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Neuroprotective Activity of *Amaranthus tricolor* Leaves Extract for Haloperidol Induce Catalepsy by Behavior Method

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Abstract This research study evaluates the effect of the neuroprotective activity of the dried leaves extract of *Amaranthus tricolor* (LEAT) on haloperidol causing catalepsy in laboratory rats. The catalepsy is caused by intraperitoneal administration of haloperidol (1mg/kg). The composition of the LEAT extracts at low and high dosages, and the standard drugs being tested were given orally (p.o.) 30 minutes before treatment with haloperidol and catalepsy was measured using behavioral test models. The efficacy and inhibition of catalepsy were calculated by the one-way ANOVA method. According to the findings of the phytochemical screening, the LAT contains flavonoids, saponins, alkaloids, tannins, sterols, amino acids, carbohydrates proteins, &fats. An acute oral toxicity study investigation on the LAT, but not through a report of its toxicity was available. The outcomes demonstrate that the LEAT low dose considerably ($p<0.001$) decline the catalepsies score after giving haloperidol for 30, 60, 90, 120, 150, and 180 minutes. The catalepsies score was significantly ($p<0.001$) declined by both standard drug (levodopa 5mg/kg) and LAT high dose in comparison to the disease control group. The levodopa 5mg/kg with LEAT 400mg/kg also significantly ($p<0.001$) declines the catalepsy score. The research suggested that levodopa-infused LEAT significantly enhanced efficacy in comparison to the disease control group. As a result, the study concludes that *A. tricolor* combined with levodopa can potentially manage neurodegenerative disease because it affects almost all of the medals.

Keywords *Amaranthus tricolor*, Cataleptic Activity, Haloperidol, α-synuclein, Neurodegeneration

1. Introduction

Neurological diseases are led to the disorder of dopamine neurons present in the dark matter of the suspension nigra part of the brain. This precedes control movement of body posture malfunction and/or death [1-4]. Normally, the dopaminergic neuron cells secrete chemical substances such as dopamine. Dopaminergic neuron dysfunction or death decreases the production of dopamine which causes an imbalance in body posture or movement [5, 6]. In autopsy series, the major neurodegenerative causes of Parkinsonism (body posture or movement disorder) are α-synucleinopathies [lay body disorder or diseases (LBD) and multiple organ atrophy (MOA)] and other one tauopathies [progressive/intermediate supranuclear palsy (PSP/ISP) is a less well-known neurodegenerative brain condition which is called as misdiagnosed as corticobasal degeneration (CBD)] [7-9].

Haloperidol causes the defective function of different neurotransmitter/ chemical mediators such as acetylcholine, GABA, and serotonin. Haloperidol's pathological state

indicated severe oxidative stress. It also causes mice and rats to fail to balance externally imposed postures (calatopsy); therefore, taking into account the above fact, several studies have been used to manage Parkinson's [10-12]. This valuable animal study concluded that the haloperidol blocks dopamine transmission in substantia nigra parts of the brain [13-14].

The preparations containing *Amaranthus tricolor* show profitable effects on Parkinson's. In traditional medicine, *Amaranthus tricolor* is used as an astringent. A combination of *A. tricolor* root and Cucurbita is the most effective for post-abortion bleeding [14]. Experimental research shows that it can inhibit calcium retention [15]. Plants have antioxidant activity [16], hepatoprotective activity [17], neuroprotective activity [18], and antinociceptive activity [19]. Various valuable research has shown that *A. tricolor* leaf extract is antineoplastic in vitro and in vivo [19, 20, 21].

2. Methodology

2.1. Plants Material

Plants of *Amaranthus tricolor* (Amaranthaceae) were gathering at local markets in Moradabad and Rudderpur. The sample was selected based on its freshness, and leaf quality. The sample was impenitent by Prof. A. Kumar School of Biological Science, IFTM University, Uttar Pradesh, India, latter number 2016/SOS/BOT/33. Pick up the fresh leaves and run them ten times in clean water to remove dust and insects. Fresh and clean leaves are air-dried at room temperature (37 - 40 °C). The dried leaves are crushed to a choice powder using a fine grinder, which is then sieved to remove impurities. Dried plant material will be powdered and passed through a filter with 20 rings. Plant powder materials will be taken. The glowing powder will be extracted with solvent petroleum ether and then extracted sequentially with the Soxhlet apparatus. The discharges will be filtered and concentrated by adding liquids to the melted water and evaporating dry using a rotary vacuum evaporator.

2.2. Chemicals & Reagents

Every single one of the chemicals & reagents utilized in this research was generally the most pure form. The organic and inorganic chemicals & reagents utilized for extraction of dried leaves included: Petroleum ether, Chloroform, Ethanol, Potassium bromide, Iodine solution, Conc. HCL, potassium mercury iodide, NaOH, Acetic acid, Sulphuric acid, a-naphthol, n-butanol, and n-hexane were collected in SDF Chemicals Pvt. Chennai.

2.3. Method of Extraction

Powders of A. tricolor leaves have been de-fattization with solvent petroleum ether at a temperature of about 60-800C, as much as seventy-two hrs. After extraction, the execs solvent was removed, and the red-brown colored residue was collected. The marc after being extracted with petroleum ether turned to dry, after which was extracted with alcoholic solvent (ethanol 99% v/v), for as much as 72 hours in the Soxhlet apparatus. After extraction completion, the extract having solvent is eliminated via the way of means of the usage of presser reducing apparatus, and to achieve a brownish-black sticky residue. The LEAT test solution was made using CMC (1% w/v) as a suspension agent to achieve a specific concentration.

2.4. Phytochemical Investigation

Phytochemical parameter tests were carried out to identify the abundant phytoconstituent present in the ethanolic leaf extract of A. tricolors [18].

2.5. In-vivo Pharmacological Study

Wistar albino rats are 10-12 weeks old, both sexes, in good physical condition, and weigh about 150g approximately chosen from animal house facilities for in-vivo experiments. Temperature 25°C and relative humidity 40-80%, the animal chamber should be kept for 12/12 hours inter ball. Rats were provided with food pellets and water. The laboratory experiment protocol was approved by the IAEC, license number 837/PO/Re/S/04/CPCSEA.

2.5.1. Toxicity Study

Taking male Wistar albino rats, acute oral toxicity labels were performed by OECD (Organization for Economic Co-operation and Development) guideline 423. The scheduled rats were divided into three experimental groups having three rats in each group. Rats were monitored regularly for one hour after feeding test samples and occasionally for another four hours and regularly therefore 7 days [22].

2.5.2. Grouping of Animals

Rats were given catalepsy inducing drug (Haloperidol 1 mg/kg i.p.) for 14 days continuously to cause catalepsy. Oral LEAT and standard medications were administered 30 minutes prior to haloperidol treatment. In this study, there are a total of six groups every group having 6 animals (n = 6).

Group I: Control group, 0.5 % w/v sodium carboxy methyl cellulose (SCMC) was administrated.

Group II: Negative control group, receives 0.5 % w/v SCMC followed by haloperidol.

Group III, IV: Test group, LEAT at a dose of 200 and 400 mg/kg orally followed by haloperidol.

Group V: Standard group, received Levodopa (5 mg/kg orally) followed by haloperidol.

Group VI: Mixed dose, containing Livodopa with LEAL

400 mg/kg orally followed by haloperidol.

In Vivo, pharmacological activity was conducted on the last day of the experiment and observed at every 30-minute interval for 180 minutes. The length of time the rat kept its front feet oblong and settled on a raised bar was examined as a stimulating score [19].

2.5.2.1. Catalepsy Block Method (0-3.5 Scale)

Distension was measured every 30 minutes, then for 3 hours. The stimulation of individual rats was measured in stages by the scoring method described below. The technique assesses the capability of animals to act in response to superficially imposed posture [23].

Step I: the starved rat was lying on a table in its home cage. They can convert your desire into a result.

Stage II: If the rat calms down when touching its back or pushing it gently, a score of 0.5 is assigned.

Step III: The rat's front legs are alternately positioned on a 3 cm high block. A score of 0.5 was added for each foot in the first movements if the rat didn't fix the position within 15 seconds.

Step IV: The procedure is the same as step III but block height is increased (9 cm). If the rat didn't exact its pose within the allotted 15 seconds, a score of 1 per foot was added to the results from the first and second stage. As a result, 3.5 was chosen as the cutoff score for all animals, which represents the overall level of catalepsy.

2.5.2.2. Locomotors Activity

Using an actophotometer, the effect on the locomotor motion was evaluated for 10 minutes every 30 minutes for three hours. An actophotometer can be used to quickly measure locomotor motion. The photovoltaic cells are connected in a circuit with a meter. When the animal cuts the ray of light incident on the photocell, the count is recorded. The occupancy scale can contain a circular or square field in which the animal is in motion [24].

2.5.3. Histopathology Studies

Isolated brains of different groups were sectioned into a longitudinal section with a thickness of 5 μM after being embedded in paraffin wax and immobilized with 10% formalin solution. Hematoxylin and eosin stain were applied to the sections of histological analysis [25].

3. Result

3.1. Phytochemical Analysis

The numerous phytochemical screening results show various phytochemical constituents in the leaves of *Amaranthus tricolor*. The research finds that the phytochemical study consists of presence of Flavonoids, Saponins, Alkaloids, Steroids, Sterols, Amino Acids, Carbohydrates, proteins, and Tannins in the LEAT shown in Table 1. According to the Shinoda test and zin chloride test, flavonoids with a crimson red or occasionally green to blue color are present in ethanolic leaf extracts. The foam formation in ethanolic extract indicated the presence of saponins in the test. In Mayer's, Dragendroff's, Wagner's, and Hager's tests, the presence of alkaloids was found in the ethanolic extracts. In the Salkowski and Liberman-Burchard test, steroids with a bluish-red to cherry color in the chloroform layer and a bluish-green color are present, in ethanolic extracts. The Ninhydrin, Biuret, and Millon's tests exhibited the existence of amino acids and protein. Molisch's, Benadich's, and Fehiling's tests measured the presence of carbohydrates, with orange-red precipitate. The ferric chloride and lead acetate test exhibits the presence of tannins in ethanolic extracts.

Table 1. Phytoconstituent presence in ethanolic leaves extract of *Amaranthus tricolor* (LEAT)

Class	Test	Outcome
Flavonoids	Shinoda Test	+++
	Zinc hydrochloride test	+++
Saponins	Foam Test	++
Alkaloids	Mayer's Test	++
	Dragendroff's Test	+
	Wagner's Test	+
	Hager's Test	+++
Steroids	Salkowski Test	+
	Libermann-Burchard Test	+
Amino Acids	Ninhydrin Test	+
	Biuret test	+
Carbohydrates	Molisch's Test	++
	Benedict's test	++
	Fehling's Test	++
Protein	Millon's Test	++
Tannins	Ferric chloride test	+
	Lead acetate test	+

'+' indicates the bioactive chemical component present, '−' indicates the bioactive chemical component absent, ++' and '+++' indicate the moderate and strong present of bioactive chemical components

3.2. Oral Toxicity Study

An oral toxicity study investigation on the LEAT, but not through a report of its toxicity was published. It is critical to understand the correct drug dosage to achieve the best therapeutic results. According to OECD standards, the present research was designed to assess the acute oral toxicity of LEAT in experimental animals (albino rats). There was no deadliness observed at any dose level in Table 2.

3.3. In-vivo Pharmacological Study

3.3.1. Cataleptic Activity by Block Method

The outcomes demonstrate that the LEAT 200 mg considerably reduces the catalepsies outcome after giving haloperidol treatment for 30, 60, 90, 120, 150, and 180 minutes. After 14 days the catalepsies score was significantly reduced by both levodopa 5 mg and LEAT 400 mg compared to the negative control group. The combination drug-treated group (levodopa + LEAT 400 mg) also significantly reduces the catalepsies score versus the negative control group (Table 3).

3.3.2. Locomotors Activity

The result was found that the ethanolic LEAT 200 mg increased the locomotor outcome following 30, 60, 90, 120, 150, and 180 min haloperidol administration. Ethanolic LEAT 400 mg and levodopa 5mg additional increased the locomotor outcome on 14 days in comparison to the negative control group and the mixed drug (levodopa + LEAT 400 mg) treated group containing more significantly enhanced locomotor scores compared to the negative control group (Table 4).

3.4. Bran Histopathology Studies of Different Drug-treated Groups

The neuron histopathological study marked that neurotoxin, with the purpose of haloperidol, creates noticeable hypertrophic change, greater intracellular gap, permeation of neutrophils, reduced concentration of cells, alteration of cellular composition, hemorrhage, and neuron damage, and even cell death shown in figure 1. Additionally, these neurons were much smaller, pyknotic, and darkly stained with similar tiny nuclei as compared to animals given with normal vehicles that had not shown any negative effects shown in figure 1b. Figures 1a, 1c, and 1d show a considerable reverse of neurological damage or neuronal abnormalities in rats given with control and LEAT at dosages of 200 and 400 mg/kg, and figure 1e also shows a more significant reversal of neuronal damage or neuronal changes in animals treated with standard drug (levodopa 5 mg/kg). Treatment with the combined drug (Levodopa 5mg/kg and 400mg/kg LEAT) shows in Figure 1f significant improvement in neuronal damage compared to standard drug-treated rats.

Table 2. Results of oral toxicity study

Test group	No. of animal used	Test substance used	Dose mg/kg	Oral toxicity study- 24 hours	Oral toxicity study- 24 hours
Limit test	03	Formulation of ethanolic extract of *Amaranths tricolor* leaves	Control	00	00
	03		500	00	00
	03		2000	00	00

Table 3. Mean cataleptic outcome after administration of 0.5 % SCMC (1 ml), Haloperidol (1 mg), ethanolic LEAT (200 mg), and ethanolic LEAT (400 mg)

Groups	Time (min after treatment)					
	30	60	90	120	150	180
I	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
II	3.50±0.00***	3.50±0.00***	3.50±0.00***	3.50±0.00***	3.50±0.00***	3.50±0.00***
III	2.25±0.11***	2.50±0.14***	2.56±0.28***	2.65±0.10***	2.71±0.09***	2.61±0.06***
IV	1.58±0.37***	1.71±0.15***	1.75±0.37***	1.80±0.13***	1.83±0.12***	1.75±0.07***
V	0.91±0.06**	1.06±0.15***	1.21±0.28***	1.25±0.10***	1.26±0.09***	1.10±0.08***
VI	0.70±0.09*	0.71±0.12**	0.80±0.25***	0.85±0.09***	0.90±0.06***	0.85±0.13***

All data are exhibited as mean ± S.E.M., n =6 in every group, Evaluation of data according to ANOVA followed by student Newman Keuls post hoc test. *p <0.05, **p <0.01 and ***p <0.001 as compared to negative control group.

Table 4. Mean locomotor outcome after administration of 0.5 % SCMC (1 ml), Haloperidol (1 mg), ethanolic LEAT (200 mg), and ethanolic LEAT (400 mg)

Groups	Time (min. after treatment)					
	30	60	90	120	150	180
I	232.2±10.07	235.7±9.64	249.2±7.24	252.7±8.55	239.5±19.14	253.7±11.44***
II	17.67±1.78***	21.83±1.13***	24.33±3.27***	26.00±2.72***	28.33±1.56***	34.33±1.60***
III	54.00±8.69***	65.33±6.45***	69.50±6.40***	72.67±6.02***	74.67±5.17***	79.17±6.46***
IV	114.3±9.59***	119.3±8.16***	126.8±11.15***	138.8±11.70***	139.2±7.10***	143.3±5.15***
V	153.2±11.67***	163.0±7.76***	169.7±5.76***	161.7±7.89***	168.5±6.02***	176.3±4.76***
VI	179.7±13.25**	186.2±13.96**	190.5±15.50***	192.0±15.79***	176.7±12.82***	183.0±19.05***

All data are exhibited as mean ± S.E.M., n =6 in every group, Evaluation of data according to ANOVA followed by student Newman Keuls post hoc test. *p <0.05, **p <0.01 and ***p <0.001 as compared to negative control group.

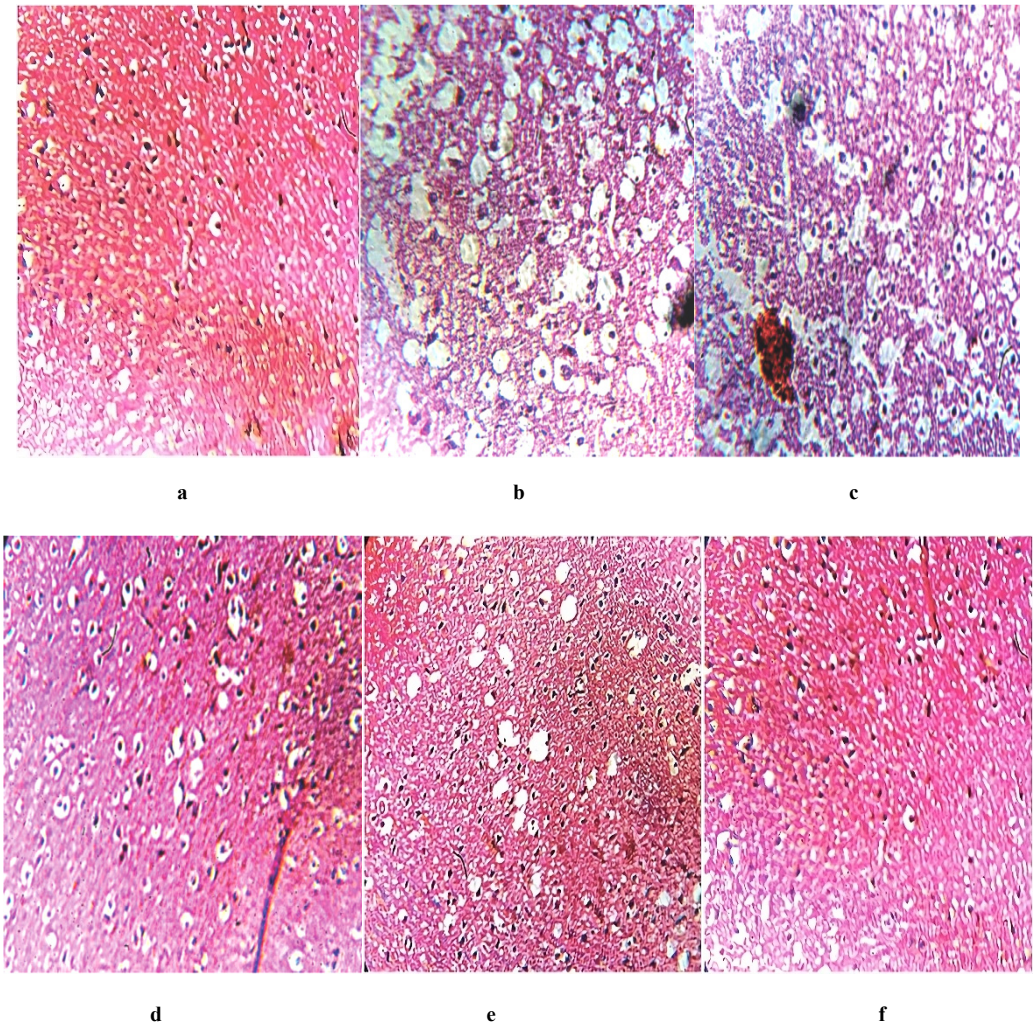

Figure 1. Substantia nigra zona of parkinson brain (a) Control group, (b) Negative control group, (c and d) Ethanolic extract of LEAT 200 and 400 mg/kg b. wt., (e) Livodopa group, and (f) Mixed group (Livodopa and 400 mg/kg LEAT)

4. Discussion

Dopamine replacement therapy is the backbone of current neurodegenerative disease treatment, although it has long-term side effects, including dyskinesia. Along with Parkinson's disease, a wide range of neurodegenerative illnesses can be treated with herbs [26, 27]. In the present research, we used the neurological disorders chemical inducer haloperidol to assess the effects of LEAT, a plant traditionally used for treating the condition, in rodents [28].

The study conducted a comparative statistical analysis to examine the synergistic effect of a mixed treatment group receiving levodopa (5 mg/kg) and LEAT (400 mg/kg p.o.). This formulation resulted in a considerable rise in the inhibition of catalepsy, which compensated for the individual dosages in the standard drug-treated and test drug-treated animal groups. Catalepsy restraint (a decrease in behavioral scores with different drug-treated groups at a similarly different time interval) indicated a significant effect in a formulation-dependent manner. Also, it has a similar effect on locomotor activity performance by actophotometer. The synergistic effect of the group VI drug-treated mixed group formulation significantly increases the locomotion scores compared to the other individual doses associated with the standard group (group V) and the test group (group III, and IV). The protective function of neuroglial cells (an increase in locomotor scores with the other drug-treated groups) indicated a synergistic effect of the mixed drug-treated groups. The significantly increased locomotion scores compared to other individual doses related to the standard group (group V) and the test drug-treated groups (group III and group VI). A reduction in the degree of locomotor distention indicates a reduction in the imbalance between the dopamine (inhibitory) and cholinergic (excitatory) systems in the brain [29].

The key pathophysiology of Parkinson's disease (PD) is the accumulation of α-synuclein. Large aggregates of α-synuclein form circular smooth eosinophilic visceral inclusions (LB) in the nerve body and fibers composed of insoluble α-synuclein polymers (Lewy neuritis) in

neuronal processes and astrocytes and oligodendrocytes, α-synuclein is toxic. Its accumulation disturbs the structure and functions of the endoplasmic reticulum, mitochondria, and Lysosomes and interferes with microtubular transportation. The substantia nigra's (SN) neurons that produce dopamine are affected by PD's essential pathology. A-9 neurons are a particular subset of neuromelanin-containing dopaminergic neurons that are primarily spared from cell death in the SN compared to other types of neurons, and glial cells. The substantia nigra becomes severely depigmented in advanced neurological disease as a result of the loss of pigmented neurons. A limited quantity of neuromelanin produced by dying neurons is released and picked up by macrophages, astrocytes, and neutrophils.

The collapse of the nigrostriatal pathway, which results from this serious cellular defect, decreases dopamine levels in the substantia nigra (SN). The main motor symptoms of PD are delivery to be caused by decreased dopaminergic transmission. Recent research has demonstrated that the breakdown of the axon terminal that represents the striatum occurs before nerve cell loss in the SN [30]. The locus Cornelius, basal nucleus of miners, the dorsal motor nucleus of the vagus nerves, pedunculopontine nucleus, regrowth nucleus, hypothalamus, and complimentary bulb are just a few subcortical nuclei that show normal cell defeat in addition to the SN. The cholinergic, adenosinergic, glutamatergic, GABA energic, noradrenergic, serotonin, and histamine pathways are a few nondopaminergic neurotransmitter pathways that are affected [31-33].

5. Conclusions

In the above-mentioned beneficial animal investigation, we came to the conclusion that levodopa-infused LEAT significantly enhanced efficacy as a balance to the disease control group. As a result, the study concludes that A. tricolor combined with levodopa can potentially manage neurodegenerative disease because it affects almost all of the medals. It can be used to lessen the negative effects of commercially marketed medications. To investigate the processes underlining the CNS function of the various potent extraction fractions, however, and to identify the active ingredient in charge of these pharmacological activities, more research is required.

Conflicts of Interest

The Authors declare no conflicts of interest.

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