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Original article

Neuroprotective potential of *Cordia dichotoma* in Parkinson's syndrome induced by haloperidol: An animal study

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ABSTRACT

Background: Parkinson's disease (PD) is one of the major neurodegenerative disorders and the prevalence is expected to increase during the next couple of decades. There is a need for safe and effective therapeutic regimen that can effectively manage this neurotoxicity. The leaves and several other parts of *Cordia dichotoma* are known to possess number of medicinal properties. The purpose of this study was to examine the neuroprotective role of *Cordia dichotoma* in an experimental model of haloperidol-induced P.D.
Materials and methods: Five groups of rats were randomly assigned into different groups. Intraperitoneal haloperidol 1 mg/kg was given to the inducer group and 0.5% CMC to the normal control. The reference standard was syndopa 10 mg/kg, p.o., and the test group animals received *C. dichotoma's* ethanolic extract at 200 and 400 mg/kg orally for one week. Rats exposed to haloperidol were assessed for behavioral, neurochemical, and histopathological parameters.
Results: *C. dichotoma* leaves extract dose-dependently increased behavioral activity and muscle coordination. The extract at 400 mg/kg was found to increase significantly ($P < 0.001$) the central square activity in open-field test, compared to haloperidol treated rats. In stepping test, both tested doses of *C. dichotoma* (200 mg and 400 mg/kg) were found to significantly ($P < 0.001$) reduce akinesia, besides these doses also decreased the catatonic responses induced by haloperidol. Further, the extraction treatment (200 mg and 400 mg/kg) significantly ($P < 0.001$) decreased malonaldehyde and increased antioxidant enzymes like catalase compared to the control group. Histopathological changes in the test group showed a significant reduction in haloperidol damage to normal morphology in cortical, hippocampus, substantia nigra, and pyramidal.

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Conclusion: The observations of the study suggest that *Cordia dichotoma* attenuated the haloperidol-induced neurological changes, indicating that the plant might benefit in the treatment of Parkinson's disease. The activity of *Cordia dichotoma* could be linked to its antioxidant property. Since, the drug is traditionally used in different parts of world; it could be a promising agent if more research establishes its safety and efficacy in other experimental models of Parkinson's Disease.

1. Introduction

In 1817 Dr. James Parkinson characterized PD as a "shaking palsy." Chronic, progressive dementia of the brain with motor and nonmotor symptoms. The disease's progressive loss of mobility and muscle control affects patients, families, and carers. Striatal dopaminergic neuron loss leads to PD motor symptoms. Nonmotor symptoms support nondopaminergic neuronal loss (DeMaagd and Philip, 2015). Parkinson's disease (PD) is prevalent among the elderly, with a higher incidence in men, irrespective of race or socioeconomic status. The prevalence of this medical condition ranges from 1.5 to 2.0% among those aged 60 and older, whereas it rises to 4% among those aged 80, as earlier mentioned. The substantia nigra, which summarises dopamine (DA), and necroses dopaminergic neurons, reduces DA in the synaptic cleft. By distributing free radicals, MAO-B degrades dopamine, causing glutamate accumulation, oxidative stress, and excitotoxicity. PD causes rigidity, bradykinesia, tremor, postural instability, and diminished function. The second most common cause of elderly parkinsonism after PD is drug-induced parkinsonism (Marino et al., 2020).

Haloperidol (HP) is a major contributor to induced Parkinson's globally (Shin and Chung, 2012). Schizophrenia is treated with initial antipsychotic haloperidol (HP). Haloperidol causes extrapyramidal symptoms like parkinsonism and tardive dyskinesia, limiting its use. Pathological causes include elevated reactive oxygen compounds (ROC) and reduced antioxidant protection mechanisms (Rajaram et al., 2015). HP blocks dopamine receptors, increasing turnover. Their metabolism can produce ROS. HP decreases antioxidant enzymes and generates free radicals (Kadir et al., 2022). Levodopa with a peripheral decarboxylase inhibitor is the standard treatment for PD. Dopamine precursors like levodopa, carbidopa, orphenadrine, benztropine, and selegiline reverse PD symptoms. Prolonged use of these drugs can cause severe undesirable effects, including nausea, vomiting, mania, respiratory issues, dyskinesia, hallucinations, convulsions, anxiety, and more. PD drugs have side effects and cannot stop dopaminergic neuron degeneration (Naemi et al., 2020).

Due to their lower side effects and cost, natural anti-Parkinson products have become more popular. Plant-derived medicines are the first line of defense against disease and are still the main source of new drugs. *Cordia dichotoma* (*C.dichotoma*) belonging to the family *Boraginaceae* is native to several regions of world such as America, Africa, China, India, Australia and Mexico. *C.dichotoma* is one of the popular folk medicines for treating several ailments (Pawar et al., 2018). Stems, barks, fruits, flowers, roots and leaves are commonly used parts of plant for medicinal purpose (Jamkhande et al., 2013. Fruits are frequently used for treating cough and chest-related disorders; kernels are used for the treatment of tinea; barks are utilized for treating fever, abscesses, tumors, ulcerative colitis; leaves are popular for treating diarrhea, burns, liver diseases, abdominal problems, kidney diseases, infertility issues and jaundice (Raghuvanshi et al., 2022). Some of the important phytoconstituents isolated and identified in *C.dichotoma* are triterpenoids, phenolics, amino acids, flavonoids, and carotenoids. Polyphenols, chlorophyll *A*, quercetin, and quercitrin (Tripathi, 2023). Considering the medicinal properties associated wth *C.dichotoma* and usefulness of naturally derived medicines in neurodegenerative diseases, the present study was planned to investigate the neurological protection against haloperidol-induced PD in experimental rats' model.

2. Materials and methods

2.1. Drugs and reagents

In Bangalore, carboxymethyl cellulose (CMC) was purchased from SD Fine Chemicals Ltd. Haloperidol, and Syndopa (combination of L-dopa and carbidopa) were procured from Bangalore's Sigma Aldrich. All other reagents, including tris buffer and sodium and potassium dihydrogen phosphate, were highly analytical.

2.2. Plant collection and authentication

The leaves of *C. dichotoma* were collected from the nearby Tirupati forest (Andhra Pradesh). The plant was officially authenticated and confirmed by Dr. K. Madhava Shetty, Department of Botany, Sri Venkateshwara University, Tirupati; a reference number (0511/02/08/2011) is preserved at Herbarium in Oxford College of Pharmacy Bengaluru.

2.3. Plant extraction

The plant *C. dichotoma* leaves were rinsed and shade-dried to remove contaminants and other debris. Grinding leaves that were dried were passed over sieve No. 14. 50 g of dried pulverized *C. dichotoma* leaves were placed in a Soxhlet extraction tube as a tiny and extracted with 500 mL of ethanol at 60–65C for 3–4 h. The hot extract was filtered and dried using a rotating vacuum evaporator system and then preserved at −18C for further study. The ethanolic leaves extraction *C. dichotoma* residue was dispersed in the same solvents for analysis.

2.4. Experimental rats

Grouping cages contained male and female Wistar rats weighing 180 to 200 g and aged 2 to 3 months. A temperature of 25 ± 2C, a light–dark cycle of 12 h, and a 50 ± 5% relative humidity were required. Food and water were freely available to the rats. Before the experiments, the animals were habituated to the lab. Six creatures make up each group. From 08:00 to 16:00, all tests were conducted. These preclinical experiments were authorized by the Oxford Institutional Animal Ethics Committee (IAEC), TOCP/07/IAEC/2021–22.

2.5. Experimental design

Five groups of six experimental animals were administered: (a) Group 1: Treated 0.5% carboxymethylcellulose orally daily for one

week. (b) Group 2: Haloperidol (1 mg/kg, i.p. daily for one week) (c) Group 3: Given Syndopa (L-dopa + carbidopa) 10 mg/kg (Ittiyavirah and Ruby, 2014) and Haloperidol 1 mg/kg i.p. (Mezzomo et al., 2022) for one week. Group 4: One week of low-dose *C. dichotoma* 200 mg/kg p.o. *C. dichotoma* 400 mg/kg p.o (Hatware et al., 2018). Test drug *C. dichotoma* (200 and 400 mg/kg) and standard drug syndopa (10 mg/kg, p.o.) were given 30 min earlier than haloperidol treatment for one week (Kabra et al., 2020; Ittiyavirah and Ruby, 2014).

3. Neurobehavioral studies on experimental rats

3.1. Open field test

The study used 61 × 61 squares with one central square. The animal was centrally positioned in the open field devices and allowed to move freely for 5 min. Behaviors include: (Ambulation: crossed squares to measure it, Rearing frequency: Increasing hind limbs. Self-grooming: Number of times animal groomed face and licked/washed/scratched body and Central Square Activity: crossings central square (Calderon and Bolanos, 2011).

3.2. Stepping test

Akinesia is an independent impairment. The stepping test determined akinesia. The rat was permitted to balance on its forelimbs and move while its rear legs were elevated, and its forelimb steps were monitored for 30 s (Amin et al., 2017).

3.3. Catatonia test

Haloperidol-induced catalepsy was tested at 30-minute intervals until 180 min in the traditional bar test. To evaluate catalepsy, animals were put on the bench with their hindquarters and forelimbs on a 1 cm diameter horizontal bar 6 to 9 cm above the bench. Animal movement times (mean of three consecutive tests; interval: 1 min) have been monitored by stopwatches. For 30 s or more, cataleptic animals maintained this posture (Chitra et al., 2017).

3.4. Biochemical assessment

Oxidative variables in the brain's tissue homogenization have been analysed for malondialdehyde (MDA) (Ellman et al., 1961 and Lowry et al., 1951) and dopamine levels (Rahman and Eswaraiah, 2022), the amount of protein (Mecheri et al., 2019) and Anadozie et al., 2019), and catalase (CAT) (Mecheri et al., 2019; Nayan et al., 2022) activity of enzymes.

3.5. Histopathological investigation

The brains of the control and treatment groups were fixed in 10% formalin, embedded in paraffin wax, and separated to a thickness of 5 mm. Before the histopathological investigation, the tissue specimens were treated with hematoxylin and eosin (Krishna et al., 2019).

3.6. Statistical data analysis

All values are presented as mean ± SEM (standard error of the mean). Graph-Pad Prism 7.0 was used for examining the data using one-way ANOVA (between control and treatment groups) in Dunnett multiple comparison tests. The statistically significant value has been established accordingly.

4. Results

4.1. Neurobehavioral studies

4.1.1. Open field test

The observation of the open field test is represented in Table 1. Administration of haloperidol (1 mg/kg) was found to be significantly ($P < 0.001$) reduced different parameters such as ambulation, rearing, grooming, and activity in a central square compared to control. Syndopa (combination of L-dopa + carbidopa) was tested as a standard at 10 mg/kg and its administration with haloperidol (1 mg/kg) significantly ($P < 0.001$) enhanced the tested parameters compared to the haloperidol group.

CD at a lower dose (200 mg/kg) with haloperidol (1 mg/kg) increased significantly ($P < 0.001$) the duration of ambulation and rearing compared to haloperidol. The higher dose of CD (400 mg/kg) when administered with haloperidol was found to increase significantly ($P < 0.001$) all the tested parameters of the open-field test.

4.1.2. Akinesia (stepping test)

Fig. 1 represents the values of the stepping test. Haloperidol at 1 mg/kg was observed to reduce significantly ($P < 0.001$) compared to control. Syndopa (10 mg/kg) when tested with haloperidol was found to enhance the duration ($P < 0.001$) compared to haloperidol along group. CD tested at two doses (200 mg and 400 mg/kg) with haloperidol was also found to enhance significantly ($P < 0.001$) the stepping duration.

4.1.3. Catalepsy test

The findings recorded for the catalepsy test indicated that haloperidol (1 mg/kg) significantly ($P < 0.001$) increased catatonia compared to control group. Syndopa with treated with haloperidol

Table 1
The effect of *C. dichotoma* leaves on the open field test, the Akinesia (stepping) test, and the catalepsy test in haloperidol-induced Parkinson's syndrome.

Groups	Open field test			
	Ambulation (min)	Rearing (min)	Grooming (min)	Activity in a central square (min)
Control	62.5 ± 0.76	55.33 ± 0.88	25.5 ± 1.02	7.16 ± 0.60
Haloperidol (1 mg/kg)	34.5 ± 1.26[a]	9.33 ± 0.66[a]	10.66 ± 0.88[a]	1.5 ± 0.22[a]
Syndopa (10 mg/kg) + Haloperidol (1 mg/kg)	54.5 ± 1.26[b]	45.16 ± 1.25[b]	22.16 ± 1.64[b]	6.66 ± 0.49[b]
CD (200 mg/kg) + Haloperidol (1 mg/kg)	44.5 ± 1.47[b]	30.66 ± 0.88[b]	13.33 ± 1.05 [ns]	3.33 ± 0.49 [ns]
CD (400 mg/kg) + Haloperidol (1 mg/kg)	49.5 ± 0.76[b]	40.5 ± 0.76[b]	19.5 ± 0.99[b]	6.16 ± 0.47[b]

Values are mean SEM for n = 6. The data was evaluated using a one-way ANOVA and a post hoc Tukey multiple comparison test. Furthermore, a difference exists from the control group ($p < 0.001$), b is distinguished from the haloperidol group ($p < 0.001$), and ns is not significantly distinct from the haloperidol group ($p > 0.05$).

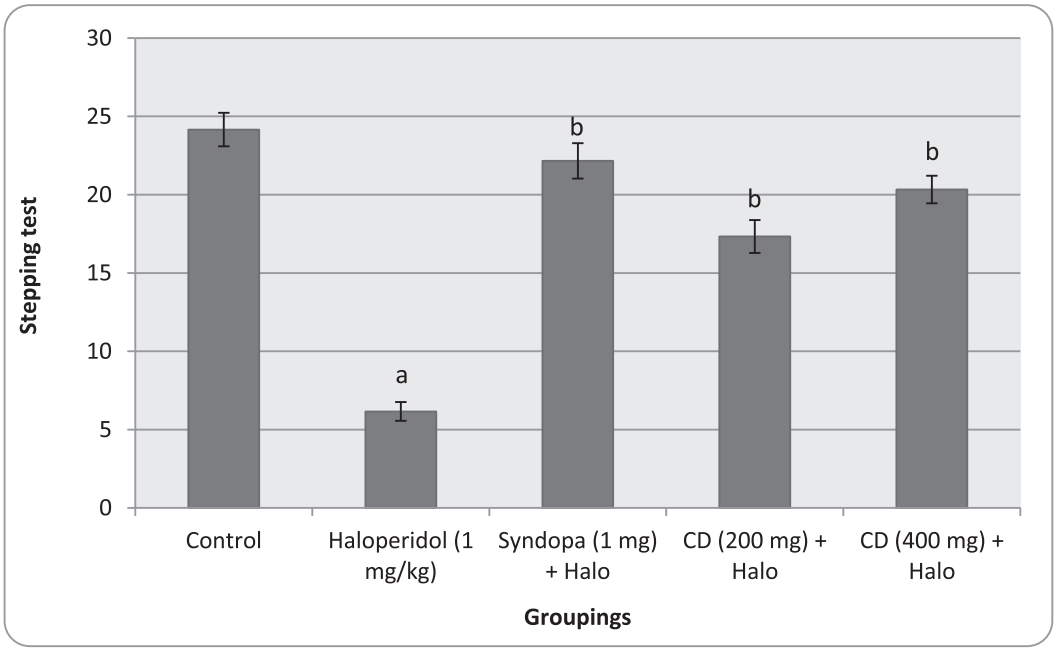

Fig. 1. Effect of *C. dichotoma* leaves on akinesia in haloperidol-induced Parkinson's syndrome. Values are mean SEM for n = 6. The data was evaluated using a one-way ANOVA and a post hoc Tukey multiple comparison test. Furthermore, a difference exists from the control group ($p < 0.001$), b is distinguished from the haloperidol group ($p < 0.001$), and ns is not significantly distinct from the haloperidol group ($p > 0.05$).

was observed to minimize significantly ($P < 0.001$) catatonia when the data was compared with haloperidol alone group. CD at both the lower and higher doses (200 mg and 400 mg/kg) was found to decrease the catatonic action of haloperidol (Fig. 2).

4.1.4. Biochemical assessment

The biomarker estimation suggested that haloperidol (1 mg/kg) significantly ($P < 0.001$) increased the protein content and MDA levels as well as reduced the dopamine and catalase levels when compared to a control group. The administration of syndopa at 10 mg/kg was found to reverse the changes induced by haloperidol.

Syndopa administration significantly ($P < 0.001$) reduces the protein content and MDA. Syndopa also exhibited significant ($P < 0.001$) elevation in the dopamine and catalase levels compared to the haloperidol alone group. Both the lower and higher tested doses of CD (200 mg and 400 mg/kg) were observed to significantly ($P < 0.001$) reverse the changes induced by haloperidol. The test drugs reduced the protein content and MDA activity while dopa-

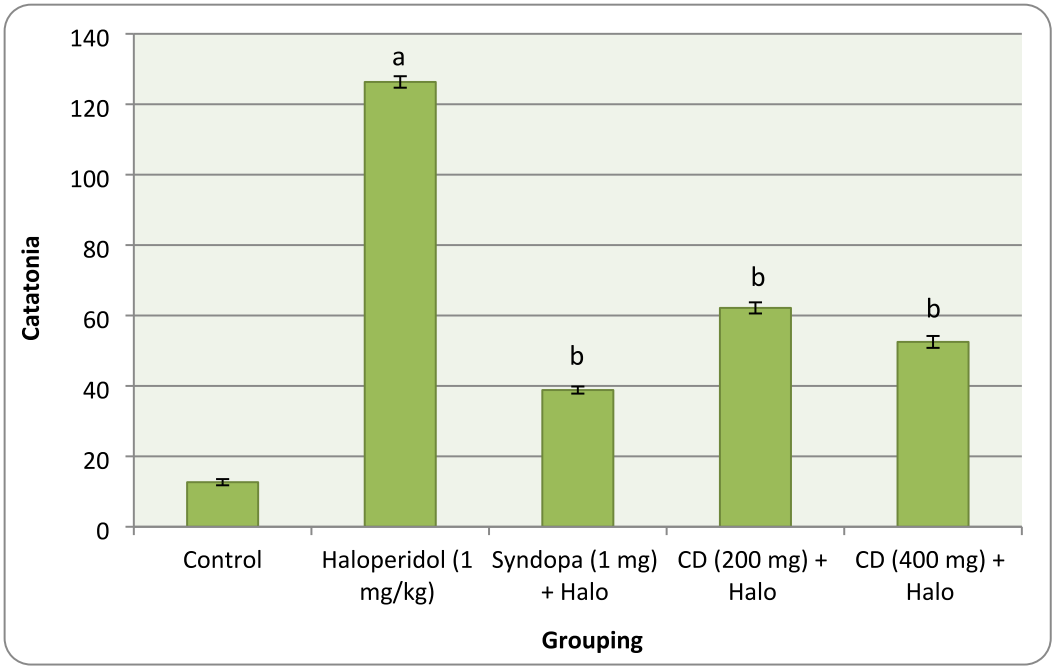

Fig. 2. Effect of *C. dichotoma* leaves on catalepsy in haloperidol-induced Parkinson's syndrome. Values are mean SEM for n = 6. The data was evaluated using a one-way ANOVA and a post hoc Tukey multiple comparison test. Furthermore, a difference exists from the control group ($p < 0.001$), b is distinguished from the haloperidol group ($p < 0.001$), and ns is not significantly distinct from the haloperidol group ($p > 0.05$).

Table 2
Effect of *C. dichotoma* leaves on protein content, dopamine levels, catalase, and MDA in haloperidol-induced Parkinson's disease.

Groups	Protein content (mg/g)	Dopamine Levels (ng/g)	Catalase (U/mg)	MDA (µmol/L)
Control	54.16 ± 0.62	457.6 ± 0.46	31.97 ± 0.61	3.49 ± 0.16
Haloperidol (1 mg/kg)	87.05 ± 0.51[a]	291.86 ± 1.25[a]	14.23 ± 0.59[a]	7.68 ± 0.38[a]
Syndopa (10 mg/kg) + Haloperidol (1 mg/kg)	59.70 ± 0.49[b]	336.41 ± 3.01[b]	23.04 ± 0.18[b]	4.57 ± 0.13[b]
CD (200 mg/kg) + Haloperidol (1 mg/kg)	67.54 ± 0.49[b]	307.58 ± 2.66[b]	20.13 ± 0.64[b]	5.34 ± 0.20[b]
CD (400 mg/kg) + Haloperidol (1 mg/kg)	62.88 ± 0.39[b]	317.06 ± 0.51[b]	22.42 ± 0.24[b]	4.16 ± 0.06[b]

Values are mean SEM for n = 6. Data was examined using a one-way ANOVA and a post hoc Tukey multiple comparison test. a ($p < 0.001$) significant distinction between the untreated and haloperidol groups.

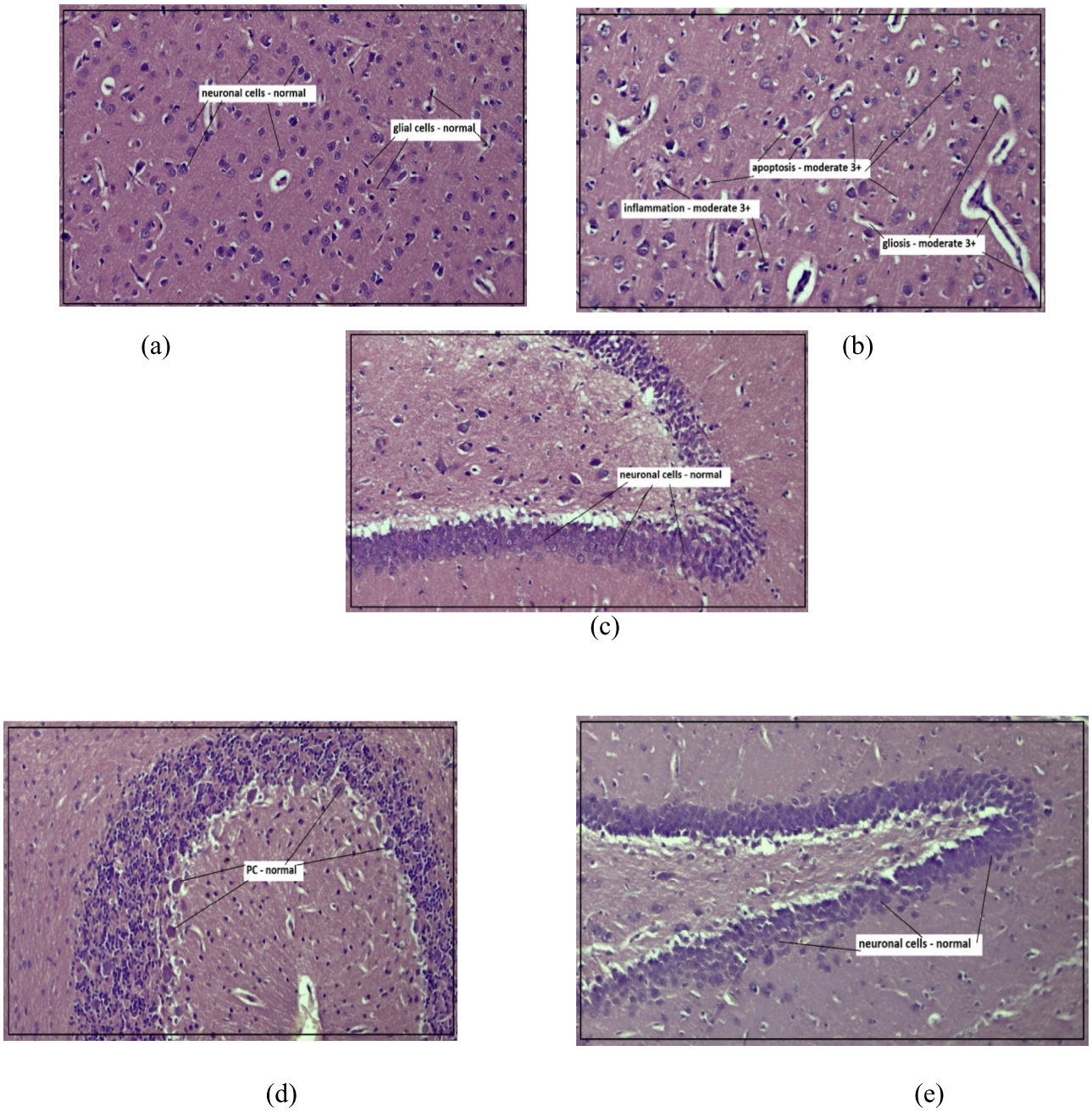

Fig. 3. The impact of *C. dichotoma* on histological alterations in the brain. (a) Control group—cortical area with normal microglial and neuronal cell morphology—NAD+ (X100). (b) Haloperidol group—Cortical area displaying apoptosis with inflammation and gliosis—moderate 3+ (degenerative alterations) (X100) (c) Syndopa and Haloperidol group—hippocampus with neuronal cells normal morphology—NAD+ (X100). (d) *C. dichotoma* (200 mg/kg) and haloperidol group—pyramidal area Purkinje cells (PC) normal morphology—NAD+ (X100). (e) *C. dichotoma* (400 mg/kg) and haloperidol group showed normal hippocampal neuronal cells and NAD+ (X100).

mine and catalase levels were found to be increased when tested with haloperidol (Table 2).

4.2. Histopathological studies

The histology study showed a substantial recovery from neuronal injury and a reduction in necrosis, confirming *C. dichotoma's* neuroprotective effect in Fig. 3.

5. Discussion

Parkinson's disease (PD) is a neurological disorder marked by the degeneration of neurons in the substantia nigra that produce dopamine.. This degenerative process results in tremors, bradykinesia, gait disturbances, postural abnormalities, and rigidity. Although the issue of regulating dopaminergic neuronal transmission in Parkinson's disease (PD) remains unresolved, it is commonly acknowledged that oxidative stress plays a fundamental role in the vulnerability of these neurons (Serra et al., 2001; Polydoro et al.,2004). Moreover, a considerable body of preclinical and clinical research has postulated that the unregulated generation of reactive oxygen species (ROS) is a potential mechanism behind the lethal consequences induced by haloperidol (Sharma et al., 2018).

The current experimental investigation included three behavioral evaluation parameters, including the Open Field Test, Akinesia (Stepping Test), and Catalepsy Test, to assess the effects of haloperidol-induced Parkinson's disease in rats. This study investigated the effects of pre-treating rats with an ethanolic extract of leaves from *C. dichotoma* at doses of 200 and 400 mg/kg, as well as a standard drug called syndopa (combination of L-dopa + carbidopa) at a dose of 10 mg/kg. The treatment was administered for a duration of 7 days. The results showed a significant reduction ($p < 0.001$) in the cataleptic score and an increase ($p < 0.001$) in various behavioural parameters such as the number of steps taken, ambulation, rearing, grooming, and activity in the central square. These effects were observed consistently throughout the entire observation period when compared to rats treated with haloperidol. The administration of the test medication at dosages of 200 and 400 mg/kg and syndopa at a dose of 10 mg/kg resulted in a highly significant ($p < 0.001$) improvement of neuromuscular strength. The neuroprotective effects were most pronounced in rats treated with an extract of *C. dichotoma* leaves at 400 mg/kg. These effects were found to be comparable to the group treated with syndopa.

Haloperidol generated brain oxidative stress, evidenced by increased MDA and reduced Catalase compared to control group rats. Compared to haloperidol-treated rats, syndopa and test medication reduced MDA and increased catalase ($p < 0.001$). Daily haloperidol dosing raised protein concentrations and lowered dopamine levels. Syndopa and test medication treatment decreased levels of proteins and raised dopamine levels in the blood compared to haloperidol treatment ($p < 0.001$).

Histopathology of the brain showed normal neuronal cells in the test drug-treated and syndopa groups, but the haloperidol-treated group showed apoptosis with inflammation causing neuronal damage.

C. dichotoma protects against oxidative stress. *C. dichotoma* has antioxidant capabilities, according to several studies (Hussain et al., 2020). Antioxidants may protect PD neurons from intracellular ROS generation (Bhangale and Acharya, 2016). Thus, antioxidants may help treat Parkinson's disease and protect neuron workouts. *C. dichotoma* may treat PD symptoms by restoring dopamine and modulating the antioxidant system, as demonstrated by the above behavioral and neurochemical properties. Therefore, *C. dichotoma* may be beneficial as a protective treatment for PD.

6. Conclusion

The ethanolic extract of *C. dichotoma* leaves safeguarded against haloperidol-induced Parkinson's disease, comparable to syndopa. Our investigations reveal that *Cordia dichotoma* G. Forst. might prevent and alleviate extrapyramidal adverse effects from antipsychotic medications in clinical use. The compound could be a potential agent for treating the complications induced by haloperidol naturally. The neuroprotective effect demonstrated by *C. dichotoma* leaves extract in this study demands further research into its molecular mechanism and explore possibility of its clinical implication.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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