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INVIVO EVALUATION OF ANTIPARKINSON INHIBITING ACTIVITY OF METHANOLIC EXTRACTION BY MEASA LANCEOLATA (MEML) IN A HALOPERIDOL MODEL OF CATALEPSY IN RATS

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ABSTRACT

Background :-This study investigates the therapeutic potential of the methanolic extract of Maesa lanceolata (MEML) in managing Parkinson's disease (PD) symptoms, using a rat model of haloperidol-induced catalepsy. Method- We assessed the anticonvulsant effects of MEML and its impact on exploratory behaviors in haloperidol-treated rats, comparing the effects with the standard PD drug, benztropine. Rats were divided into different groups and administered either MEML or haloperidol alone. Catalepsy and exploratory behaviors were monitored at various time intervals. Results- demonstrated that MEML, at a dose of 400 mg/kg, significantly reduced the catalepsy scores in treated rats, exhibiting an anticataleptic effect comparable to that of the standard drug. Furthermore, MEML significantly enhanced exploratory behaviors, including head dipping and line crossing activities, in haloperidol-treated rats. These behaviors, typically diminished during catalepsy, are indicative of motor and coordination capabilities, suggesting that MEML could also alleviate these PD symptoms. We hypothesize that the observed effects of MEML may be attributed to its potential regulation of neurotransmitters, including dopamine, serotonin, and glutamate, as well as antioxidant enzyme systems. Conclusion- findings highlight the value of exploring plant-based treatments in neurodegenerative diseases, setting the foundation for future investigations. However, to corroborate these findings and unravel the precise mechanisms of action, further comprehensive studies on different extracts and isolated principles of Maesa lanceolata are warranted.

Keywords: Methanolic extract of Maesa lanceolata (MEML), Parkinson's Disease (PD) , D2- Dopamine , deep brain stimulation (DBS) , 5-hydroxytryptamine (5-HT).

INTRODUCTION

In recent years, herbal preparations have become increasingly popular as an alternative to synthetic drugs, which are often associated with unwanted side effects.

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Patients may be attracted to the seemingly low risk of side effects and optimistic anecdotal evidence of herbal medicines, particularly when conventional treatments have high failure rates or numerous side effects.

The earliest known use of plants for medicinal purposes can be traced back to the Rigveda, dating back as far as 3500 BC. Ayurveda, which is considered a supplementary hymn designed for more detailed

instruction, is a strong foundation of ancient Indian medicine. Traditional systems of medicine, such as those originating from India, China, Tibet, Thailand, and Vietnam, have evolved over hundreds of years through the transfer of knowledge and practices from generation to generation. Despite the significant advancements of modern medicine and medical research, ancient systems of medicine remain a major component, effectively used in the control and alleviation of diseases. The traditional system of medicine finds tremendous faith and enormous favour from all class of people in all parts of the world, to the far-sighted enlightened administrators in countries of third world, this faith of the population on traditional medicine and herbal remedies is an asset [1]. The use of herbal preparations for medicinal purposes has become increasingly popular in recent years. Many people are turning to herbal remedies as an alternative to synthetic drugs, which are often associated with unwanted side effects. This is particularly true in cases where conventional treatments have high failure rates or numerous side effects. Patients are attracted to the seemingly low risk of side effects and optimistic anecdotal evidence of herbal medicines

For example, ginseng has been shown to have anti-inflammatory and antioxidant properties and may be useful in the treatment of cardiovascular disease, diabetes, and cancer. Turmeric has been shown to have anti-inflammatory, antioxidant, and anticancer properties and may be useful in the treatment of a wide range of diseases, including arthritis, Alzheimer's disease, and cancer.

The prevalence of herbal medicines has been increased from 2.5 % (1990) to 12.1% (1997) [2]. The growing concerns in the recent part over the toxic effects of various synthetic drugs have forced the researchers to consider some steps for preventing the misuse of such drugs.

It is generally believed that around 25% of the active ingredients used in modern medicines were derived from plants. At the same time it is well known that hardly 5000 over 2,50,000 flowering plants have been looked scientifically for their medicinal properties [3].

Based on the strong traditional knowledge on the use of plants as therapeutic agents, a rational approach is developed to use medicinal plants as a lead for the discovery of active molecule, with one of the largest reservoirs of bioresources. It is imperative that India develops a concerted, integrated, structural and modern approach in this area and gain a competitive edge in the international market place for the discovery and development of plant based drugs for a variety of diseases for which currently adequate or appropriate remedies are not available [4].

Natural products have played a significant role in the management of neuropsychiatric disorders. Sen and Bose published their first report on the use of *Rauwolfia serpentina* in the treatment of insanity. This plant from Ayurveda was a major breakthrough for understanding hypertension, depression and Parkinson's disease [5].

The importance of herbal medicines in parkinson's disease:

Parkinson's disease existed in ancient India and was called *kampavatha*. The haloperidol-induced catalepsy model in rats is a useful tool for studying the pathophysiology of PD and for evaluating potential therapeutic interventions. The mechanism of haloperidol-induced catalepsy involves the blockade of dopamine receptors in the striatum, leading to a reduction in dopamine levels. Dopamine depletion is considered a cardinal feature in the development of PD in humans and animal models.

The dopamine system plays a critical role in the regulation of movement. Dopamine is a neurotransmitter that is involved in the control of motor function, reward, and motivation [6,7]. The dopaminergic neurons in the substantia nigra project to the striatum, where they modulate the activity of medium spiny neurons (MSNs). The MSNs, in turn, project to other areas of the basal ganglia, which are involved in the control of movement. The reduction in dopamine levels in the substantia nigra leads to a reduction in the activity of the MSNs and a disruption of the normal functioning of the basal ganglia. The haloperidol-induced catalepsy model in rats has been used to study the effects of drugs that target the dopaminergic system. For example, drugs that enhance dopamine availability or prevent its breakdown provide protection against PD in humans and animal models. Therefore, compounds that exhibit antiparkinsonian effects in the haloperidol-induced catalepsy model may have potential as therapeutic agents for the treatment of PD.

The mainstay of treatment for PD is the administration of levodopa, a precursor of dopamine that can cross the blood-brain barrier and be converted to dopamine in the brain. While levodopa can provide significant relief of symptoms, its effectiveness wanes over time, and it is associated with a number of adverse effects, including dyskinesias. In recent years, there has been growing interest in the development of new therapies for PD that target non-dopaminergic systems. For example, there has been increasing interest in the use of deep brain stimulation (DBS) to treat PD. DBS involves the implantation of electrodes into specific areas of the brain, where they can modulate neural activity. While the precise mechanism of action of DBS is not fully understood, it is thought to involve the modulation of multiple neurotransmitter systems, including the dopaminergic, serotonergic, and noradrenergic systems [8]. Secondary or symptomatic parkinsonism results from a variety of causes that includes infections, toxins, drugs, vascular lesions, tumors and trauma. Among these, neuroleptic drugs are considered to the commonest cause

of secondary parkinsonism today [9,10]. The results indicated that haloperidol was less potent in inducing catalepsy in diabetic rats than in control rats, at doses ranging from 0.032 to 0.56 mg/kg. This reduced potency could be due to alterations in dopamine receptor binding in the presence of diabetes, as has been suggested in previous reports [11]. In acute and chronic haloperidol treatment consistent and prolonged increase in dorsolateral striatum and nucleus acumens DA release and a transient increase in dorsolateral striatum GABA release. Basal dorsolateral striatum GABA levels were two folds higher in the chronically treated rats. Administration of haloperidol was associated with the prolonged (> 150 min) catalepsy in the drug naive rats which was greatly diminished or absent in chronically treated rats, may be due to elevated basal dorsolateral striatum GABA release [12]

Basal dorsolateral striatum GABA levels were two folds higher in the chronically treated rats. Administration of haloperidol was associated with the prolonged (> 150 min) catalepsy in the drug naive rats which was greatly diminished or absent in chronically treated rats, may be due to elevated basal dorsolateral striatum GABA release [13]. Biphasic responses of dopaminergic agonists apomorphine, lisuride and pergolide was differentiated on dose dependent manner. In lower doses, these drugs lowered the latency period of haloperidol induced catalepsy in rats. In higher doses increased the latency period. These findings tend to prove one evidence to confirm that more than one group of dopamine receptors are involved in typical biphasic response [14]. The study aimed to understand the mechanism by which stimulation of somatodendritic and/or postsynaptic 5-hydroxytryptamine (5-HT, serotonin) -1A receptors might help alleviate acute parkinsonian-like symptoms induced by typical antipsychotics.The ability of 5-HT1A receptor agonists like 8-OH-DPAT to counteract the parkinsonian-like effects of haloperidol could represent a promising strategy to improve the safety and efficacy of antipsychotic treatment [15]. As per plant profile is considered, Measa lanceolata is a medicinal plant belonging to the family Sapindaceae, known for its therapeutic potential in traditional medicine. It is primarily found in tropical and subtropical regions, particularly in Southeast Asia and Africa, where it thrives in well-drained soils and mixed deciduous forests. The plant is characterized by its lanceolate leaves, small fragrant flowers, and drupaceous fruits. The bark, leaves, and roots of Measa lanceolata have been widely used in folk medicine to treat various ailments, including respiratory disorders, skin infections, and gastrointestinal disturbances [16].

Traditional Uses

- Traditional uses of Measa lanceolata include the application of its bark for wound healing, the use of leaf decoctions to manage fever and respiratory infections, and the consumption of its fruits for their nutritional and mild laxative benefits. Ethnomedicinal surveys indicate that indigenous communities utilize the plant for treating dysentery, skin conditions, and inflammatory disorders. Recent pharmacological studies have validated some of these traditional claims, highlighting the plant's antimicrobial, anti-inflammatory, antioxidant, hepatoprotective, anticancer, antidiabetic, cardioprotective, and neuroprotective activities.

AIM AND OBJECTIVES

The research objectives for this study are designed as follows:

- To assess the effect of the methanolic extract of *Measa lanceolata* in haloperidol-induced Parkinsons Disease.
- To assess the efficacy activity of drug in Parkinson's Disease.

MATERIALS AND METHODS

- **Materials Used: -**
  - Powdered plant material.
  - Soxhlet apparatus.
  - **Solvents:** Ethanol
  - **Reagents:** Mayer's reagent, Dragendroff's reagent, Hager's reagent, Wagner's reagent and Fehling's A & B.
  - **Chemicals:** HCl, H_2SO_4, Tannic acid, α-Napthol, Acetic anhydride, Glacial acetic acid, NaOH, Pyridine, Sodium nitroprusside, Dil. Ammonia, Dil. Ferric chloride, 10% NaCl, 10% Lead acetate solution and Zinc dust.

Collection and extraction of the Plant material

The leaves of *Measa lanceolata* was collected from Talakona forest, Chittoor dist of Andhra Pradesh, India. The leaves of *Measa lanceolata* were collected, cleaned, dried in shade and pulverized in a grinder-mixer to obtain a coarse powder and then passed through a 40-mesh sieve. The air-dried powdered plant material (200gm) was extracted with ethanol by using Soxhlet apparatus for 48hrs. The solvent is removed from extracts by distillation under reduced pressure. The concentrated extract was kept in a dessicator and was used for further experiment. The extract was weighed and its percentage in terms of air-dried weight of plant material was calculated and also the consistency of the extracts was noted.

Preliminary Phytochemical studies:

The concentrated extracts were subjected to chemical tests as per the methods mentioned below for the identification of the various constituents.

(1) Detection of Alkaloids

Small portions of solvent-free chloroform, alcohol and aqueous extracts were stirred separately with a few drops of dilute hydrochloric acid and filtered. The filtrate was tested with various alkaloidal reagents.

a. Mayer's test: Filtrates were treated with potassium mercuric iodide (Mayer's reagent) and the formation of cream coloured precipitate was observed for the presence of alkaloids.

(2) Detection of Carbohydrates and Glycosides

Small quantity of alcohol and aqueous extracts were dissolved separately in distilled water and filtered. The filtrate was subjected to various tests to detect the presence of different carbohydrates.

a. Molisch's test: Filtrates were treated with alcoholic solution of α -Naphthol and a few drops of conc. Sulphuric acid were added through the sides of the test tube. The formation of violet ring at the junction of the liquids was observed for the presence of carbohydrates.

(3) Detection of Phytosterols

Petroleum ether, benzene, acetone and alcohol extracts were refluxed separately with solution of alcoholic potassium hydroxide till complete saponification took place. Saponified mixtures were diluted with distilled water and extracted with solvent ether. Ethereal extract was evaporated to dryness and the residue subjected to Liebermann-Burchard's test.

- **Liebermann-Burchard's test**

Ethereal residues were treated with a few drops of acetic anhyride; boiled, cooled, and 1 ml of sulphuric acid was added through the sides of the test tube. Formation of brown ring at the junction of two liquids and green colour in the upper layer indicates the presence of steroids and triterpenoids.

(4) Detection of Fixed oils and Fats

a. Spot test: A small quantity of petroleum ether and benzene extracts were pressed separately between two filter papers. Formation of oil stains on the filter paper was observed for the presence of fixed oil.

(5) Detection of Saponins

- **Foam test:** About 1 ml of alcohol and aqueous extracts were diluted separately with distilled water to 20 ml and shaken in a graduated cylinder for 15 minutes. Formation of any froth above the surface was observed for the presence of saponins.

Experimental Procedure

Female Wistar rats weighing between 150-250 grams were utilized for the study. The initial dosage level of the methanolic Extract of Measa lanceolata (MEML) was set at 2000 mg/kg body weight (p.o), as the majority of crude extracts exhibit an LD 50 value exceeding 200 mg/kg (p.o). The dosage volume administered was 0.2ml per 100g body weight to overnight fasted rats, with water available ad libitum. Food was withheld for an additional 3-4 hours following the administration of MEML, and the rats were observed for signs of toxicity.

The body weight of the rats was recorded both before and after the MEML administration, and any changes in skin and fur, eyes, mucous membranes, and functions of the respiratory, circulatory, autonomic and central nervous systems were observed. The rats' motor activity and behavioral patterns were also assessed. Any signs of tremors, convulsions, salivation, diarrhea, lethargy, sleep, and coma were noted. The onset of toxicity and other signs of toxicity were also documented.

Pharmacological Studies

PD induced by chronic haloperidol administration in experimental rats [17,18,19,20]

Haloperidol (10 mg/kg, ip) was administered daily to the rats for a period of 20 days to induce parkinsons disease. Plant extract and standard drugs were administered orally 30 min before to the haloperidol treatment. The animals were divided in to five groups, each containing 6 animals.

GROUP I: The animals received 1% tween 20 (5 ml/kg, po) and served as control.

GROUP II: The animals received haloperidol (10 mg/kg, ip) and served as negative control.

GROUP III: The animals received haloperidol (10 mg/kg, ip) and treated with Benztropine (1.0-5.0 mg/kg, po) suspended in 1% tween 20. This group served as standard.

GROUP IV: The animals received haloperidol (10 mg/kg, ip) and treated with MEML (200 mg/kg, po) suspended in 1% tween 20.

GROUP V: The animals received haloperidol (10 mg/kg, ip) and treated with MEML (400 mg/kg, po) suspended in 1% tween 20.

Invivo pharmacological studies were carried out on last day of the experiment, and then the animals were sacrificed for biochemical parameters.

Effect of the MEML and standard drug on haloperidol induced catalepsy in rats (Block method 0-3.5 scale) [21]

The effect of test drug and standard drugs on haloperidol induced catalepsy was studied by the following method. Severity of catalepsy was measured every 30 min, thereafter up to a total duration of 3 hours. Catalepsy of an individual rat was measured in a stepwise

manner by a scoring method as described below. The method assessed the ability of an animal respond to an externally imposed posture.

STAGE I: The rat was taken out of the home cage and placed on a table. Rat moves freely no score was given.

STAGE II: If the rat failed to move when touched gently on the back or pushed, score of 0.5 assigned.

STAGE III: The front paws of the rat were placed alternately on a 3 cm high block. If the rat failed to correct the posture within 15 sec, a score of 0.5 for each paw was added to the score of Step I.

STAGE IV: The front paws of the rat were placed alternately on a 3 cm high block. If the rat failed to correct the posture within 15 sec, a score of 1 for each paw was added to the scores of Step I, Step II. Thus for an animal, the highest score was 3.5 (cut-off score) and that reflects in total catalepsy.

Effect of the MEML and standard drug on exploratory behavior (Head dipping) [22]

The exploratory behavior, specifically head dipping, of the subjects was assessed for a duration of 10 minutes at 30-minute intervals for up to 3 hours using a hole board apparatus. This device, made from plywood, measured 60 cm by 60 cm and was 3 mm thick. To prevent alterations in animal behavior due to reflections, the upper surface of the board was given a matte finish. The board was fitted with 9 uniformly spaced holes, each with a diameter of 5 cm. Each rat was allowed a 10-minute acclimatization period before the count of the number of holes explored through head dipping was noted during the total observation time. It was important to ensure that multiple events (i.e., two or more rapid head dips) were not counted multiple times. A fresh exploration was only considered when the animal distinctly dipped its head once, engaged in another activity such as grooming or taking a short walk, and then returned to head dipping. Each activity was tested on one animal at a time

Effect of the MEML and standard drug on exploratory behaviour (Line crossing) [23]

The study assessed the impact on exploratory behavior, specifically line crossing, through the use of a hole board made of plywood with dimensions of 60 cm x 60 cm and a thickness of 3 mm. The upper surface of the mat was designed to prevent reflections that could potentially alter the behavior of the animal. The board consisted of 9 evenly distributed lines. Each rat was given 10 minutes to acclimate to the environment before the observation period began. The number of line crossings during the entire observation period, which lasted for 10 minutes at 30-minute intervals up to 3 hours, was recorded. To ensure accurate data, measures were taken to avoid multiple events.

RESULTS

Preliminary Phytochemical Screening

The percentage yield and consistency of various extracts of leaves of *Measa lanceolata* were presented in the table 3. The methanol extract gives the high percentage of yield and it was found to be 18.96%w/w.

The results of phytochemical studies of extract of leaves of *Measa lanceolata* were presented in the table 4. From the results of the phytochemical screening of extract of *Measa lanceolata* it is concluded that the medicinal value of this plant may be attributed due to the presence of various phytoconstituents viz., alkaloids, carbohydrates, triterpenoids, flavonoids, tannins, gums and mucilage. The methanol extract gives high percentage yield. Hence, we have evaluated the methanol extract of the leaves of *Measa lanceolata* for screening the various pharmacological potential.

Acute Oral Toxicity Study

The study examined the acute toxicity of methanolic extract of *Measa lanceolata* (MEML) in rats according to the OECD guidelines 423. The body weight of the rats before and after administration was noted, and no significant changes were observed. Additionally, there were no visible signs of toxicity, such as changes in skin and fur, eyes, mucous membranes, respiratory, circulatory, autonomic and central nervous system, and motor activity and behavior patterns. The absence of signs of toxicity suggests that MEML is safe for use in rats. Moreover, the study also assessed the onset of toxicity and the signs of toxicity, such as tremors, convulsions, salivation, diarrhea, lethargy, sleep, and coma. However, no signs of toxicity were observed in any of the rats treated with MEML at the tested doses. This further supports the safety of MEML for use in rats.

Finally, in the subsequent study, there were no observed deaths or signs of toxicity at the same dose levels used in the acute toxicity study. This finding is in agreement with the OECD guidelines for acute toxic class methods, which recommend the use of a stepwise procedure to determine the acute toxicity of chemicals. The results suggest that MEML has a low potential for acute toxicity in rats and can be considered safe for use at the tested dose levels. Overall, the study suggests that MEML is safe for use in rats and has a low potential for acute toxicity at the tested dose levels. However, further studies are needed to evaluate the chronic toxicity and long-term effects of MEML to fully assess its safety and efficacy.

***In Vivo* Pharmacological Activity**

Effect of MEML on Haloperidol Induced Catalepsy (0-3.5 SCALE)

The table 6 presents findings from an experimental study conducted on the effect of methanolic extract of *Measa lanceolata* (MEML) on haloperidol-induced catalepsy in rats. The cataleptic response was measured at six different time points (30, 60, 90, 120, 150, and 180 min) and was scored on a scale of 0-3.5. Higher scores indicate a more severe cataleptic response. The results showed that there was a significant difference ($P<0.01$) between the control group (Group I) and the negative control group (Group II) in terms of catalepsy scores. The negative control group had significantly higher catalepsy scores at all time points compared to the control group, indicating that haloperidol effectively induced catalepsy in the animals. However, treatment with MEML led to a significant decrease in catalepsy scores, indicating its anticataleptic action. Specifically, the group treated with MEML at a dose of 400 mg/kg (Group IV) showed a significant decrease in catalepsy scores at all time points compared to the negative control group (Group II). Interestingly, this group had catalepsy scores comparable to those of the standard drug group (Group III), which also showed significant anticataleptic action compared to the negative control group.

Furthermore, there was a significant difference ($P<0.01$) between the negative control group (Group II) and the MEML treated groups (Groups IV and V) in catalepsy scores. MEML at a dose of 400 mg/kg (Group V) showed significant anticataleptic action at 30, 150, and 180 min after haloperidol challenge. Overall, the results suggest that MEML has significant anticataleptic action in haloperidol-induced catalepsy in rats, particularly at a dose of 400 mg/kg. The findings also indicate that this dose of MEML is comparable to the standard drug used in the study in terms of its anticataleptic action

Effect of MEML on Exploratory Behavior

The tables present data on the effect of methanolic extract of *Measa lanceolata* (MEML) on exploratory behavior in rats challenged with haloperidol. Exploratory behavior was measured using two parameters: head dippings (Table 6) and line crossings ..

Table 6 shows that the negative control group (II) exhibited a significant decrease in head dippings at all time points after haloperidol challenge when compared to the control group (I). However, the MEML treated groups (IV and V) showed a significant increase in head dippings compared to the negative control group (II) at 90, 120, 150, and 180 min after haloperidol challenge. Group III, which was treated with the standard drug, also showed a significant increase in head dippings compared to the negative control group at all time points ($P<0.01$).

Table 7 shows that the negative control group (II) had significantly fewer line crossings at all time points after haloperidol challenge compared to the control group (I). However, the MEML treated groups (IV and V) showed a significant increase in line crossings compared to the negative control group (II) at all time points after 60 min. Similarly, Group III, which was treated with the standard drug, showed a significant increase in line crossings compared to the negative control group at all time points ($P<0.01$). Overall, the results indicate that MEML treatment increases exploratory behavior in rats challenged with haloperidol. The reduction in exploratory behavior seen in the negative control group was attenuated by MEML treatment. The anti-parkinson's action of MEML may be attributed to its ability to increase exploratory behavior. The dose of 400 mg/kg of MEML was found to be most effective in increasing exploratory behavior, particularly in terms of head dippings.

Effect of MEML on Histopathological Changes of Brain

The study also examined the effect of methanolic extract of Measa lanceolata (MEML) on histopathological changes in the brain of rats challenged with haloperidol. Brain sections were examined for any changes in cellular architecture, including necrosis and degeneration of brain cells. The brain sections of the normal control group (not treated with haloperidol) showed normal cellular architecture with no apparent signs of necrosis or degeneration (Fig. 10). In contrast, brain sections of rats treated with haloperidol showed significant disarrangement of normal brain cells with necrosis and degeneration of brain cells.

However, treatment with MEML at a dose of 200 and 400mg/kg, p.o, resulted in a significant protective effect in a dose-dependent manner. The brain sections of rats treated with MEML at these doses showed no signs of necrosis and had a significantly improved cellular architecture compared to the negative control group (haloperidol-treated rats). Interestingly, the protective effect of MEML was comparable to that of the standard drug group (Group III), indicating its potential as a therapeutic agent for haloperidol-induced neurological damage.

Table 1: Indicates CNS activities of some important Indian medicinal plants in literature

Analgesics	Antidepressants	Anticonvulsants
Corchorus depressus, Embelirabes, Gossypium indium, Azadirachata indica,	Mucuna pruriens, Saraca indica, Withania somnifera.	Withania somnifera, Convolvulus pluricaulis, Erythrina varicgata, Pongamia pinnata.

Psidium guara.		
Anti-stress agents	**Antiparkinson's**	**Anxiolytic**
Ocimum sanctum, Eleutherococcus senticosus, Centella asiatica.	Mucuna pruriens, Kava, Evening primose, Ginkgo biloba, Fava bean, Belladonna, Henbane, Thornapple, Oat, Passion flower, Jimson weed.	Withania somnifera, Azadirachata indica, Nardostachys jatamansi, Acorus calamus.

Table 2: Indicates Percentage yield and Consistency of Measa lanceolata extracts

Parameter	methanol extract
Percentage of yield (w/w)	18.96
Consistency	Sticky
Colour	Dark greenish black

Table 3: Indicates Phytochemical studies of Measa lanceolata extract

Tests	Methanol extract
Alkaloids	+
Carbohydrates	+
Steroids	-
Triterpenoids	+
Flavonoids	+
Glycosides	-
Saponins	-
Tanins	+
Fixed Oils	–
Gums & mucilage	+

– / + = Absence / Presence

Table 4: Indicates Acute Toxicity class method OECD guidelines 423

S.No	Groups	Dose/kg b.w	Weight of animals		Signs of Toxicity	Onset of Toxicity	Duration of Study
			Before Test	After Test			
1	MEML	2000 mg	176 g	181 g	No signs of Toxicity	Nil	14 days
2	MEML	2000 mg	186 g	191 g	No signs of Toxicity	Nil	14 days
3	MEML	2000 mg	206 g	211 g	No signs of Toxicity	Nil	14 days

Table 5: Indicates Effect of MEML on catalepsy (0-3.5 scale)

Group	Catalepsy					
	30 min	60 min	90 min	120 min	150 min	180 min
I	0.00	0.00	0.00	0.00	0.00	0.00
II	$2.4\pm0.12^{a**}$	$3.2\pm0.19^{a**}$	$3.8\pm0.00^{a**}$	$3.3\pm0.00^{a**}$	$3.4\pm0.00^{a**}$	$3.2\pm0.00^{a**}$
III	$0.84\pm0.11^{b**}$	$1.19\pm0.11^{b**}$	$1.37\pm0.12^{b**}$	$1.06\pm0.04^{b**}$	$1.11\pm0.04^{b**}$	$0.75\pm0.11^{b**}$
IV	$2.1\pm0.14^{b*}$	2.6 ± 0.13^{bns}	$2.3\pm0.14^{b**}$	$2.07\pm0.12^{b**}$	$2.27\pm0.11^{b**}$	$2.14\pm0.14^{b**}$
V	$1.32\pm0.12^{b**}$	$1.85\pm0.14^{b**}$	$1.81\pm0.11^{b**}$	$1.71\pm0.27^{b**}$	$1.72\pm0.15^{b**}$	$1.68\pm0.11^{b**}$

The values are expressed as mean ± SEM of 6 animals. Comparisons were made between : a-Group I with Group II; b-Group II with Group III, IV, V; Statistical significance test for comparison was done by ANOVA , followed by Dunnett's 't' test. **P<0.01, *P<0.05, ns- Non significant.

Table 6: Effect of MEML on exploratory behaviour-head dipping

Group	Head dipping					
	30 min	**60 min**	**90 min**	**120 min**	**150 min**	**180 min**
I	7.32±0.410	7.67±0.24	8.19±0.64	7.39±0.24	6.58±0.45	6.31±0.35
II	$0.4\pm0.22^{a**}$	$0.82\pm0.34^{a**}$	$0.14\pm0.14^{a**}$	$0.4\pm0.25^{a**}$	$0.31\pm0.19^{a**}$	$0.6\pm0.25^{**}$
III	$4.12\pm0.34^{b**}$	$6.85\pm0.32^{b**}$	$9.15\pm0.52^{b**}$	$8.79\pm0.29^{b**}$	$8.85\pm0.39^{b**}$	$7.29\pm0.24^{b**}$
IV	0.3 ± 0.26^{bns}	1.37 ± 0.27^{bns}	$2.6\pm0.27^{b**}$	$3.14\pm0.27^{b**}$	$3.15\pm0.18^{b**}$	$2.89\pm0.29^{b*}$
V	0.81 ± 0.11^{bns}	$3.5\pm0.25^{b**}$	$4.11\pm0.34^{b**}$	$5.34\pm0.34^{b**}$	$4.49\pm0.24^{b**}$	$4.11\pm0.47^{b**}$

The values are expressed as mean ± SEM of 6 animals. Comparisons were made between : a-Group I with Group II; b-Group II with Group III, IV, V; Statistical significance test for comparison was done by ANOVA , followed by Dunnett's 't' test. **P<0.01, *P<0.05, ns- Non significant.

Table 7: Effect of MEML on exploratory behaviour-Line crossing

Group	Line crossing					
	30 min	**60 min**	**90 min**	**120 min**	**150 min**	**180 min**
I	79.41±3.64	75.14±3.49	82.51±4.19	79.79±1.81	89.23±3.39	$76.23\pm3.15^{a**}$
II	$7.32\pm0.52^{a**}$	$4.34\pm0.24^{a**}$	$2.29\pm0.52^{a**}$	$2.159\pm0.39^{a**}$	$3.4\pm0.69^{b**}$	$3.84\pm1.11^{b**}$
III	$37.28\pm2.61^{b**}$	$59.12\pm3.21^{b**}$	$73.2\pm4.21^{b**}$	$77.28\pm4.71^{b**}$	$82.3\pm4.42^{b**}$	$81.19\pm5.24^{b**}$
IV	11.20 ± 0.34^{bns}	$22.10\pm1.50^{b*}$	$25.49\pm1.9^{b**}$	$36.29\pm1.4^{b**}$	$40.4\pm2.68^{b**}$	$34.8\pm2.03^{b**}$
V	13.48 ± 0.41^{bns}	$31.27\pm3.19^{b**}$	$45.2\pm2.12^{b**}$	$57.4\pm3.9^{b**}$	$65.1\pm2.52^{b**}$	$57.2\pm2.49^{b**}$

The values are expressed as mean ± SEM of 6 animals. Comparisons were made between : a-Group I with Group II; b-Group II with Group III, IV, V; Statistical significance test for comparison was done by ANOVA , followed by Dunnett's 't' test. **P<0.01, *P<0.05, ns- Non significant.

Figure 1: Flow chart for acute toxic class method (OECD guidelines 423) starting dose of 2000mg/kg body weight.

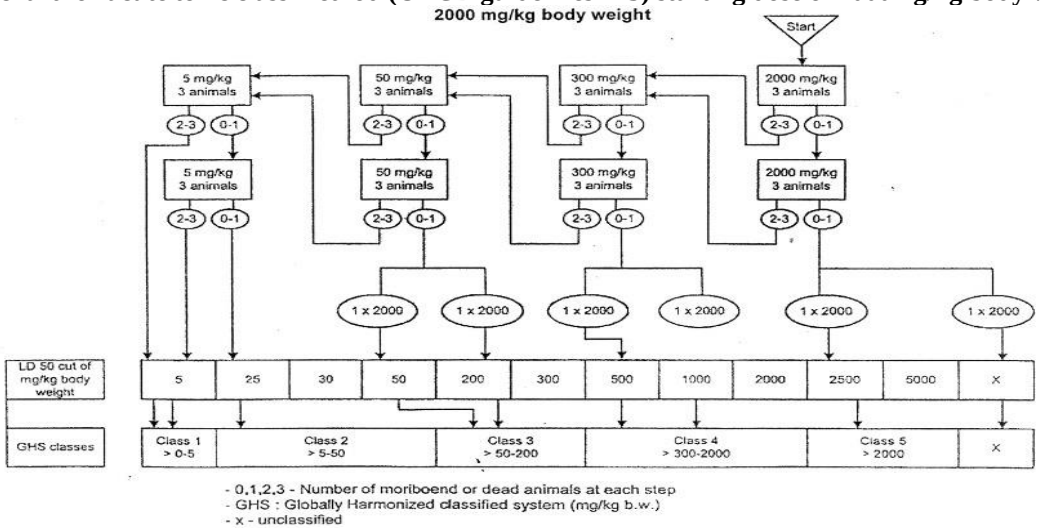
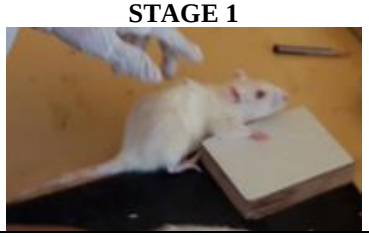


Figure 2: indicates Cataleptic stages in rats

STAGE 1



STAGE 2

STAGE 3

STAGE 4

Figure 3: Indicates Exploratory behavior (head dipping) was measured using hole board.

Figure:4 indicates Effect of MEML on catalepsy.

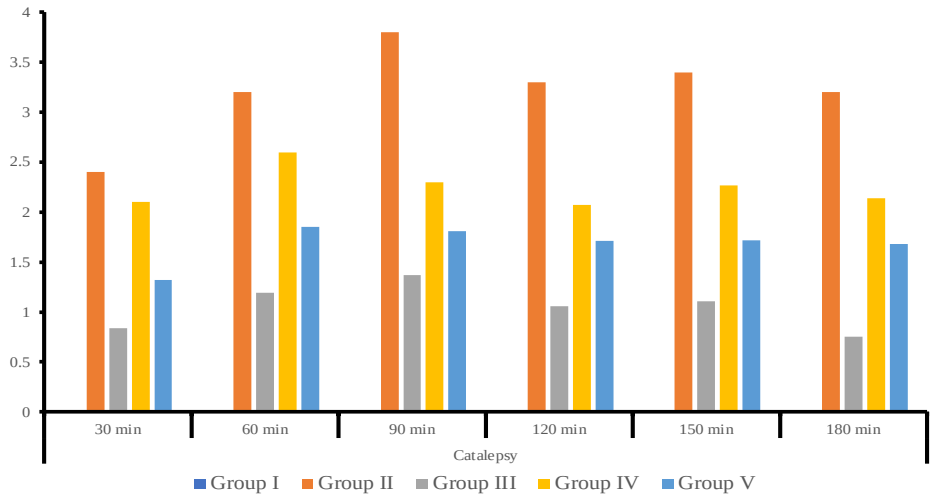


Figure 5: Effect of MEML on exploratory behaviour-head dipping.

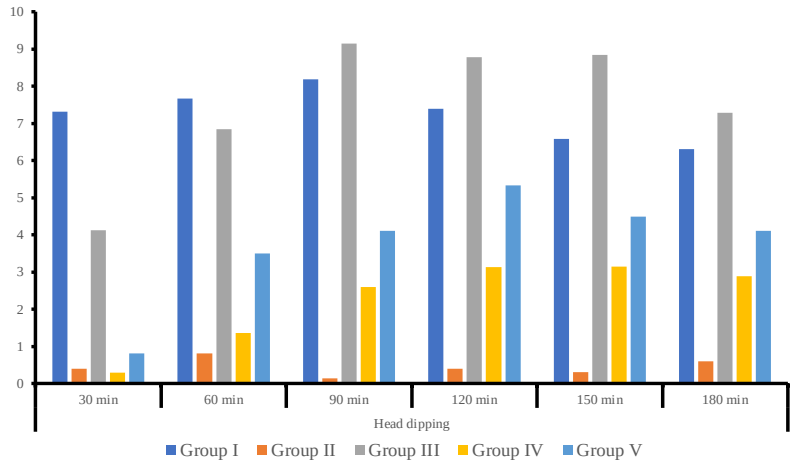


Figure 6:-indicates Effect of MEML on exploratory behaviour-Line crossing.

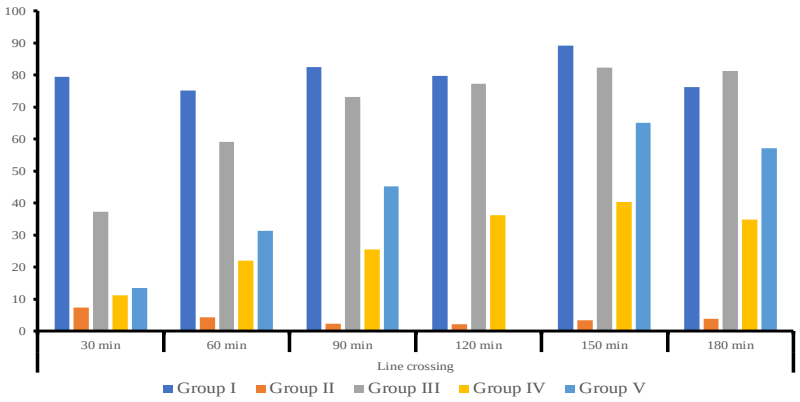
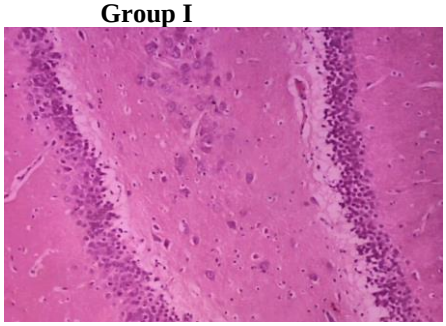
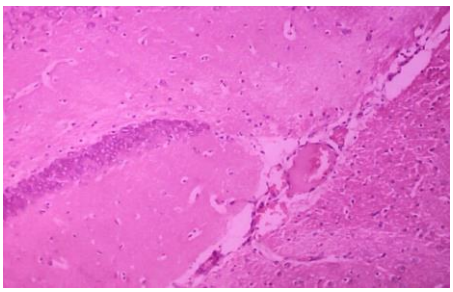


Figure 5: Histopathological Studies on Brain

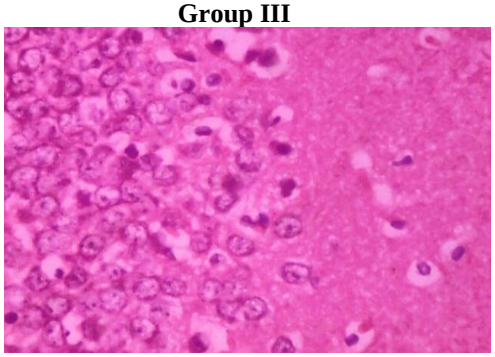
Group I



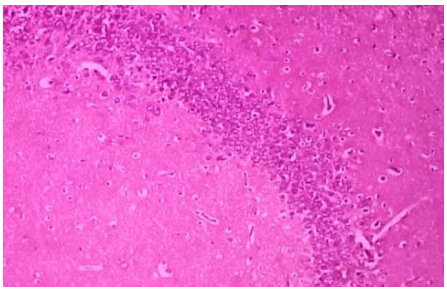
Group II



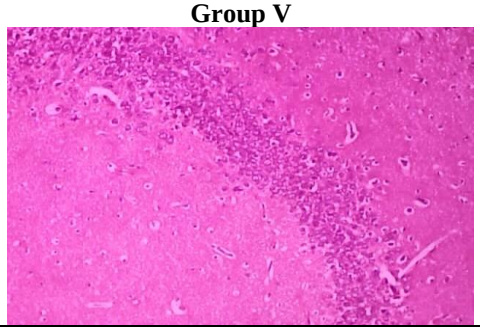
Group III



Group IV



Group V



DISCUSSION

The current research sheds light on the anticataleptic effects of the methanolic extract of *Measa lanceolata* (MEML) in a haloperidol model of catalepsy in rats. The model is widely utilized to evaluate potential drugs for their antiparkinsonian effects. The disease under study, Catalepsy, a condition characterized by an individual's failure to react to external stimuli and remain motionless, is considered a significant animal model of Parkinson's disease. It is induced by neuroleptics like haloperidol, mainly act by blocking dopamine D2 receptors, emulating the dopamine depletion seen in PD. Parkinson's disease (PD) is a progressive neurodegenerative disorder that affects millions of people worldwide. It is characterized by the degeneration of dopaminergic neurons in the substantia nigra, leading to a reduction in dopamine levels, which is implicated in the development of PD in humans and animal models.

Measa lanceolata, also known as yellow trumpetbush or yellow bells, is a plant widely distributed in tropical and subtropical regions. It has been used traditionally for the treatment of various ailments, including fever, inflammation, and pain. Recently, it has been reported to possess antioxidant, anti-inflammatory, and neuroprotective properties. The methanolic extract of *Measa lanceolata* (MEML) was screened for its potential therapeutic effects in the haloperidol model of catalepsy in rats. The MEML, at a dose of 400 mg/kg, demonstrated a pharmacological effect comparable to the standard drug. The results of this study point to a remarkable effect of MEML on the cataleptic state induced by haloperidol. The significant reduction of catalepsy in rats treated with MEML suggests a potential antidopaminergic effect, as shown in Table 4. The values are expressed as mean ± SEM of 6 animals, with significant differences determined by ANOVA followed by Dunnett's 't' test. In Group II, the catalepsy score was significantly higher than in Group I, indicating a prominent cataleptic effect of haloperidol. However, upon administration of MEML (Groups III, IV), the cataleptic score decreased significantly, indicating a marked anticataleptic effect of MEML. It's worth noting that the comparison was made between Group I and Group II, and Group II and Groups III, IV, V.

The exploratory behavior of the rats, as shown in Tables 5 and 6, was also significantly impacted. The parameters used to measure this behavior, head dipping and line crossing, were significantly reduced in the haloperidol group, indicating a substantial reduction in exploratory behavior due to catalepsy. However, the administration of MEML managed to reverse these effects significantly, suggesting a potential role of MEML in improving the motor functions impaired by catalepsy.

Oxidative stress plays a crucial role in PD pathogenesis. The dopaminergic neurons in the substantia nigra are particularly vulnerable to oxidative damage due to a combination of factors: high monoamine oxidase-B activity, autoxidation of dopamine, accumulation of iron and neuromelanin. All of these factors can lead to a decrease in glutathione (GSH), an essential antioxidant in cells. A reduction in GSH might impair H2O2 clearance and promote the formation of hydroxyl radicals (OH.), thus increasing oxidative stress. MEML, with its antioxidant properties, can provide neuroprotection against this oxidative stress, potentially aiding in the prevention and control of PD [24].

In addition to dopamine, other neurotransmitter systems, such as the noradrenaline and serotonin systems, also play a role in the pathophysiology of PD. Changes in the noradrenergic system, particularly in the locus coeruleus, have been reported in PD. Furthermore, the serotonergic neurotransmission in the central nervous system has been reported to exacerbate neuroleptic-induced catalepsy. Extensive evidence indicates that dysfunction in the noradrenaline system may contribute to PD symptomatology. [25-26] Morphological changes in the locus coeruleus, an eminently noradrenergic brain stem area, have been reported in PD. Additionally, several studies have reported that enhancing serotonergic neurotransmission in the central nervous system exacerbates neuroleptic-induced catalepsy. Certain drugs, by antagonizing the stimulatory effects of 5-HT3 receptor activity on dopamine release, decreases dopamine levels in the nigrostriatal and mesolimbic pathways. This suggests that the serotonergic system may also play a role in the pathophysiology of PD and the therapeutic effects of MEML.

Flavonoids, a group of plant-derived compounds, have been shown to have neuroprotective effects. They are capable of modulating intracellular signals to promote cellular survival [27-28]. This study indicates the presence of flavonoids in MEML, suggesting that the neuroprotective action of MEML could be due to these compounds. The findings of this study suggest that MEML may ameliorate the symptoms of haloperidol-induced catalepsy in rats. The mechanism by which this occurs may be attributed to one or more pharmacological/biochemical mechanisms, including the enhancement of the bioavailability of circulatory dopamine by upregulating dopaminergic signaling, as well as the antioxidant action of MEML, which shows neuroprotection. The presence of flavonoids in MEML may also contribute to its neuroprotective effects. In addition, MEML may have beneficial effects on the noradrenaline and serotonergic systems, which are implicated in the pathophysiology of PD. Overall, these findings provide promising evidence for the potential therapeutic effects of MEML in the management of PD. However, further studies are needed to elucidate the specific mechanisms by which MEML exerts its effects, as well as to determine its safety and efficacy in humans. Nonetheless, the findings of this study highlight the potential of natural products, such as MEML, as a source of new and effective treatments for PD and other neurodegenerative disorders.

CONCLUSION

In conclusion, this study significantly contributes to the understanding of the potential therapeutic benefits of the methanolic extract of *Measa lanceolata* (MEML) in managing Parkinson's Disease symptoms. MEML demonstrated notable anticataleptic activity and improved exploratory behaviors in haloperidol-induced catalepsy in rats, similar to standard Parkinson's Disease drugs. These findings suggest that MEML might function by modulating key neurotransmitters and antioxidant enzyme systems, crucial in the pathophysiology of Parkinson's Disease. While these initial results are promising, it is important to emphasize that further investigations are required to validate these findings, elucidate the precise mechanisms of action, and evaluate the effects of different extracts and isolated principles of *Measa lanceolata* on other central nervous system disorders. This research sets a foundation for future studies and brings us a step closer to discovering novel, plant-based treatments for neurodegenerative diseases such as Parkinson's.

LIMITATIONS

Our presenty study has limitations, The haloperidol-induced catalepsy model reflects acute dopaminergic blockade and may not capture the progressive nature of Parkinson’s disease. The use of crude methanolic extract of *Measa lanceolata* (MEML) limits identification of specific active compounds. Neurochemical and histological evaluations were not performed, and dose optimization or toxicity profiling was not conducted. Additionally, the absence of a standard drug as a positive control and the exclusive focus on catalepsy restrict the scope and comparative value of the findings.

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