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EVALUATION OF ANTI-PSYCHOTIC POTENTIAL OF ETHANOLIC EXTRACT OF *Crossandra infundibuliformis* LEAVES ON EXPERIMENTAL ANIMALS

[1]Krupa N, [2]Karunakar Hegde,

[1]PG Scholar, [2]Professor and Head

[1]Department of Pharmacology, Srinivas College of Pharmacy,

Valachil, Post Farangepete, Mangalore, Karnataka, India - 574143

Abstract: *Crossandra infundibuliformis*, commonly known as the firecracker flower, is widely utilized in traditional medicinal practices such as Ayurveda and Siddha for the treatment of various conditions, including diabetes, leprosy, ulcers, headaches, conjunctivitis, and skin disorders. This study aims to evaluate the antipsychotic potential of ethanolic extracts derived from the leaves of *Crossandra infundibuliformis*. The leaf extracts were prepared using the maceration method. Two doses of 200 mg/kg and 400 mg/kg body weight of the *Crossandra infundibuliformis* leaf extract were selected and administered for 21 days for rats and 15 days for the mice, to evaluate their antipsychotic activity. The antipsychotic effects were assessed using the Pole Climb Avoidance Test in rats, where Haloperidol at a dose of 1 mg/kg (i.p.) served as the standard, and the Ketamine-induced stereotypic behaviour model in mice, with Olanzapine at a dose of 5 mg/kg (i.p.) as the reference drug. The ethanolic extract of *Crossandra infundibuliformis* leaves demonstrated significant dose-dependent inhibition of conditioned avoidance response (CAR) in rats, as indicated by an increased amount of time spent on the grid floor. In the ketamine-induced stereotypic behaviour model in mice, administration of the extract over 15 days significantly reduced behaviours such as falling, weaving, head-bobbing, and turning. These findings indicate that the ethanolic extract of *Crossandra infundibuliformis* exhibits significant antipsychotic activity in experimental animals.

Keywords - Antipsychotic activity, *Crossandra infundibuliformis* leaf, Olanzapine, Pole-climbing, Stereotypic behaviour.

I. INTRODUCTION

Psychosis is defined by symptoms such as delusions, hallucinations, and disorganized thinking while the individual remains aware of their surroundings.[1] The term "schizophrenia," was introduced by Swedish psychiatrist Eugen Bleuler in 1908, originates from Greek words “Schizo” means “Split” & “Phrene” which means “Mind”.[2] Psychosis is a central aspect of schizophrenia spectrum disorders, which can also manifest in mood disorders, substance use issues, and medical conditions.[3] The global rate of first psychotic episodes is about 50 per 100,000 people, with schizophrenia impacting around 24 million individuals (0.32%) worldwide, typically emerging in late adolescence or early adulthood.[4] Symptoms are classified as positive (e.g., hallucinations and delusions), negative (e.g., social withdrawal and lack of motivation), and cognitive (e.g., difficulties with memory and decision-making), significantly affecting everyday functioning.[1] Unfortunately,

public misconceptions often associate schizophrenia with insanity and unpredictable behavior, resulting in stigma, delays in seeking treatment, and poorer outcomes for those living with the disorder.[5]

The cause of schizophrenia remains unclear, but it involves genetic, environmental, and neurological factors. With 80% heritability, genes related to synapse function and immunity are implicated. Environmental influences include prenatal stress, childhood trauma, cannabis use, and urban living. Additionally, disruptions in dopamine, glutamate, and GABA signaling, along with altered brain development and immune function, contribute to the disorder's complexity.[6]

Antipsychotics are the primary treatment for schizophrenia spectrum disorders, typically starting with low doses that are gradually increased. There is debate over the effectiveness of second-generation antipsychotics compared to first-generation ones. Common first-generation medications include chlorpromazine, haloperidol, flupenthixol, and pimozide, while second-generation options include olanzapine, clozapine, risperidone, and aripiprazole.[7] Treatment is challenging, as typical and atypical antipsychotics often provide insufficient control of symptoms and come with many undesirable side effects.[3]

Crossandra infundibuliformis is a plant recognized for its medicinal properties, particularly in traditional healing practices. Its roots and leaves are traditionally used to treat various ailments, including diabetes, ulcers, leprosy, and skin conditions, with its flowers also aiding in the relief of fever and headaches.[8] In the Virudhunagar district of Tamil Nadu, the Paliyar tribes utilize a mixture of flowers and pepper to promote wound healing. This plant is rich in beneficial natural compounds such as flavonoids, phenolic acids, and saponins, which contribute to its antioxidant, antimicrobial, and neuroprotective effects. These compounds also play a crucial role in supporting the central nervous system by interacting with neurotransmitters, and they show promise in addressing conditions like psychosis.[9]

Medicinal plants have been essential in healthcare for thousands of years, providing bioactive compounds like flavonoids, phenols, alkaloids, saponins, and tannins, known for their antioxidant properties.[10] Many people, particularly those with chronic health conditions, seek more holistic treatment options when they feel that conventional medical approaches are not effective enough.[9] Ethnobotanical research plays a key role in pharmacology and drug discovery, as plant-derived compounds can be used directly as treatments, act as drug precursors, or inspire the development of new therapeutic agents.[11]

II. MATERIALS AND METHODS

2.1 Collection and authentication of the *Crossandra infundibuliformis*:

The fresh leaves of *Crossandra infundibuliformis* used for the study were collected in April locally from Machina, Karnataka, India. The taxonomist Dr. Siddaraju M. N, (Assistant Professor and Research Guide, Department of Botany, University College Mangalore) authenticated the plant.

2.2 Drugs and Chemicals:

Haloperidol and Olanzapine were obtained from Yarrow chem, Ketamine injection from Pakson Pharm PVT LTD, 95% Ethanol from KSBCL.

2.3 Preparation of ethanolic extract of *Crossandra infundibuliformis* leaves:[12]

The fresh leaves of *Crossandra infundibuliformis* were washed and then shade-dried at room temperature. After drying, the leaves were powdered using a mechanical grinder. 100 g of the dried powdered material was then macerated with 300 mL of ethanol at room temperature. The extract was filtered and evaporated using a rotary vacuum evaporator at 40°C. Finally, the dried extract was stored in airtight container and kept in a freezer at 4°C until further use.

2.4 Preliminary phytochemical evaluation:[13]

The ethanolic extract of *Crossandra infundibuliformis* leaf was subjected to qualitative tests for the identification of different phytoconstituents.

2.5 Experimental animals:

Healthy albino rats (150-250g) and mice (20-30g) both of either sex were maintained under standard lab conditions (temperature 22 ± 2°C, relative humidity 60±5%, and 12 h light/dark cycle) with free access to a standard pellet diet and water ad libitum. After at least one week of acclimatization, the experiment was conducted between 8:00 and 14:00 hours. The experimental study protocol was reviewed and approved by the Institutional Animal Ethics Committee (Approval No. SCP/IAEC/F150/P213/2023). All the procedures

were performed under the Institutional Animal Ethics Committee constituted as per the direction of the Committee for Control and Supervision of Experiments on Animals (CCSEA).

III. Experimental Methods:

3.1 Pole Climbing Avoidance in Rats:[14]

The pole-climbing apparatus is a 25 × 25 × 40 cm soundproof, dimly lit with chamber with a grid floor that delivers mild shocks. A central wooden pole (2.5 cm diameter) offers shock- free area. A 2.8 kHz speaker and 28 V light serve as conditioned stimuli (CS) by emitting a sound or light. In the experiment, a rat is exposed to a neutral CS, typically a sound or light, followed 20 seconds later by a 1.5 mA foot shock. During training, a bell sound consistently precedes the electric shock administered via the grid floor.

Experimental design:[15]

The Wistar albino rats (150–250 g) of either sex were randomly divided into four groups of six animals each. The different groups were assigned as follows:

Groups	Treatment
Group I: Control	Vehicle 1ml/100g, p.o.
Group II: Standard	Haloperidol (1mg/kg, i.p.)
Group III: Test drug	200 mg/kg p.o. of CILE (*Crossandra infundibuliformis* leaf extract)
Group IV: Test drug	400 mg/kg p.o. of CILE (*Crossandra infundibuliformis* leaf extract)

Procedure:[14]

In the pole-climbing apparatus, rats were trained to climb a pole to avoid a 20V shock delivered via the grid floor when a buzzer sounded. Training persisted until they responded within 3 seconds of the buzzer. During testing, a 4-second conditioned stimulus (CS) was presented before a 26-second unconditioned stimulus (US) shock. Climbing the pole during the CS alone was considered an avoidance response while climbing during both stimuli was classified as an escape response. Each test session included 20 trials or lasted up to 60 minutes.

Evaluation:

All the data were expressed in terms of the number of avoidances and escape failures relative to the group, The effect of conditioned avoidance response was expressed as a percentage of animals, that failed to climb the pole within 30 seconds in response to, subsequently delivered electric foot shocks.

3.2 Ketamine-induced Stereotypic Behaviour in Mice

Principle:[16]

As an NMDA receptor antagonist, ketamine induces psychotic effects by blocking NMDA receptors on GABA interneurons, which increases neural firing and boosts glutamate and dopamine release in the prefrontal cortex and limbic areas. This interaction between glutamate and dopamine is associated with schizophrenia. Sub-chronic ketamine use triggers positive psychotic symptoms, while long-term use results in negative and cognitive symptoms linked to psychosis.

Experimental design:[15]

Mice of either sex weighing between 20-30g were divided into 5 groups of 6 animals each.

Groups	Treatment
Group I: Control	Vehicle 1 ml/100g, p.o.
Group II: Toxic Control	Ketamine (50 mg/kg i.p.)
Group III: Standard	Ketamine (50 mg/kg i.p.) + Haloperidol (1 mg/kg, i.p.)
Group IV: Test drug	Ketamine (50 mg/kg i.p.) + 200 mg/kg p.o. of CILE (*Crossandra infundibuliformis* leaf extract)
Group V: Test drug	Ketamine (50 mg/kg i.p.) + 400 mg/kg p.o. of CILE (*Crossandra infundibuliformis* leaf extract)

Procedure: [17]

Each mouse was individually placed in a plastic cage (37 × 24 × 30 cm) with floor markings divided into quadrants. Mice were allowed to acclimate for at least 30 minutes before the experiment began. After administering the final ketamine dose (50 mg/kg, i.p.), specific stereotypic behaviours were observed and recorded, including the frequency of falls, head-bobbing (neck movements up, down, and side-to-side), weaving (grooming and rearing), and rotations. These behaviours were tracked every 15 minutes over 60 minutes by counting each occurrence.

Evaluation:

After the last dose of Ketamine, stereotypic behaviours were produced by the mice. These stereotypic behaviours were measured by counting the total number of fallings, turning, head bobbing, and weaving behaviours at an interval of 15 minutes over 60 min.

3.3 Statistical Analysis:

All data were expressed as Mean ± SEM. The statistical significance between groups was compared using one-way ANOVA, followed by Dunnet's test multiple comparisons.

VI. RESULTS

4.1 Preliminary Phytochemical Screening:

The preliminary phytochemical analysis of the extract confirmed the presence of several bioactive compounds, including flavonoids, phenolic compounds, alkaloids, tannins, carbohydrates, saponins, phytosterols, and amino acids.

4.2 Pharmacological Assessment of Antipsychotic Activity

The antipsychotic activity was evaluated using Pole Climbing Avoidance in rats and Ketamine-induced stereotypic behaviour in mice. The results are mentioned below:

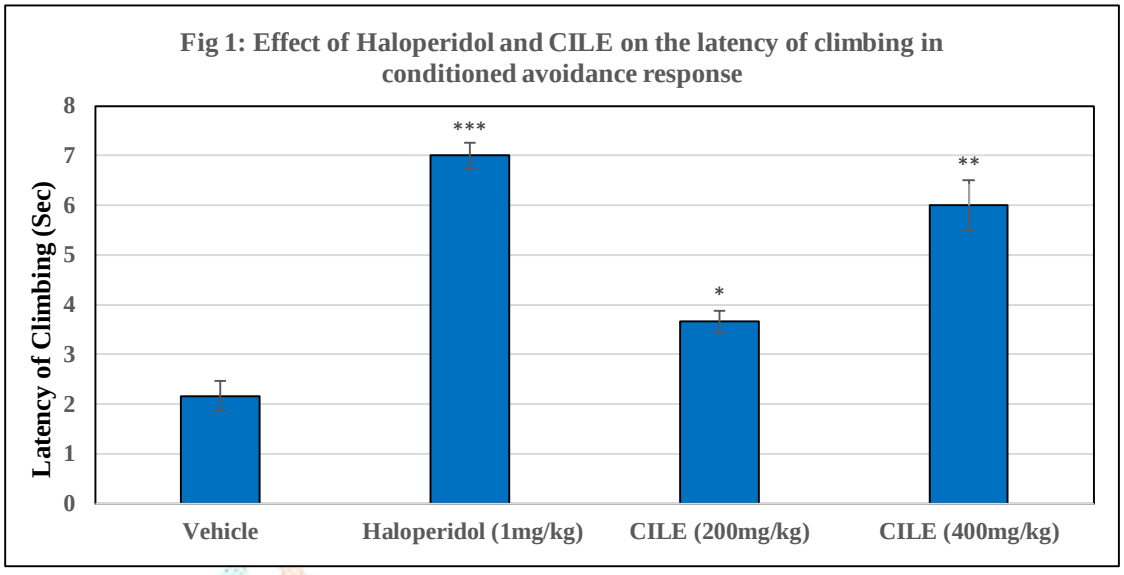
4.2.1 Cook's Pole Climbing Avoidance in Rats

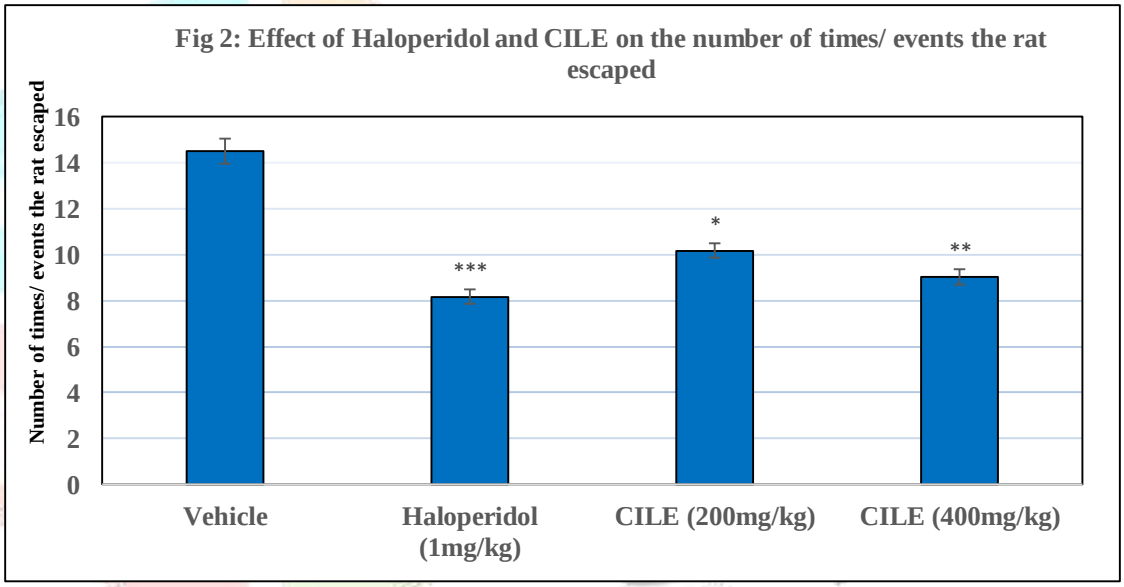
All treated animals demonstrated a marked reduction in escape response when compared to the vehicle control group. Administration of Haloperidol at a dose of 1 mg/kg significantly diminished the escape response. Similarly, treatment with *Crossandra infundibuliformis* leaf extract (CILE) also led to a substantial decrease in escape response. The comparative efficacy of the treatment groups is represented in table 1 below.

Table 1: Effect of Haloperidol and CILE in Conditioned Avoidance Response Rats

Group	Treatment	Latency of pole climbing (sec)	Number of times/ events the rat escaped	% Reduction in no. of times escaped
I	Vehicle	2.167 ± 0.307	14.5 ± 0.563	0
II	Haloperidol (1mg/kg, i.p.)	$7 \pm 0.258^{***}$	$8.167 \pm 0.307^{***}$	43.67
III	CILE (200mg/kg)	$3.667 \pm 0.211^{*}$	$10.167 \pm 0.311^{*}$	29.88
IV	CILE (400mg/kg)	$6.0 \pm 0.516^{**}$	$9.032 \pm 0.333^{**}$	33.33

All the Results are expressed as mean ± SEM; (n = 6). Statistical significance was determined using one-way ANOVA followed by Dunnett's test. *p<0.05, **p<0.01, ***p<0.001 is statistically significant compared to the control group.





4.2.2 Ketamine-Induced Stereotypic Behaviour in Mice

In the current study, Ketamine (50 mg/kg, i.p.) notably induced stereotypic behaviours in mice, including falling, weaving, head-bobbing, and turning. *Crossandra infundibuliformis* leaf extract (CILE) (200 mg/kg and 400 mg/kg, p.o.) reduced these stereotypic behaviours in a dose-dependent manner when compared to the ketamine-treated group. The standard antipsychotic drug olanzapine (5 mg/kg, i.p.) effectively reversed ketamine-induced behaviours. Treatment with CILE has led to a marked reduction in these stereotypic behaviours.

Table 2: Effect of Olanzapine and CILE on Ketamine-induced Falling Behaviour

Group	Treatment	Falling Behaviour			
		15min	30min	45min	60min
I	Vehicle	0±0	0±0	0±0	0±0
II	Ketamine (50mg/ kg)	13.333±0.21$^{\#}$	10.5±0.764$^{\#}$	8.5±0.428$^{\#}$	5.5±0.563$^{\#}$
III	Ketamine (50mg/kg) + Olanzapine (5mg/ kg)	3.67±0.333***	2.8±0.31***	1.8±0.31***	1.33±0.21***
IV	Ketamine (50mg/kg) +CILE (200mg/kg)	7±0.26*	5.68±0.211*	4.5±0.244*	2.5±0.244*
V	Ketamine (50mg/kg) + CILE (400mg/kg)	4.9±0.18**	4.167±0.31**	2.9±0.31**	2.03±0.211**

All values are expressed as mean± SEM n=6, and statistical significance was determined by one-way analysis variance (ANOVA) followed by a Dunnett's test. $^{\#}p<0.001$ when compared with the vehicle-treated control group. $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$, when compared with the ketamine treated group.

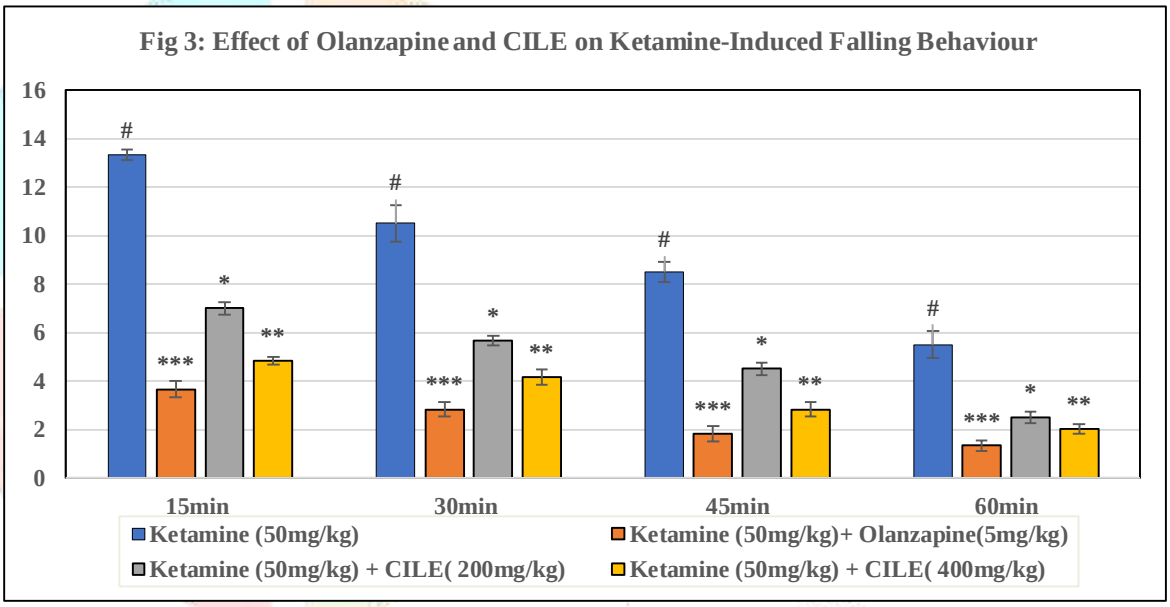


Table 3: Effect of Olanzapine and CILE on Ketamine-induced Weaving Behaviour

Group	Treatment	Weaving Behaviour			
		15min	30min	45min	60min
I	Vehicle	0±0	0±0	0±0	0±0
II	Ketamine (50mg/ kg)	4.83±0.167$^{\#}$	5.167±0.167$^{\#}$	3.67±0.211$^{\#}$	3.17±0.168$^{\#}$
III	Ketamine (50mg/kg) + Olanzapine (5mg/ kg)	1.8±0.224***	1.6±0.333***	1±0.258***	0.68 ±0.211***
IV	Ketamine (50mg/kg) + CILE (200mg/kg)	3.3±0.211*	3.167±0.17*	2.17±0.157*	1.33±0.212*
V	Ketamine (50mg/kg) + CILE (400mg/kg)	2.33±0.211**	2.18±0.167**	1.32±0.22**	0.8 ±0.224**

All values are expressed as mean± SEM n=6, and statistical significance was determined by one-way analysis variance (ANOVA) followed by a Dunnett's test. #p<0.001 when compared with the vehicle-treated control group. *p<0.05, **p<0.01, ***p<0.001, when compared with the ketamine treated group.

Fig 4: Effect of Olanzapine and CILE on Ketamine-Induced Weaving Behaviour

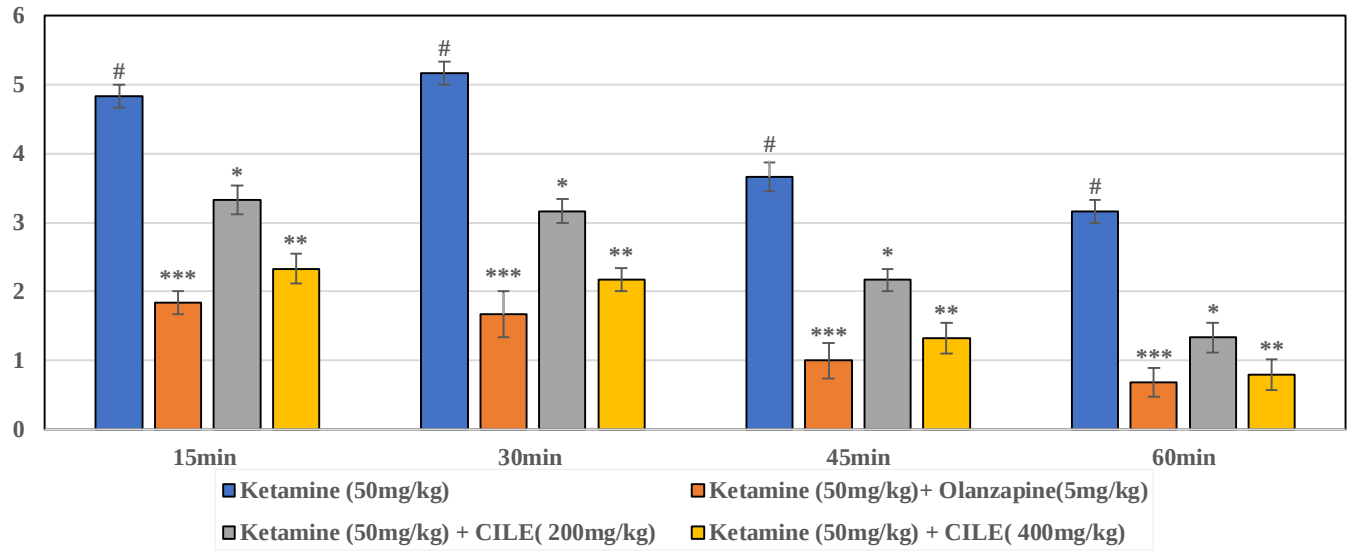


Table 4: Effect of Olanzapine and CILE on Ketamine-induced Head-bobbing Behaviour

Group	Treatment	Head-bobbing Behaviour			
		15min	30min	45min	60min
I	Vehicle	0±0	0±0	0±0	0±0
II	Ketamine (50mg/ kg)	5.167±0.307#	5±0.258#	3.833±0.41#	3.167±0.307#
III	Ketamine(50mg/kg)+Olanzapine (5mg/ kg)	1.5±0.224***	1.68 ±0.333***	1.33±0.3***	1±0.211***
IV	Ketamine (50mg/kg) + CILE (200mg/kg)	3.33±0.211*	3.167±0.31*	2±0.25*	1.667±0.211*
V	Ketamine (50mg/kg) + CILE (400mg/kg)	2.5±0.224**	2.33±0.211**	1.5±0.213**	1.3±0.201**

All values are expressed as mean± SEM n=6, and statistical significance was determined by one-way analysis variance (ANOVA) followed by a Dunnett's test. #p<0.001 when compared with the vehicle-treated control group. *p<0.05, **p<0.01, ***p<0.001, when compared with the ketamine treated group.

Fig 5: Effect of Olanzapine and CILE on Ketamine-Induced Head-bobbing Behaviour

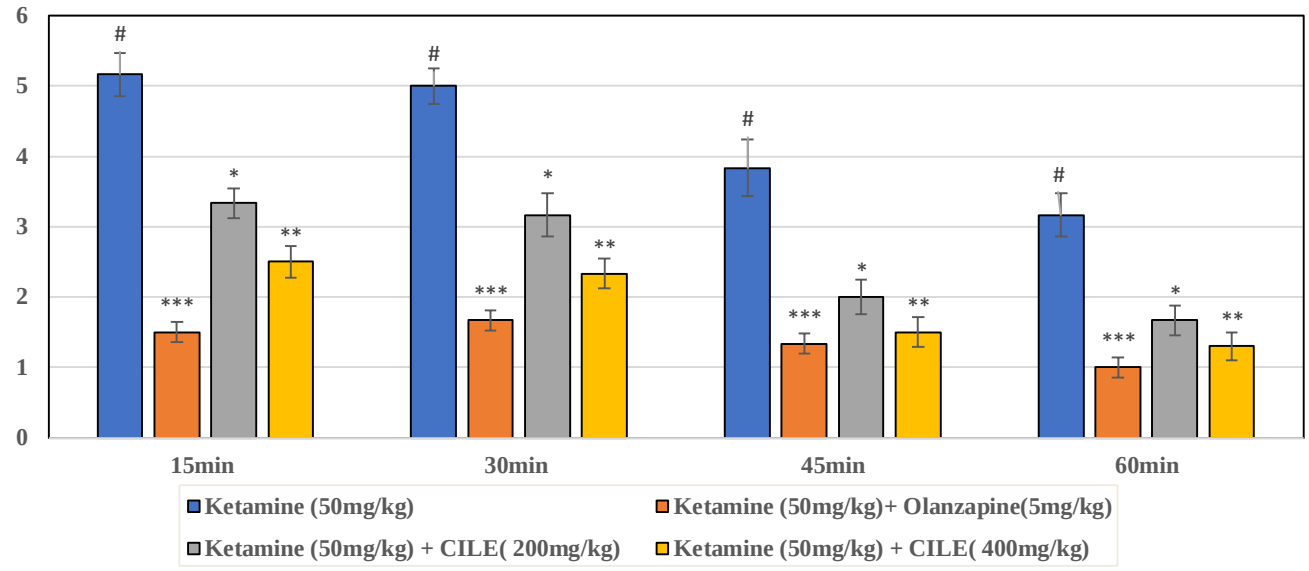
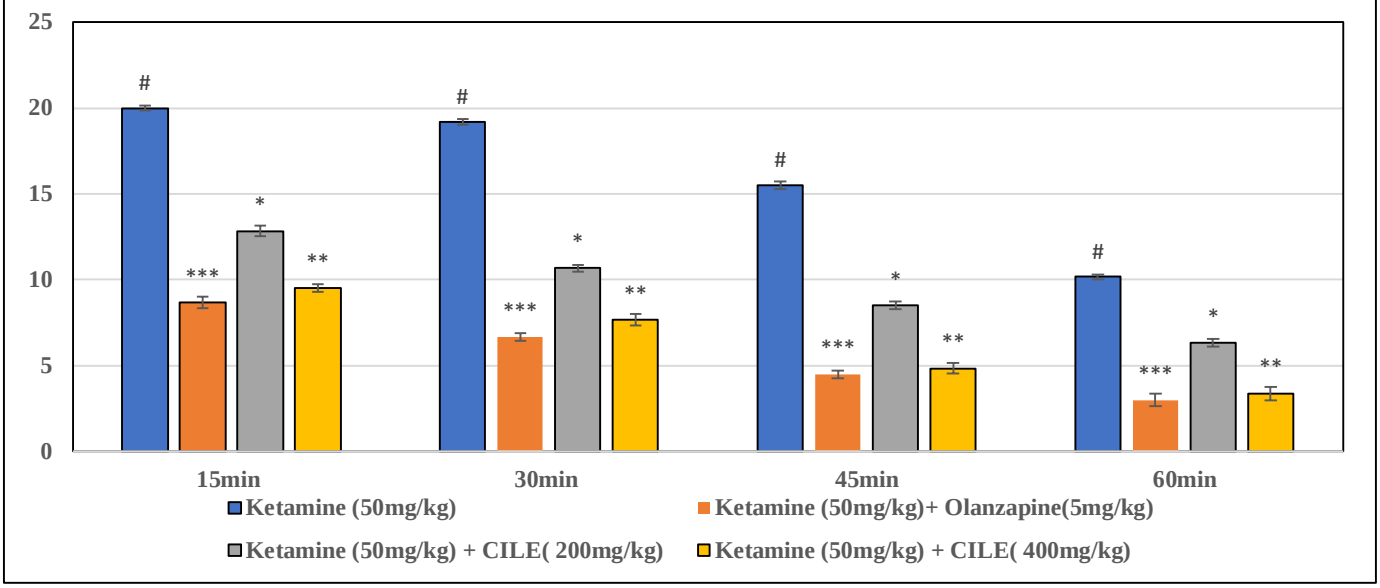


Table 5: Effect of Olanzapine and CILE on Ketamine-induced Turning Behaviour

Group	Treatment	Turning Behaviour			
		15min	30min	45min	60min
I	Vehicle	0±0	0±0	0±0	0±0
II	Ketamine (50mg/ kg)	20± 0.13$^{\#}$	19.17 ±0.18$^{\#}$	15.5±0.224$^{\#}$	10.18 ±0.16$^{\#}$
III	Ketamine+(50mg/kg)+Olanzapine (5mg/ kg)	8.68±0.33***	6.7±0.211***	4.5±0.234***	3±0.365***
IV	Ketamine (50mg/kg) + CILE (200mg/kg)	12.8±0.307*	10.67±0.219*	8.5±0.228*	6.33±0.215*
V	Ketamine (50mg/kg) + CILE (400mg/kg)	9.5±0.224**	7.68±0.34**	4.83±0.309**	3.38±0.401**

All values are expressed as mean± SEM n=6, and statistical significance was determined by one-way analysis variance (ANOVA) followed by a Dunnett's test. $^{\#}p<0.001$ when compared with the vehicle-treated control group. *p<0.05, **p<0.01, ***p<0.001, when compared with the ketamine treated group.

Fig 6: Effect of Olanzapine and CILE on Ketamine-Induced Turning Behaviour



V. DISCUSSION

Schizophrenia is a serious neuropsychiatric disorder affecting about 1% of the global population, with similar prevalence across genders and ethnic groups, making it a significant public health challenge. It ranks as the seventh most expensive medical condition due to its societal burden and is characterized by psychotic symptoms, social and occupational decline, and difficulties in understanding its causes and treatment.[18] Symptoms are generally categorized into psychotic, negative, and cognitive types, with disturbances in thought and perception making reality differentiation challenging.[19]

Schizophrenia is driven by subcortical dopamine dysregulation, with contributions from the frontal cortex and NMDA receptor dysfunctions. It has a strong genetic and environmental basis, with treatments focusing on dopamine receptor blockers.[19, 20]

The Pole climb avoidance apparatus is essential for differentiating between neuroleptic and sedative effects in animal studies, particularly in rats. Neuroleptic drugs mainly affect dopamine pathways, impairing avoidance behaviour at lower doses and impacting escape behaviour at higher doses, whereas sedatives reduce both behaviours at comparable doses.[21] Haloperidol, a first-generation antipsychotic, treats positive symptoms of schizophrenia by blocking dopamine D_2 receptors, particularly in the mesolimbic pathway, with its peak effectiveness at approximately 72% receptor occupancy; however, it also affects noradrenergic, cholinergic, and histaminergic receptors, leading to some side effects. Ketamine-induced stereotypy is another model often used to evaluate new antipsychotic candidates, as ketamine, an NMDA receptor blocker, creates schizophrenia-like symptoms.[22] Olanzapine, an atypical antipsychotic, is valuable in ketamine research as it helps reduce dopamine-related abnormal behaviours by blocking dopamine D_2 and serotonin 5-HT_{2A} receptors. Although it has fewer motor side effects than older antipsychotics, it may lead to weight gain and metabolic changes. Its ability to address both positive symptoms and cognitive impairments makes it an important reference for developing new antipsychotic medications.[23]

Phytopharmaceuticals are valued for their therapeutic effects, with leaf extracts containing flavonoids, phenols, alkaloids, and saponins. Flavonoids reduce inflammation and oxidative stress, alkaloids support schizophrenia treatment by modulating neurotransmitters, and polyphenols provide neuroprotective benefits. Saponins may also aid the dopaminergic system.[3]

Crossandra infundibuliformis leaf extract (CILE) administered for 21 days at 200 mg/kg and 400 mg/kg significantly inhibited CAR in rats, showing time-dependent effects. In the ketamine-induced stereotypy model, 14 days of CILE treatment at these doses demonstrated significant, dose-dependent antidopaminergic activity. These findings suggest CILE's potential as an antipsychotic for managing stereotypic behaviours and cognitive symptoms in schizophrenia, though further study on its bioactive compounds is needed to confirm its effects.

VI. CONCLUSION

This study shows that the ethanolic leaf extract of *Crossandra infundibuliformis (*CILE) has significant antipsychotic effects, comparable to Haloperidol and Olanzapine in animal models, with the 400 mg/kg dose showing greater efficacy than 200 mg/kg. Phytochemical analysis reveals flavonoids, phenols, phytosterols, alkaloids, saponins, amino acids and tannins which may likely contribute to its antipsychotic and antioxidant properties. CILE presents promise as a natural treatment option for psychosis, with future research needed to identify bioactive compounds, clarify mechanisms, and assess long-term safety and efficacy.

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