*et al.*,2012). Thus, results have found that R.M showed a significant decrease in ketamine-induced enhanced immobility in the FST dose-dependently and these results are compared with the result of risperidone and these results suggest that R.M may have an antipsychotic activity that may ameliorate the negative symptoms of psychosis.

It has been known that the dopaminergic pathway is mainly involved in the hyperlocomotion activity in schizophrenia (Benturquia*et al.*, 2008, Korchynska*et al.*,2022). Previously, it was found that ketamine raises dopamine release and also inhibits its uptake from the synapse partially due to the antagonism of NMDA receptors located on GABAergic inhibitory neurons(Wu*et al.*, 2021). Our results found that R.M significantly reversed the ketamine-induced hyperlocomotion, suggesting the antipsychotic activity of R.M might be due to its action on NMDA receptors thus modulating dopaminergic activity and ultimately showing efficacy against positive symptoms of schizophrenia.

Impairments in learning, executive functions and long and short-term cognitive deficits are the cognitive dysfunctions associated with schizophrenia(Smucny *et al.*,2022). The Y-Maze has been employed most commonly to evaluate memory performance in rodents. Our findings showed that memory impairment caused by ketamine (20mg/Kg), by decreasing number of alternations in the Y-maze, was reversed by extract of R.M and also by Risperidone. Mechanistically, inhibition of NMDA receptors impairs memory formation and learning dysfunction by decreasing the phosphorylation of CaMK-II. Ketamine disrupts LTP by inhibiting NMDA receptors (Mouri et al., 2007;Luo*et al.*, 2021) and this memory deficit was overcome by the R.M extract in Y-maze test analysis by improving the percent alternations in animals.

There are very important comorbidities with schizophrenia such as depression, anxiety, PSTD and obsessive-compulsive disorders (Buckley*et al.*, 2008;Etchecopar-Etchart*et al.*, 2021). Among these comorbidities the most prevalent comorbidity is depression.

The correlations/overlaps between depression and schizophrenia are at the level of oxidative imbalance and reduction of BDNF in the brain (Angelucci *et al.*,2005;Nieto*et al.*, 2021). Therefore, in the present study, the antidepressant activity of *Rosa moschata* was also investigated along with antipsychotic effects.

It was evaluated that the extract of *Rosa moschata* has significant antidepressant activity in FST and TST by decreasing the time of immobility. Thus, the antidepressant activity of *Rosa moschata* along with strong antipsychotic effects make it advantageous in ameliorating the symptoms related to schizophrenic conditions comorbid with depression.

CONCLUSION

Based on the results obtained from the experiments, it was concluded that the extract of *Rosa moschata* has the potential in ameliorating the symptoms of schizophrenia and also produced antidepressant activity. Further research work is needed to elucidate the mechanistic pathway(s) involved in the antipsychotic and antidepressant activity of the *Rosa moschata.*

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