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Synergistic Interplay of Dopaminergic and Serotonergic Agents with Citral in Mitigating Motor Deficits: A Rodent Model Evaluation

Vandana Gupta[1], Lokesh Verma[*2]

[1]Sanjeev Agarwal Group of Education, Bhopal

[*2]Sanjeev Agarwal Group of Education, Bhopal

***Corresponding Author:**

Lokesh Verma

Email ID: lokeshvns.verma@gmail.com

ABSTRACT

Dopaminergic and serotonergic systems play vital roles in motor function, and imbalances in these systems can lead to motor deficits. Dopamine, primarily involved in movement initiation and coordination, is often reduced in conditions like Parkinson's disease, causing tremors and rigidity. Serotonin, while also impacting motor control, is more broadly involved in regulating mood, arousal, and motivation, all of which can indirectly affect motor performance. Interactions between these neurotransmitter systems are complex, with serotonergic neurons modulating dopaminergic activity and vice versa. In present study an attempt was made to study the Effect of Haloperidol, Citral, Serotonin analogue antagonist/antagonist on Citral, induced cataleptic effect, Dopamine analogue antagonist/antagonist on cataleptic effect of citral in Actophotometer test. Citral (75 mg/kg) affected the locomotor activity in rats in comparison to control group. Selective 5-HT2A receptor antagonist Glemanserin (MDL-11,939) at low dose (1 mg/kg) 5-HT2A/2C antagonist ritanserin at high dose (10 mg/kg) with citral potentiate inhibition of locomotor activity with citral in rats

Ipsapirone (5 mg/kg) a selective 5-HT1A receptor agonist and RU 24969 is a 5-HT1A and 5-HT1B receptor agonist restore Locomotor activity in rats caused by citral. Ropinirole (5 mg/kg) and Pramipexole (5 mg/kg) Dopamine analogue agonist reverse the Citral induced inhibition of locomotor activity and increases the Locomotor count.

Keywords: *Citral, Haloperidol, Dopamine analogue antagonist, Seratonin analogue antagonist catalepsy*

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1. INTRODUCTION

Both dopaminergic and serotonergic systems play crucial roles in motor function, and imbalances in these systems can lead to motor deficits. Dopamine, primarily involved in movement initiation and coordination, is often reduced in conditions like Parkinson's disease, causing tremors and rigidity. Dopaminergic System and Motor Deficits result in Parkinson's disease which is characterized by the degeneration of dopaminergic neurons in the substantia nigra, leading to a significant reduction in dopamine levels in the brain [1]. This dopamine deficiency is a major contributor to the motor symptoms of Parkinson's, including tremors, rigidity, slowness of movement (bradykinesia), and postural instability. Dopamine also plays a role in other motor disorders, such as Huntington's disease and Tourette's syndrome, although the specific mechanisms may differ. Dopamine acts as a neurotransmitter in the basal ganglia, a brain region crucial for movement control. It facilitates smooth, coordinated movements by influencing the activity of motor neurons [2].

Serotonin also contributes to motor control, although its role is more complex and less direct than dopamine's. Serotonergic neurons project to the motor cortex and spinal cord, influencing muscle tone, posture, and movement initiation. Serotonin is involved in regulating motivation and fatigue, which can indirectly affect motor performance. For example, low serotonin levels may lead to apathy and reduced physical activity. Serotonin can modulate dopamine activity in the brain, and these interactions are important for fine-tuning motor control [3]. For instance, serotonin can inhibit the firing of dopaminergic neurons in certain brain regions.

The dopaminergic and serotonergic systems are not isolated but rather interact to fine-tune motor function. This interaction can be seen in conditions like Parkinson's disease, where disruptions in both systems can contribute to motor and non-motor symptoms. Understanding the interplay between these systems is crucial for developing effective therapies for motor disorders. For example, medications that modulate both dopamine and serotonin activity may be more effective than those targeting only one neurotransmitter. Serotonin's influence on mood, motivation, and other functions can also contribute to non-motor symptoms in motor disorders, such as depression and anxiety, which can further impact motor performance [4].

Citral is a linear monoterpene aldehyde, present in more than 85% of lemongrass essential oils. This compound is also found in a wide diversity of plant leaves and fruits, such as limes, oranges, lemons, tomatoes, myrtle trees, and African basil. Citral is a mixture of two isomers named neral (cis-3,7-dimethyl-2,6-octadien-1-al) and geranial (trans-3,7-dimethyl-2,6-octadien-1-al). Typically, commercial compositions between both compounds are complementary, and this mixture ranges from 48 to 52% of each one. Additionally, this compound is generally recognized as safe (GRAS) by the Food and Drug Administration (FDA) and is commonly used as a citrus base flavoring in different products. Citral has exhibited a broad spectrum of biological activities, where it has been described as an effective antimicrobial agent against different Gram-positive and Gram-negative bacteria, fungi, and parasites of clinical relevance. Recent studies have shown that citral has an inhibitory effect against planktonic cells and can also affect biofilms produced by a different microorganism of clinical and food relevance [5-6].

It is established that the recruitment of dopaminergic mechanisms in the setting up of adaptive responses in threatening conditions will depend on the type of emotional stimuli triggering the coping reaction. For instance, it has been reported that the main characteristics of classical neuroleptic drugs in doses that did not induce catalepsy is the reduction of conditioned avoidance behaviors leaving unchanged unconditioned escape responses in the two-way avoidance test. Thus, studying how dopaminergic mechanisms are involved in the mediation of distinct kinds of motivational responses could help our understanding on the neural substrates of fear and anxiety [7-8].

Serotonin plays a complex role in neuroleptic-induced catalepsy, often acting as a modulator of dopamine-mediated movement. Some studies suggest that serotonin can either enhance or antagonize catalepsy depending on the specific receptor subtype and the dose of the antipsychotic. For example, serotonin agonists can sometimes potentiate haloperidol-induced catalepsy, while 5-HT2 receptor antagonists may reduce it. The relationship between serotonin and catalepsy is not straightforward. Serotonin can influence dopamine-mediated motor activity through various pathways, including the modulation of dopamine release and the regulation of dopaminergic neuronal activity [9-10]. In present study an attempt was made to study the Effect of Haloperidol, Citral, Serotonin analogue antagonist/antagonist on Citral, induced cataleptic effect, Dopamine analogue antagonist/antagonist on cataleptic effect of citral in Actophotometer test.

Subjects: Albino wistar rats, with weights ranging from 200 to 350 g participated in this experiment. The animals were individually housed in 40 × 20 × 24 cm Plexiglas cages with wood shavings as bedding and maintained on a regular 12:12 h light / dark cycle. All behavioural tests were conducted during the light period of the cycle, starting at 9:00 am. All animals had access to food and water without restrictions throughout the duration of the experiment.

Drug and solution:

Haloperidol, Citral, Serotonin analogue antagonist (ritanserin and Glemanserin), Serotonin analogue agonist (Ipsapirone and RU 24969), Dopamine analogue Agonist (Ropinirole and Pramipexole), Dopamine analogue antagonists (Haloperidol and Raclopride) were used in present study were dissolved in sterile saline solution. Various concentrations were made according to doses of respective drug substances.

Model (Actophotometer test)

An actophotometer measures an animal's locomotor activity by detecting movements that interrupt beams of light. When an animal crosses a beam of light, it activates a photoelectric cell, which sends a signal to a counter that records the movement. This principle allows researchers to quantify spontaneous or induced activity in animals, often used in studies of drug effects.

The spontaneous locomotor activity of each animal was recorded individually for 10 min using actophotometer, which enables movement of the animal across a light beam to be recorded as a locomotion count. This test can demonstrate a CNS depressant or stimulant activity profile. The animals were allowed to adapt to the new environment for at least 5 min and then the locomotor activity was counted. The test drugs and standard drugs were administered 30 min before the assessment of locomotor activity. Counts were then taken after 60 min.

RESULTS

Effect of Haloperidol administration on rats in actophotometer test

Table 1: Effect of haloperidol on actophotometer test

Treatment	Locomotor activity observed for 10 min	
	Before	after
Solvent (5ml/kg)	220.2 ± 6.9	221.4 ± 6.2
Haloperidol (0.5 mg/kg)	218.1 ± 5.8	152.2 ± 5.4*
Haloperidol (1mg/kg)	215.7 ± 3.6	102.7 ± 6.7**

Values are mean ± SEM (n=6); *P <0.05, **P <0.01 compared to respective control group

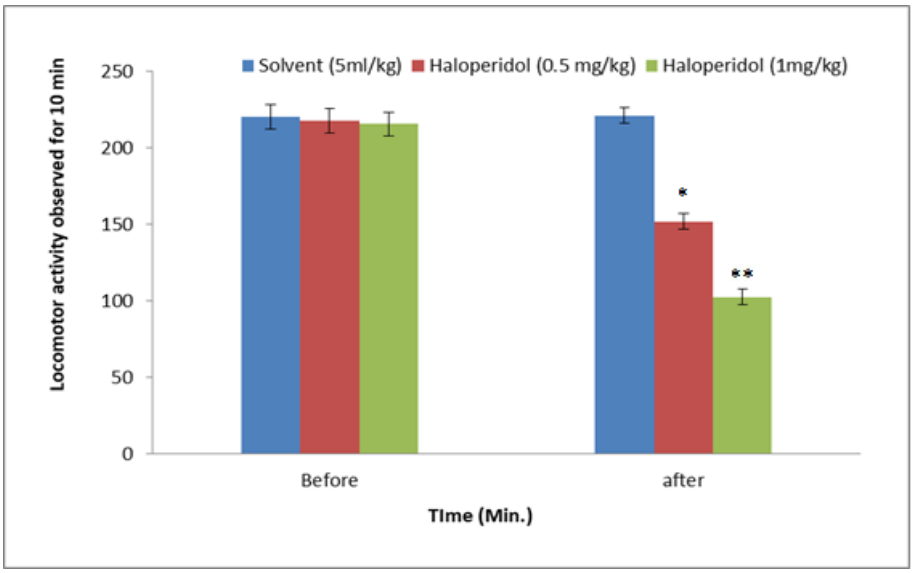

Figure 1: Effect of haloperidol on actophotometer test

Haloperidol (1 mg/kg) treatment significantly decreased the locomotor activity of rats as compared to respective vehicle treated control. The low dose of Haloperidol (0.5 mg/kg) also shows significant decrease in locomotor count.

Effect of citral administration on rats in actophotometer test

Table 2: Effect of citral on actophotometer test

Treatment	Locomotor activity observed for 10 min	
	Before	after
Solvent (5ml/kg)	220.2 ± 6.9	221.4 ± 6.2
Citral (25 mg/kg)	219.1 ± 5.8	198.2 ± 5.4
Citral (50 mg/kg)	216.7 ± 3.6	122.7 ± 6.7*
Citral (75 mg/kg)	218.2 ± 6.9	118.3 ± 5.2*

Values are mean ± SEM (n=6); *P <0.05, **P <0.01 compared to respective control group

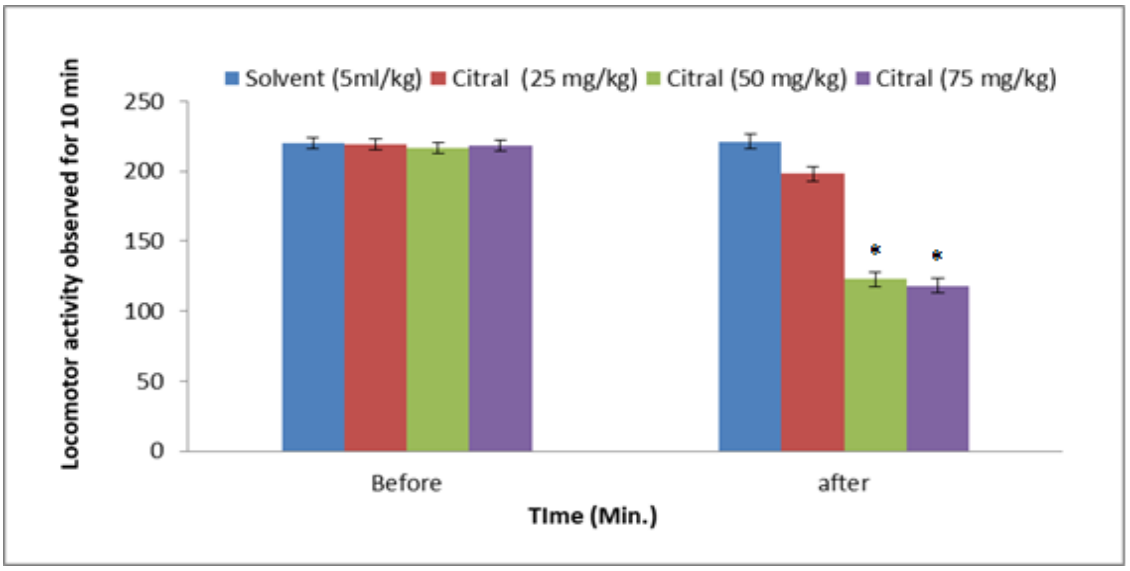

Figure 2: Effect of citral on actophotometer test

Administration of Citral 25 mg/kg and 50 mg/kg do not produce any significant difference from normal control animals administered with saline. Citral (75 mg/kg) affected the locomotor activity in rats in comparison to control group

Effect of Citral + Haloperidol administration on rats in actophotometer test

Table 3: Effect of Citral + Haloperidol in actophotometer test

Treatment	**Locomotor activity observed for 10 min**	
	Before	**after**
Solvent (5ml/kg)	220.2 ± 6.9	221.4 ± 6.2
Haloperidol (1 mg/kg) + Citral (50 mg/kg)	219.7 ± 5.6	98.7 ± 3.7**
Haloperidol (1 mg/kg) + Citral (75mg/kg)	220.2 ± 8.9	90.3 ± 4.2**

Values are mean ± SEM (n=6); *P <0.05, **P <0.01 compared to respective control group

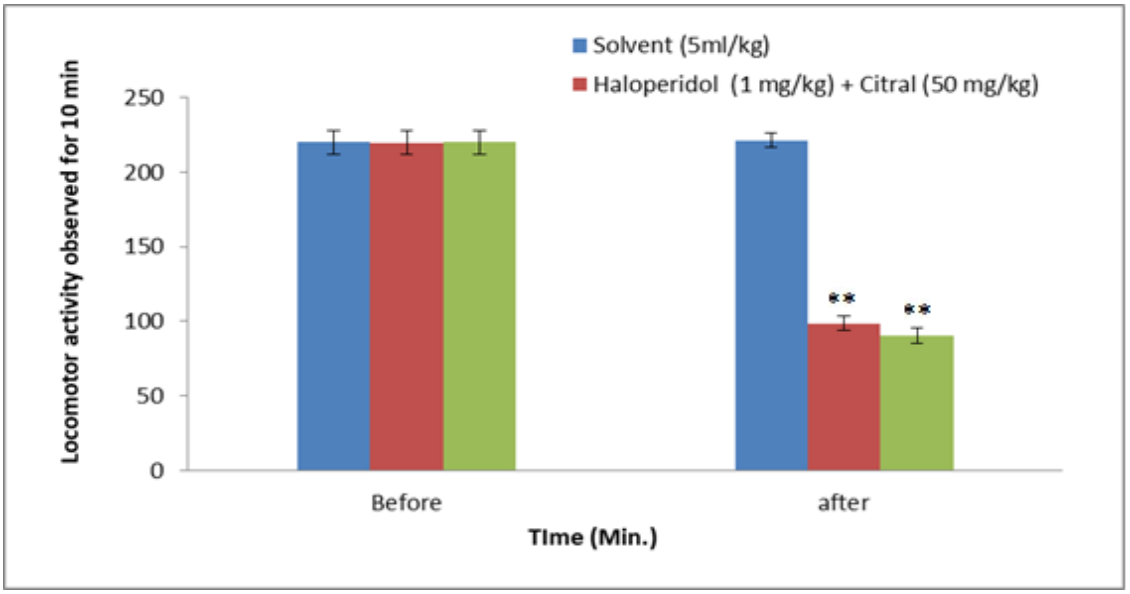

Figure 3: Effect of Citral + Haloperidol in actophotometer test

Haloperidol (1 mg/kg) with Citral (50 mg/kg) produces significant inhibition of locomotor count in rats. Animals that received haloperidol (1 mg/kg) along with Citral (75 mg/kg) produce more inhibition of locomotor count in in comparison second group animals.

Effect of serotonin antagonist with citral administration on rats in actophotometer test

Table 4: Effect of Serotonin analogue antagonist with citral in actophotometer test

Treatment	Locomotor activity observed for 10 min	
	Before	after
Solvent (5ml/kg)	221.8 ± 3.7	221.1 ± 4.5
Citral (75 mg/kg) + ritanserin (10 mg/kg)	220.7 ± 3.6	128.7 ± 3.7
Citral (75 mg/kg) + Glemanserin (1 mg/kg)	219.2 ± 6.9	136.3 ± 5.2*

Values are mean ± SEM (n=6); *P <0.05, **P <0.01 compared to respective control group

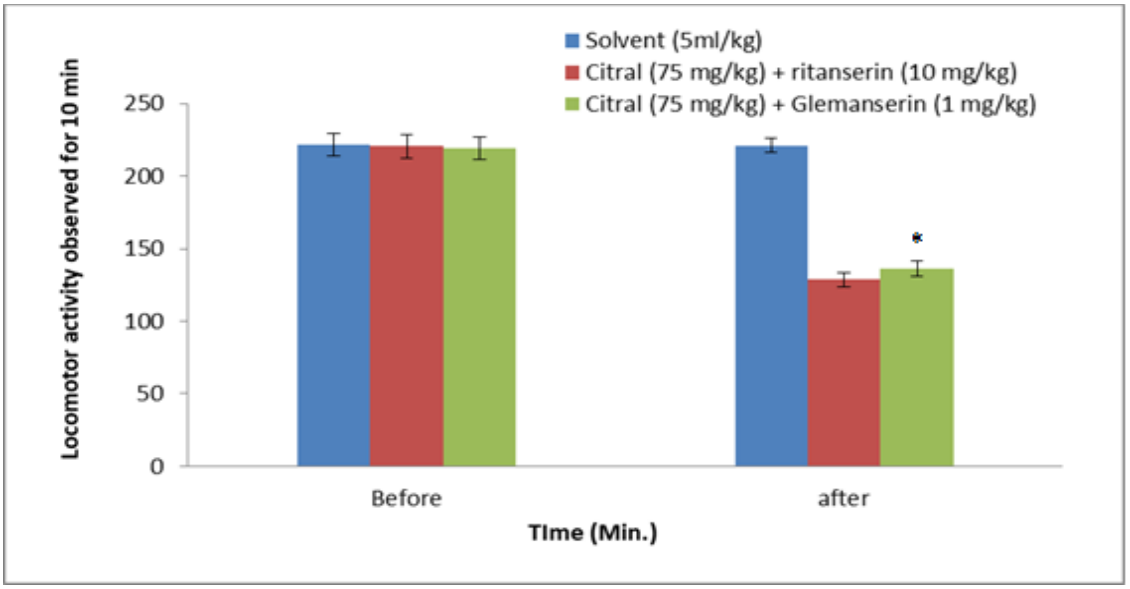

Figure 4: Effect of Serotonin analogue antagonist with citral in actophotometer test

Results showed that Selective 5-HT2A receptor antagonist Glemanserin (MDL-11,939) at low dose (1 mg/kg) potentiate inhibition of locomotor activity with citral in rats. 5-HT2A/2C antagonist ritanserin at high dose (10 mg/kg) with citral decrease the locomotors activity in rats.

Effect of serotonin agonist with citral administration on rats in actophotometer test

Table 5: Effect of serotonin agonist with citral in in actophotometer test

Treatment	Locomotor activity observed for 10 min	
	Before	after
Solvent (5ml/kg)	220.8 ± 4.7	221.9 ± 4.5
Citral (75 mg/kg) + Ipsapirone (5 mg/kg)	219.7 ± 5.6	296.7 ± 3.7**
Citral (75 mg/kg) + RU 24969 (5 mg/kg)	221.2 ± 5.9	191.3 ± 5.2*

Values are mean ± SEM (n=6); *P <0.05, **P <0.01 compared to respective control group

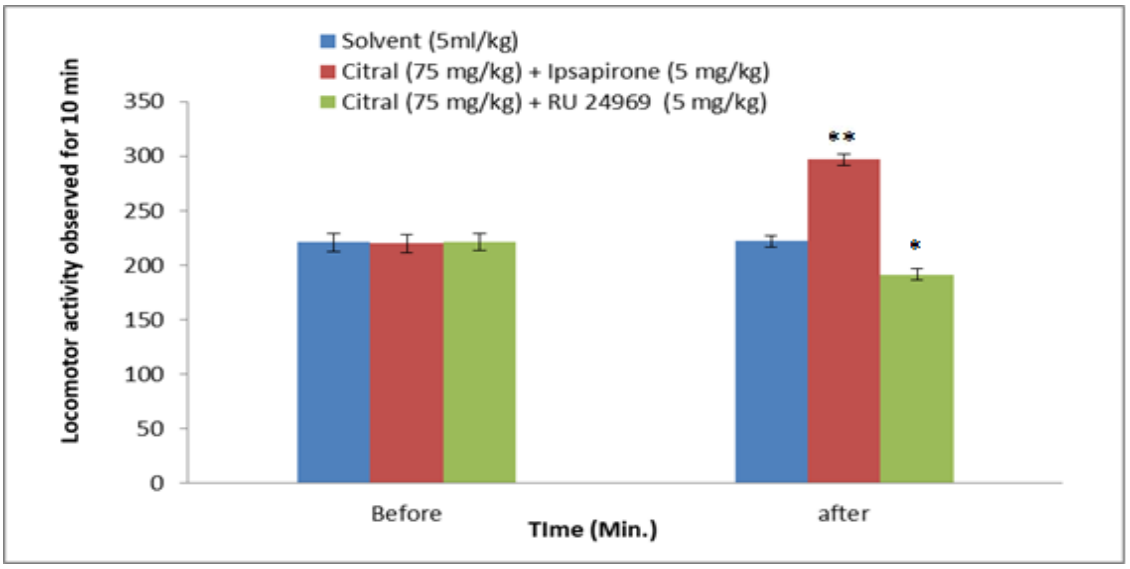

Figure 5: Effect of serotonin agonist with citral in in actophotometer test

Ipsapirone (5 mg/kg) a selective 5-HT1A receptor agonist reverse the citral induced inhibition of Locomotor activity. RU 24969 is a 5-HT1A and 5-HT1B receptor agonist restore Locomotor activity in rats caused by citral.

Effect of Dopamine agonist with citral administration on rats in actophotometer test

Table 6: Effect of Dopamine analogue Agonist with citral in actophotometer test

Treatment	**Locomotor activity observed for 10 min**	
	Before	**after**
Solvent (5ml/kg)	220.8 ± 4.7	221.9 ± 4.5
Ropinirole (5 mg/kg) + citral (75 mg/kg)	219.7 ± 5.6	203.7 ± 3.7*
Pramipexole (5 mg/kg) + citral (75 mg/kg)	221.2 ± 5.9	206.3 ± 5.2

Values are mean ± SEM (n=6); *P <0.05, **P <0.01 compared to respective control group

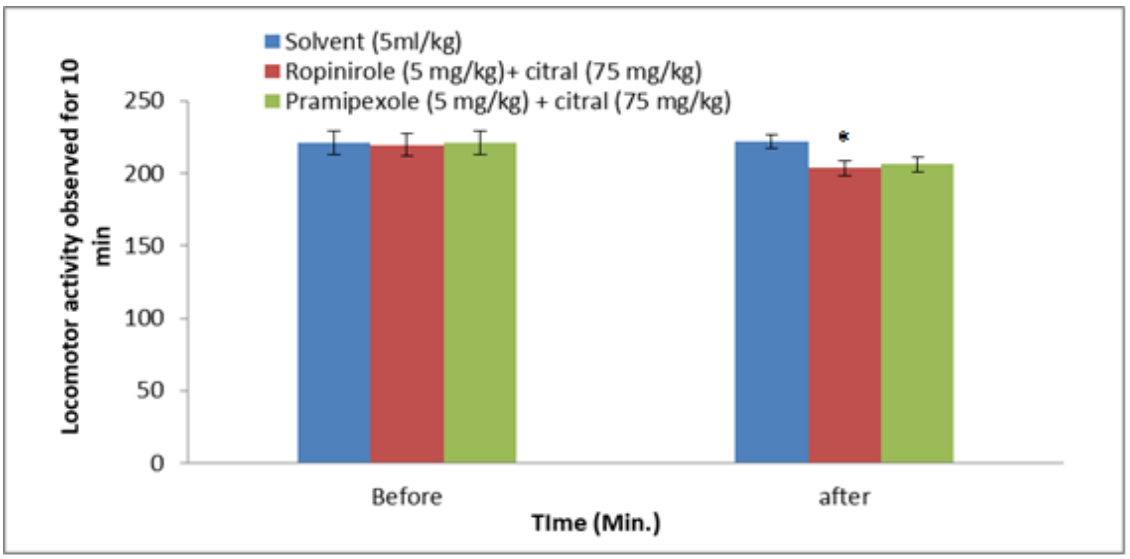

Figure 6: Effect of Dopamine analogue Agonist with citral in actophotometer test

Ropinirole (5 mg/kg) Dopamine analogue agonist reverse the Citral induced inhibition of locomotor activity and increases the Locomotor count. Pramipexole (5 mg/kg) Dopamine analogue agonist reverse the Citral induced effect in animals and increases the Locomotor count.

Effect of Dopamine analogue antagonists with citral administration on rats in actophotometer test

Table 7: Effect of Dopamine analogue antagonists with citral in actophotometer test

Treatment	Locomotor activity observed for 10 min	
	Before	after
Solvent (5ml/kg)	221.8 ± 3.7	220.9 ± 4.6
Haloperidol (1mg/kg) + citral (75 mg/kg)	220.7 ± 5.6	98.7 ± 3.7*
Raclopride (2 mg/kg) + citral (75 mg/kg)	219.2 ± 5.9	106.3 ± 4.2**

Values are mean ± SEM (n=6); *P <0.05, **P <0.01 compared to respective control group

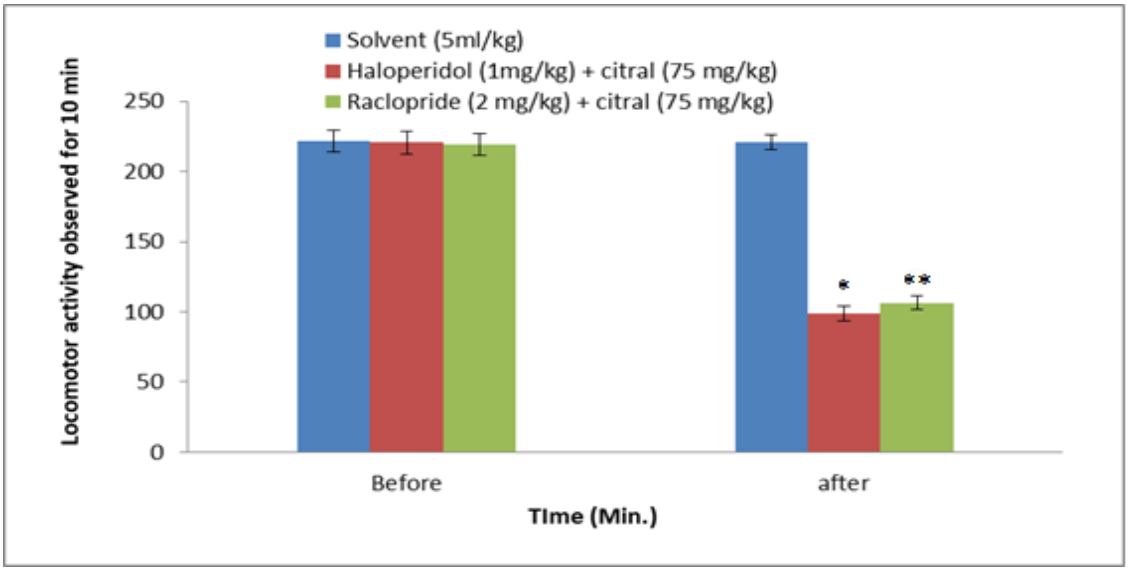

Figure 7: Effect of Dopamine analogue antagonists with citral in actophotometer test

Results showed that Dopamine analogue antagonists Haloperidol (1mg/kg) with citral potentiate inhibition of locomotor activity in rats. Haloperidol at dose 1mg/kg and Raclopride at 2 mg/kg dose with citral further inhibit locomotor activity in rats.

2. DISCUSSION

An actophotometer measures an animal's locomotor activity by detecting movements that interrupt beams of light. When an animal crosses a beam of light, it activates a photoelectric cell, which sends a signal to a counter that records the movement. This principle allows researchers to quantify spontaneous or induced activity in animals, often used in studies of drug effects.

The spontaneous locomotor activity of each animal was recorded individually for 10 min using actophotometer, which enables movement of the animal across a light beam to be recorded as a locomotion count. This test can demonstrate a CNS depressant or stimulant activity profile. The animals were allowed to adapt to the new environment for at least 5 min and then the locomotor activity was counted. The test drugs and standard drugs were administered 30 min before the assessment of locomotor activity. Counts were then taken after 60 min.

Effect of Haloperidol on actophotometer test

Haloperidol, a typical neuroleptic widely used for treatment of schizophrenia, is associated with many neurological and extrapyramidal side effects mainly parkinsonism and tardive dyskinesia. Tardive dyskinesia may be due to increase in oxidative stress and dopamine supersensitivity. Haloperidol is metabolized by an oxidase which generates large quantities of oxyradicals and a toxic pyridinium-like metabolite3 and induces oxidative stress4 . Chronic blockade of dopamine D2

receptors by neuroleptics in nigrostriatal neurones of the brain leads to increase in dopamine turnover in basal ganglia and this may lead to overproduction of free radicals such as dopamine quinone and hydrogen peroxide through the activity of MAO. Tardive dyskinesia is due to a neurotoxic effect of these free radical byproducts from catecholamine metabolism in the basal ganglia. The dopamine supersensitivity hypothesis proposes that antipsychotic drug treatment causes hypersensitization of dopamine D2 receptors, via increased density in all dopaminergic pathways. This disturbs dopamine levels in brain regions responsible for motor symptoms, resulting in motor dysfunction. Classical neuroleptics such as haloperidol remain bound to dopamine D2 receptors and accumulate in brain tissue. This leads to increased density of dopamine D2 receptors and increased uptake of dopamine, especially after withdrawal of antipsychotics, which results in tardive dyskinesia. Various neurotransmitter (dopaminergic, serotonergic, noradrenergic and GABAergic) systems abnormalities

Haloperidol (1 mg/kg) treatment significantly decreased the locomotor activity of rats as compared to respective vehicle treated control. The low dose of Haloperidol (0.5 mg/kg) also show significant decrease in locomotor count.

The dopamine system has also been regarded crucial in controlling motor activity. In the present study, haloperidol significantly decreased locomotor activity of rats. Dopamine receptor supersenstivity might be responsible for decrease in locomotor activity by haloperidol Typical neuroleptics including haloperidol, mostly act by blocking dopamine D2 receptors and result in increased dopamine turnover. This may conceivably result in increased hydrogen peroxide production and other toxic metabolites of dopamine, resulting in increased oxidative stress.

Ellagic acid significantly reversed haloperidolinduced tardive dyskinesia and catalepsy in rats probably through increase in brain dopamine and serotonin levels; and also through its antioxidant activity. Therefore, ellagic acid may be explored further for its potential in the management of neuroleptic-induced tardive dyskinesia and Parkinsonism.

Effect of citral on actophotometer test

Citral, a monoterpene aldehyde, has sedative and muscle relaxant effects, and may be involved in vasorelaxation. Citral, a naturally occurring compound found in some essential oils, has shown potential anxiolytic (anxiety-reducing) effects in animal studies. It may work by interacting with GABA and serotonin receptors in the brain. Although it is widely distributed in nature and there are many studies presenting its biological activities, its anti-neurodegenerative activity, especially under in vivo conditions, is very poorly understood.

Administration of Citral 25 mg/kg and 50 mg/kg do not produce any significant difference from normal control animals administered with saline. Citral (75 mg/kg) affected the locomotor activity in rats in comparison to control group

Effect of Citral + Haloperidol in actophotometer test

Haloperidol (1 mg/kg) with Citral (50 mg/kg) produces significant inhibition of locomotor count in rats. Animals that received haloperidol (1 mg/kg) along with Citral (75 mg/kg) produce more inhibition of locomotor count in in comparison second group animals.

Effect of serotonin antagonist with citral in actophotometer test

The development of drugs acting on the serotonergic system of brain that allow for the treatment of depression, anxiety, appetite regulation, and post-traumatic stress disorders has focused a great deal of attention on the role of serotonin in processes involving emotional states. Commensurate with our increasing understanding of the role of serotonin in behavioral processes has been the identification of at least seven serotonin (5-hydroxytryptamine; 5-HT) receptor sub-types. More recently, investigators have focused on the role of serotonin in cognitive functions, including learning and memory and in the deficits in attention and associative processes seen in schizophrenia. Serotonin receptor subtypes that have been demonstrated to occur in brain regions capable of playing a role in learning and memory.

Results showed that Selective 5-HT2A receptor antagonist Glemanserin (MDL-11,939) at low dose (1 mg/kg) potentiate inhibition of locomotor activity with citral in rats. 5-HT2A/2C antagonist ritanserin at high dose (10 mg/kg) with citral decrease the locomotors activity in rats.

Effect of serotonin agonist with citral in in actophotometer test

Ipsapirone (5 mg/kg) a selective 5-HT1A receptor agonist reverse the Citral induced inhibition of Locomotor activity. RU 24969 is a 5-HT1A and 5-HT1B receptor agonist restore Locomotor activity in rats caused by citral.

Effect of Dopamine agonist with citral in actophotometer test

Ropinirole (5 mg/kg) Dopamine analogue agonist reverse the Citral induced inhibition of Locomotor activity and increases the Locomotor count. Pramipexole (5 mg/kg) Dopamine analogue agonist reverse the Citral induced effect in animals and increases the Locomotor count. Results indicate that Dopamine analogue agonists Ropinirole and Pramipexole reverse the effect of citral on locomotor activity in rats.

Effect of Dopamine analogue antagonists with citral in actophotometer test

Raclopride is a typical antipsychotic. It acts as a selective antagonist on D2 dopamine receptors. It has been used in trials studying Parkinson Disease. Its selectivity to the cerebral D2 receptors

Results showed that Dopamine analogue antagonists Haloperidol (1mg/kg) with citral potentiate inhibition of locomotor activity in rats. Raclopride is a selective dopamine D2/D3 receptor antagonist with citral decrease the locomotor activity. The central dopamine system may play an important role in modulating memory process. Experiments have shown that blockade of pre-synaptic D2receptors impaired both acquisition and retrieval stages of memory processes following an increase in dopamine release. Haloperidol at dose 1mg/kg and Raclopride at 2 mg/kg dose with citral further inhibit locomotor activity in rats .

3. CONCLUSION

An actophotometer measures an animal's locomotor activity by detecting movements that interrupt beams of light. When an animal crosses a beam of light, it activates a photoelectric cell, which sends a signal to a counter that records the movement. This principle allows researchers to quantify spontaneous or induced activity in animals, often used in studies of drug effects.

The dopamine system has also been regarded crucial in controlling motor activity. In the present study, haloperidol significantly decreased locomotor activity of rats. Dopamine receptor supersenstivity might be responsible for decrease in locomotor activity by haloperidol Typical neuroleptics including haloperidol, mostly act by blocking dopamine D2 receptors and result in increased dopamine turnover. This may conceivably result in increased hydrogen peroxide production and other toxic metabolites of dopamine, resulting in increased oxidative stress. Selective 5-HT2A receptor antagonist Glemanserin (MDL-11,939) at low dose (1 mg/kg) 5-HT2A/2C antagonist ritanserin at high dose (10 mg/kg) with citral potentiate inhibition of locomotor activity with citral in rats. Ipsapirone (5 mg/kg) a selective 5-HT1A receptor agonist and RU 24969 is a 5-HT1A and 5-HT1B receptor agonist restore Locomotor activity in rats caused by citral. Ropinirole (5 mg/kg) and Pramipexole (5 mg/kg) Dopamine analogue agonist reverse the Citral induced inhibition of locomotor activity and increases the Locomotor count.

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