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Neuroprotective Effect of Alpha Lipoic Acid in Haloperidol-Induced Parkinsonism in Wistar Rats: A Behavioral, Biochemical, and Histopathological Evaluation

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Abstract

Background: Drug-induced parkinsonism is a common and clinically significant adverse effect of dopamine receptor-blocking agents such as haloperidol. Oxidative stress and neuroinflammation are important contributors to the neuronal injury observed in this condition, and no established neuroprotective adjunct is currently available for its management. Alpha lipoic acid (ALA), an endogenous mitochondrial cofactor with antioxidant, anti-inflammatory, and metal-chelating properties, has shown neuroprotective activity in several toxin-induced models of Parkinson's disease, but its efficacy in the haloperidol-induced model has not been well characterised.

Objective: To evaluate the neuroprotective effect of ALA against haloperidol-induced parkinsonism in Wistar rats using behavioral, biochemical, and histopathological endpoints.

Methods: Thirty adult Wistar rats were allocated to five groups (n=6): normal control, disease control (haloperidol 1 mg/kg, i.p.), standard treatment (haloperidol + levodopa/carbidopa 100/10 mg/kg), ALA low dose (haloperidol + ALA 25 mg/kg, p.o.), and ALA high dose (haloperidol + ALA 50 mg/kg, p.o.), treated for 21 consecutive days. Catalepsy (bar test), locomotor activity (actophotometer), and motor coordination (rotarod) were assessed, and striatal malondialdehyde (MDA), reduced glutathione (GSH), superoxide dismutase (SOD), and catalase (CAT) were estimated on Day 21, alongside histopathological scoring of striatal sections.

Results: Chronic haloperidol produced progressive catalepsy (142.3 ± 5.1 s on Day 21 vs 2.4 ± 0.3 s in normal controls; $p<0.001$), reduced locomotor activity (118 ± 5 vs 301 ± 7 counts; $p<0.001$) and rotarod latency (61.3 ± 3.5 vs 178.5 ± 4.2 s; $p<0.001$), together with elevated MDA, depleted GSH, and suppressed SOD and CAT (all $p<0.001$ vs normal control), and marked histopathological degeneration (score 3.8 ± 0.2). ALA attenuated all these changes dose-dependently; the 50 mg/kg dose reduced catalepsy to 21.7 ± 1.6 s, restored locomotor and rotarod performance toward normal, normalised oxidative markers, and preserved neuronal architecture (histopathology score 1.2 ± 0.1), with efficacy statistically comparable to levodopa/carbidopa on several parameters ($p>0.05$, Tukey's test).

Conclusion: Alpha lipoic acid demonstrated significant, dose-dependent neuroprotection in haloperidol-induced parkinsonism, mediated through attenuation of oxidative stress and preservation of neuronal morphology, supporting its candidacy as a neuroprotective adjunct in drug-induced extrapyramidal disorders.

Keywords: Alpha lipoic acid; haloperidol; drug-induced parkinsonism; oxidative stress; catalepsy; neuroprotection; Wistar rats

1. INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease, affecting 1–2% of individuals over 65 years of age, with global prevalence projected to exceed 12 million by 2040[1]. The cardinal motor features bradykinesia, resting tremor, rigidity, and postural instability arise from progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta, with symptom onset generally corresponding to substantial (60–80%) prior neuronal loss[2,3]. Non-motor manifestations, including autonomic, cognitive, and psychiatric disturbances, frequently precede motor onset and add substantially to disease burden[4]. While levodopa and other dopaminergic therapies provide symptomatic relief, none has been shown to halt or reverse the underlying neurodegeneration[5].

A pharmacologically distinct but clinically important variant, drug-induced parkinsonism (DIP), is produced by dopamine receptor-blocking agents and may account for up to 20-40% of parkinsonian presentations referred to movement disorder clinics[6]. Typical antipsychotics such as haloperidol are the most frequently implicated agents, acting via potent antagonism at striatal D2 receptors[7]. DIP is often clinically indistinguishable from idiopathic PD and is particularly common and under-recognised in elderly patients treated with antipsychotics for behavioral disturbances, where symptoms may persist for months even after drug withdrawal[8,9]. Because abrupt antipsychotic discontinuation is often clinically infeasible, an adjunctive agent capable of limiting drug-induced neuronal injury would represent a meaningful therapeutic addition[6].

Normal basal ganglia motor control depends on balanced direct and indirect striatal output pathways regulated by nigrostriatal dopamine[10]; D2 receptor blockade by haloperidol preferentially disinhibits the indirect pathway, producing the hypokinetic, cataleptic motor state that underlies this model[7]. Beyond direct receptor antagonism, haloperidol exposure produces secondary oxidative injury: increased lipid peroxidation and depletion of the endogenous antioxidant defences (GSH, SOD, CAT) that normally protect dopaminergic circuits from reactive oxygen species[12]. Oxidative stress arising from mitochondrial dysfunction, dopamine auto-oxidation, and impaired antioxidant capacity is now recognised as a central and self-amplifying mechanism in parkinsonian neurodegeneration generally[13], compounded by microglia-driven neuroinflammatory injury to vulnerable dopaminergic neurons[14,15].

Alpha lipoic acid (ALA), a naturally occurring mitochondrial cofactor for pyruvate dehydrogenase and α-ketoglutarate dehydrogenase, possesses amphipathic antioxidant activity, regenerates endogenous antioxidants (GSH, vitamin C, vitamin E, coenzyme Q10), chelates redox-active transition metals, and suppresses NF-κB-driven neuroinflammation[16]. Its clinical safety at doses of 300-1800 mg/day is well established from randomised trials in diabetic peripheral neuropathy[17], and structural ALA–dopamine conjugates have separately been explored for CNS antioxidant delivery[18]. ALA has shown neuroprotective efficacy in MPTP and rotenone models of PD, including preservation of dopaminergic neurons, restoration of antioxidant status, activation of the PI3K/AKT pro-survival pathway, and improved motor performance[19,20], with comparable protective effects reported in cerebral ischemia-reperfusion injury through preservation of blood brain barrier integrity[21]. Antioxidant strategies more broadly have

shown benefit against haloperidol-induced catalepsy in rodent models[22]. However, ALA's effect in the haloperidol-induced model a pharmacologically distinct and clinically relevant paradigm modelling drug-induced rather than idiopathic parkinsonism has not been comprehensively characterised. The present study was therefore designed to evaluate the neuroprotective effect of ALA against haloperidol-induced parkinsonism in Wistar rats using an integrated behavioral, biochemical, and histopathological assessment.

2. MATERIALS AND METHODS

2.1 Ethical approval

The experimental protocol was approved by the Institutional Animal Ethics Committee (IAEC) of Systemic Life Sciences (approval no. 26/IAEC-III/SLSRPL/2025). All procedures conformed to the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Government of India, and followed the principles of Replacement, Reduction, and Refinement (3Rs).

2.2 Animals

Thirty healthy adult Wistar albino rats of either sex (150–220 g) were used. Animals were acclimatised for 7 days under standard conditions (22 ± 2 °C, 50 ± 10% relative humidity, 12 h light/dark cycle) with pelleted feed and water ad libitum, before random allocation to five groups (n = 6/group).

2.3 Experimental design

Group I (normal control) received vehicle (0.9% saline, 1 mL/kg, i.p.); Group II (disease control) received haloperidol (1 mg/kg, i.p.); Group III (standard treatment) received haloperidol + levodopa/carbidopa (100/10 mg/kg, p.o.); Group IV (ALA low dose) received haloperidol + ALA (25 mg/kg, p.o.); and Group V (ALA high dose) received haloperidol + ALA (50 mg/kg, p.o.). ALA and levodopa/carbidopa were administered by oral gavage 60 minutes before haloperidol, once daily for 21 consecutive days. Doses were selected based on established literature values for haloperidol-induced catalepsy induction and ALA neuroprotective efficacy in rodent models.

2.4 Behavioral assessments

Catalepsy was assessed by the horizontal bar test (forepaws placed on an elevated rod; descent latency recorded, 180 s cut-off) on Days 1, 3, 7, 14, and 21, 60 minutes after haloperidol dosing. Spontaneous locomotor activity was measured by digital actophotometer (5-minute session, beam-break counts) at baseline and on Day 21. Motor coordination was assessed by rotarod (25 rpm, 3 cm rod diameter; 300 s cut-off), with animals pre-trained to a baseline latency ≥120 s and tested in triplicate on Day 21.

2.5 Biochemical estimations

On Day 21, animals were euthanised and striatal tissue was homogenised in ice-cold 0.1 M potassium phosphate buffer (pH 7.4) and centrifuged at 3,000 rpm for 10 minutes at 4 °C; the post-mitochondrial supernatant was used for assays, with protein content determined by the Bradford method. Lipid peroxidation was measured as MDA (thiobarbituric acid reactive substances, 532 nm) by the method of Ohkawa et al.; GSH was measured colorimetrically (DTNB, 412 nm) by the method of Ellman; SOD activity was measured by inhibition of nitroblue tetrazolium reduction (560 nm) by the method of Kono; and CAT activity was measured by hydrogen peroxide decomposition (240 nm) by the method of Aebi.

2.6 Histopathology

Striatal sections were fixed in 10% neutral buffered formalin, processed through graded alcohols, embedded in paraffin, sectioned at 5 µm, and stained with hematoxylin and eosin. Sections were examined by a blinded observer under light microscopy (100×, 400×) and scored semiquantitatively (0 = normal, 1 = minimal, 2 = moderate, 3 = severe degeneration).

2.7 Statistical analysis

Data are expressed as mean ± SEM (n = 6/group) and were analysed by one-way ANOVA followed by Tukey's multiple comparison test using GraphPad Prism (version 8.0). $p < 0.05$ was considered statistically significant.

3. RESULTS

3.1 Catalepsy

Haloperidol produced a significant, progressive increase in catalepsy duration, from 65.4 ± 2.8 s on Day 1 to 142.3 ± 5.1 s on Day 21 ($p<0.001$ vs normal control at every time point), confirming stable model induction. ALA reduced catalepsy dose-dependently at all time points; by Day 21, the high-dose group recorded 21.7 ± 1.6 s (≈85% reduction vs disease control, $p<0.001$), approaching the standard-treatment group (8.6 ± 0.9 s), while the low-dose group recorded 65.8 ± 2.8 s ($p<0.001$ vs disease control). The difference between ALA doses was statistically significant ($p<0.05$).

Table 1. Effect of alpha lipoic acid on haloperidol-induced catalepsy (bar test, seconds; mean ± SEM, n = 6)

Group	Day 1	Day 3	Day 7	Day 14	Day 21
Normal control	2.1 ± 0.3	2.3 ± 0.2	2.5 ± 0.3	2.2 ± 0.2	2.4 ± 0.3
Disease control	65.4 ± 2.8***	89.6 ± 3.1***	118.4 ± 4.2***	130.7 ± 4.8***	142.3 ± 5.1***
Standard treatment	42.6 ± 2.0###	32.4 ± 1.8###	22.5 ± 1.5###	14.2 ± 1.2###	8.6 ± 0.9###
ALA 25 mg/kg	54.3 ± 2.5#	68.2 ± 2.7#	81.4 ± 3.2##	76.5 ± 3.0##	65.8 ± 2.8##
ALA 50 mg/kg	46.5 ± 2.1##	52.8 ± 2.4##	45.6 ± 2.0###	33.4 ± 1.9###	21.7 ± 1.6###

****p<0.001 vs normal control; #p<0.05, ##p<0.01, ###p<0.001 vs disease control (one-way ANOVA, Tukey's test). One-way ANOVA (Day 21): $F(4,25) = 182.6$, $p<0.0001$.*

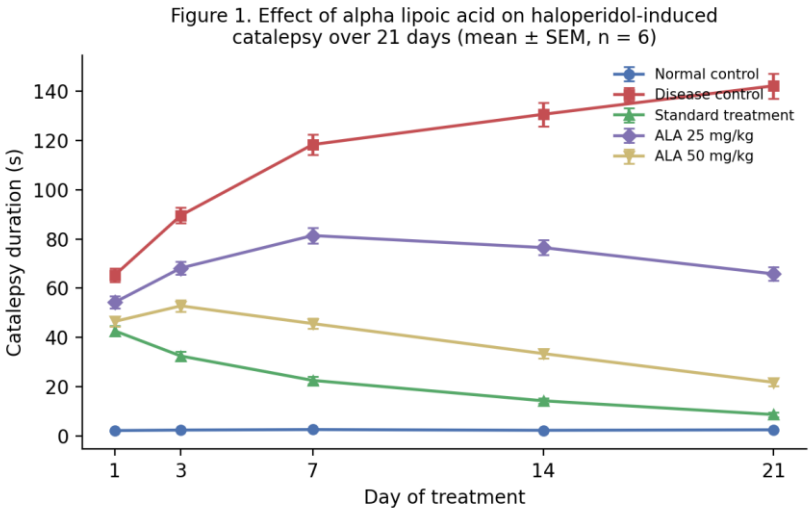

Figure 1. Effect of alpha lipoic acid on haloperidol-induced catalepsy over 21 days (mean ± SEM, n = 6).

3.2 Locomotor activity

Locomotor activity fell from a comparable baseline (~295 counts across groups) to 118 ± 5 counts in disease controls by Day 21, versus 301 ± 7 counts in normal controls ($p<0.001$). ALA treatment improved Day 21 counts dose-dependently (25 mg/kg: 198 ± 6, $p<0.01$; 50 mg/kg: 252 ± 7, $p<0.001$, vs disease control), approaching the standard-treatment group (276 ± 6 counts).

Table 2. Effect of alpha lipoic acid on spontaneous locomotor activity (actophotometer counts; mean ± SEM, n = 6)

Group	Baseline	Day 21
Normal control	298 ± 8	301 ± 7
Disease control	295 ± 9	118 ± 5***
Standard treatment	296 ± 8	276 ± 6###
ALA 25 mg/kg	294 ± 7	198 ± 6##
ALA 50 mg/kg	297 ± 8	252 ± 7###

****p<0.001 vs normal control (Day 21); ##p<0.01, ###p<0.001 vs disease control (Day 21). One-way ANOVA: F(4,25) = 145.3, p<0.0001.*

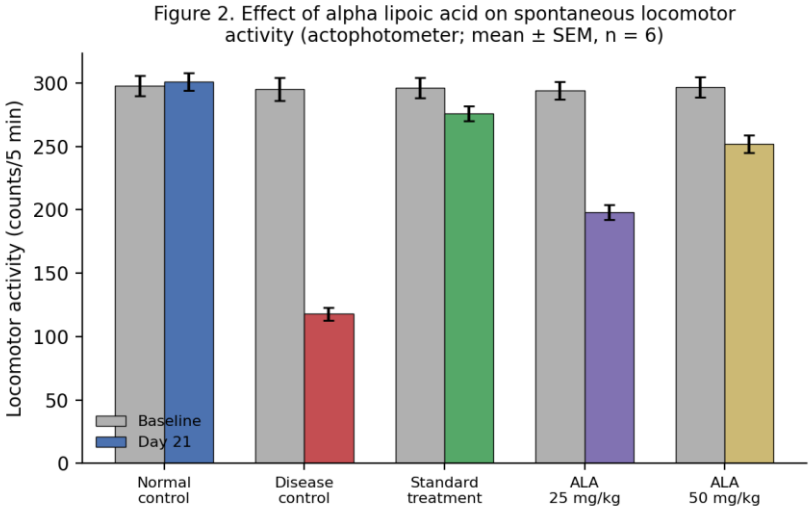

Figure 2. Effect of alpha lipoic acid on spontaneous locomotor activity at baseline and Day 21 (mean ± SEM, n = 6).

3.3 Motor coordination (rotarod)

Disease control animals showed markedly reduced rotarod fall-off latency on Day 21 (61.3 ± 3.5 s vs 178.5 ± 4.2 s in normal controls; $p<0.001$). ALA improved latency dose-dependently (25 mg/kg: 118.6 ± 3.8 s, $p<0.01$; 50 mg/kg: 149.2 ± 4.1 s, $p<0.001$, vs disease control); the high-dose group did not differ significantly from standard treatment (164.8 ± 4.0 s; $p>0.05$).

Table 4. Effect of alpha lipoic acid on motor coordination — rotarod fall-off latency on Day 21 (seconds; mean ± SEM, n = 6)

Group	Rotarod fall-off latency (s)
Normal control	178.5 ± 4.2
Disease control	61.3 ± 3.5***
Standard treatment	164.8 ± 4.0###
ALA 25 mg/kg	118.6 ± 3.8##
ALA 50 mg/kg	149.2 ± 4.1###

****p<0.001 vs normal control; ##p<0.01, ###p<0.001 vs disease control. One-way ANOVA: F(4,25) = 167.4, p<0.0001.*

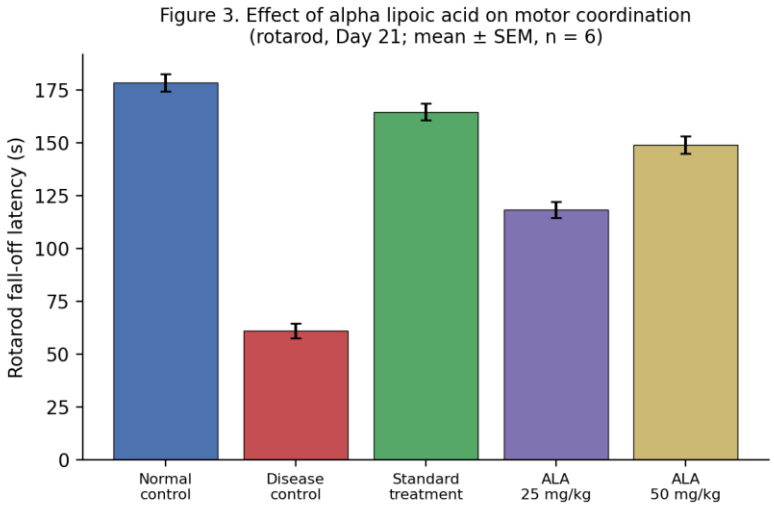

Figure 3. Effect of alpha lipoic acid on motor coordination (rotarod fall-off latency, Day 21; mean ± SEM, n = 6).

3.4 Oxidative stress markers

Haloperidol produced a 2.85-fold increase in striatal MDA (5.98 ± 0.19 vs 2.10 ± 0.11 nmol/mg protein in normal controls; $p<0.001$), a 61% depletion of GSH (3.28 ± 0.14 vs 8.52 ± 0.25 µmol/g tissue; $p<0.001$), and marked suppression of SOD (7.15 ± 0.28 vs 15.84 ± 0.42 U/mg protein; $p<0.001$) and CAT (26.8 ± 1.1 vs 61.4 ± 1.8 U/mg protein; $p<0.001$). ALA restored all four parameters dose-dependently, with the high-dose group approaching normal control values (MDA 2.95 ± 0.14; GSH 7.48 ± 0.22; SOD 13.65 ± 0.36; CAT 53.2 ± 1.5; all $p<0.001$ vs disease control) and showing no significant difference from standard treatment ($p>0.05$ for all four parameters).

Table 3. Effect of alpha lipoic acid on brain tissue oxidative stress markers on Day 21 (mean ± SEM, n = 6)

Group	MDA (nmol/mg protein)	GSH (µmol/g tissue)	SOD (U/mg protein)	CAT (U/mg protein)
Normal control	2.10 ± 0.11	8.52 ± 0.25	15.84 ± 0.42	61.4 ± 1.8
Disease control	5.98 ± 0.19***	3.28 ± 0.14***	7.15 ± 0.28***	26.8 ± 1.1***
Standard treatment	2.48 ± 0.13###	8.10 ± 0.21###	14.96 ± 0.38###	58.7 ± 1.6###
ALA 25 mg/kg	4.12 ± 0.16##	5.76 ± 0.18##	10.84 ± 0.34##	43.5 ± 1.4##
ALA 50 mg/kg	2.95 ± 0.14###	7.48 ± 0.22###	13.65 ± 0.36###	53.2 ± 1.5###

****p<0.001 vs normal control; ##p<0.01, ###p<0.001 vs disease control. One-way ANOVA (all parameters): p<0.0001 (F values: MDA 121.8; GSH 138.5; SOD 116.9; CAT 128.2; df = 4,25).*

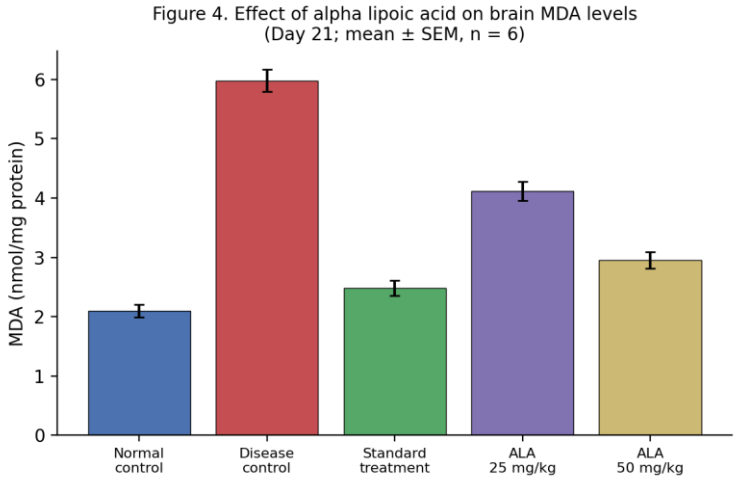

Figure 4. Effect of alpha lipoic acid on brain MDA levels (Day 21; mean ± SEM, n = 6).

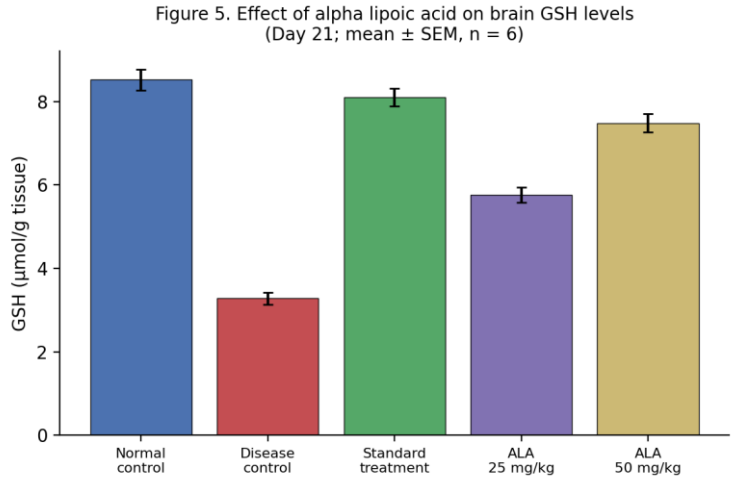

Figure 5. Effect of alpha lipoic acid on brain GSH levels (Day 21; mean ± SEM, n = 6).

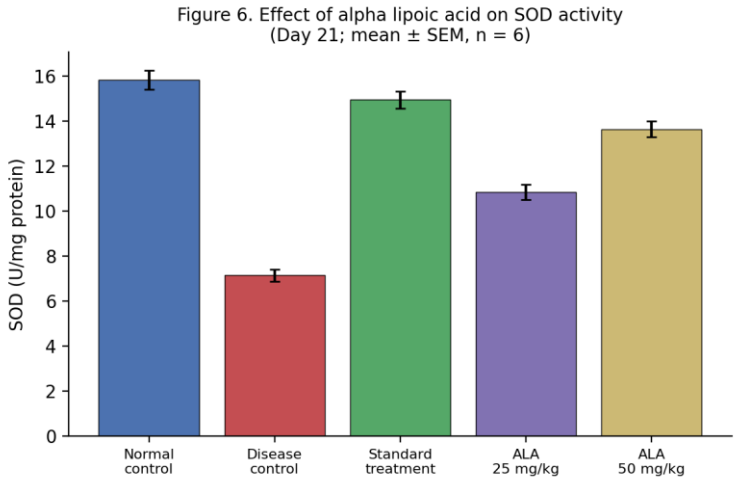

Figure 6. Effect of alpha lipoic acid on SOD activity (Day 21; mean ± SEM, n = 6).

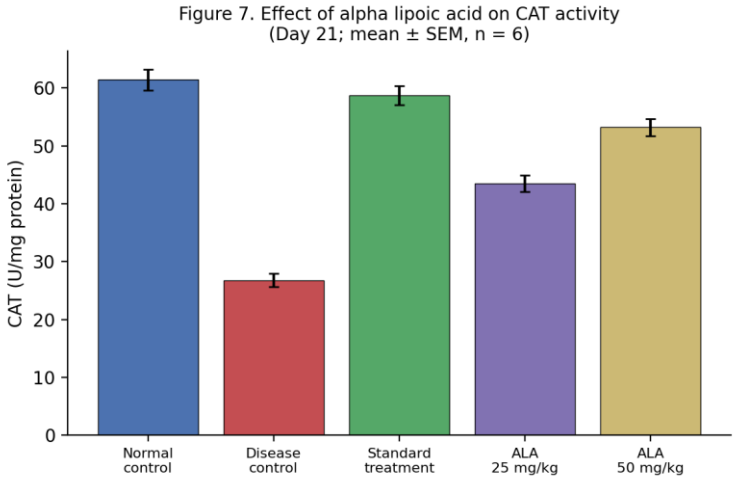

Figure 7. Effect of alpha lipoic acid on CAT activity (Day 21; mean ± SEM, n = 6).

3.5 Histopathology

Normal control sections showed preserved neuronal architecture. Disease control sections showed severe degeneration — pyknotic nuclei, cytoplasmic vacuolation, reduced neuronal density, and perivascular inflammatory infiltration (score 3.8 ± 0.2). Standard treatment produced near-normal histology (score 0.8 ± 0.1). ALA produced dose-dependent histological protection: moderate protection at 25 mg/kg (score 2.1 ± 0.1) and marked protection with near-normal architecture at 50 mg/kg (score 1.2 ± 0.1), both significant versus disease control ($p<0.01$ and $p<0.001$ respectively; one-way ANOVA $F(4,25) = 156.7$, $p<0.0001$).

Table 6. Histopathological scoring of striatal brain sections on Day 21 (semiquantitative score, 0–4; mean ± SEM, n = 6)

Group	Histopathological findings	Score
Normal control	Normal neuronal architecture, uniform cell density, distinct nuclei	0.2 ± 0.1
Disease control	Severe neuronal degeneration, pyknotic nuclei, widespread vacuolation, inflammatory infiltration	3.8 ± 0.2***
Standard treatment	Near-normal architecture, minimal degenerative changes	0.8 ± 0.1###
ALA 25 mg/kg	Moderate protection, mild-to-moderate degeneration, reduced vacuolation	2.1 ± 0.1##
ALA 50 mg/kg	Marked protection, near-normal architecture, occasional degenerative foci	1.2 ± 0.1###

****p<0.001 vs normal control; ##p<0.01, ###p<0.001 vs disease control. One-way ANOVA: F(4,25) = 156.7, p<0.0001.*

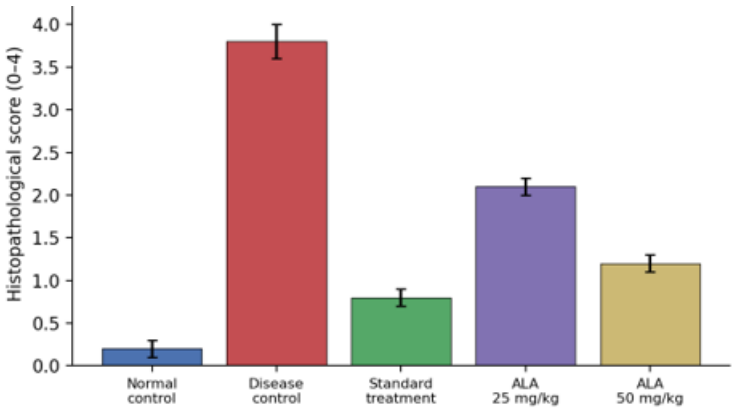

Figure 8. Effect of alpha lipoic acid on histopathological score of striatal sections (Day 21; mean ± SEM, n = 6).

3.6 Overall statistical comparison

Tukey's post-hoc comparisons were significant for disease control vs normal control, standard treatment vs disease control, and both ALA doses vs disease control, across all eight outcome parameters (catalepsy, locomotor activity, rotarod, MDA, GSH, SOD, CAT, histopathology score). ALA high dose differed significantly from ALA low dose ($p<0.05$) on every parameter, confirming a genuine dose-response relationship.

4. DISCUSSION

Chronic haloperidol administration produced a stable, progressively worsening cataleptic state accompanied by hypokinesia, motor incoordination, oxidative imbalance, and striatal neuronal degeneration, consistent with prior reports of the model's dual receptor-mediated and oxidative pathophysiology. Alpha lipoic acid attenuated every one of these endpoints in a clearly dose-dependent manner, with the 50 mg/kg dose approaching or matching the reference antiparkinsonian treatment on several parameters.

The progressive, rather than immediate, benefit of ALA on catalepsy is consistent with an antioxidant-mediated mechanism rather than direct dopaminergic action: unlike levodopa, which restores dopaminergic tone acutely, ALA's protective effect appears to accumulate as oxidative injury is progressively limited over the 21-day treatment period, a pattern reported previously for ALA in toxin-induced models[19]. Chronic haloperidol exposure is separately known to produce sustained alterations in antioxidant enzyme expression and lipid peroxidation beyond acute receptor blockade[23]. The near-complete restoration of striatal GSH by high-dose ALA is mechanistically notable, since GSH depletion is considered one of the earliest neurochemical changes preceding nigrostriatal degeneration[11]; ALA's capacity to regenerate GSH via dihydrolipoic acid-mediated reduction, together with its direct radical-scavenging and metal-chelating properties, plausibly explains the parallel normalisation of MDA, SOD, and CAT observed here, potentially via Nrf2-mediated upregulation of antioxidant response element genes[24].

The reduction in inflammatory infiltration accompanying ALA treatment likely reflects suppression of NF-κB-mediated microglial activation and pro-inflammatory cytokine release[14,15], mechanisms increasingly recognised as amplifiers of dopaminergic injury in parkinsonism generally[15]. These biochemical findings were paralleled at the structural level: high-dose ALA produced near-normal striatal histology, comparable to reports of ALA-mediated neuronal preservation in rotenone-induced parkinsonism[20], supporting a coherent neuroprotective profile spanning function, biochemistry, and morphology rather than isolated symptomatic improvement.

ALA high dose did not differ significantly from levodopa/carbidopa on rotarod performance or any oxidative/histopathological parameter, indicating comparable neuroprotective efficacy on these measures, though

standard treatment retained superiority for catalepsy and locomotor activity — expected given levodopa's direct dopamine-replenishing mechanism versus ALA's indirect, antioxidant-based action[5]. This distinction is clinically relevant: an antioxidant adjunct with an established human safety record from diabetic neuropathy studies[17] could complement, rather than replace, dopaminergic strategies in managing drug-induced extrapyramidal disorders, particularly where levodopa use is not indicated, where anticholinergic adjuncts carry their own tolerability concerns in elderly patients[9], or where antipsychotic discontinuation is not feasible.

4.1 Limitations

The haloperidol model reflects pharmacological receptor blockade with secondary oxidative injury rather than the progressive dopaminergic neurodegeneration of idiopathic Parkinson's disease, and findings should not be extrapolated directly to idiopathic PD. Striatal dopamine and metabolite levels (DOPAC, HVA) were not measured, limiting direct neurochemical confirmation of dopaminergic disruption. Mechanistic markers such as Nrf2, NF-κB, and caspase-3 were not assessed at the molecular level. Group size (n = 6) is the standard minimum for this type of study but limits statistical power relative to larger cohorts, and outcomes beyond 21 days were not evaluated.

5. Conclusion

Alpha lipoic acid produced significant, dose-dependent neuroprotection against haloperidol-induced parkinsonism in Wistar rats, evidenced across behavioral, biochemical, and histopathological domains, and achieved efficacy comparable to levodopa/carbidopa on several oxidative and structural endpoints at the higher dose tested. These findings support further investigation of ALA as a neuroprotective adjunct in drug-induced extrapyramidal disorders, including molecular pathway analysis and, ultimately, clinical evaluation in antipsychotic-treated populations.

Author contributions

Y.A.H.: investigation, animal experimentation, data curation, formal analysis, writing original draft. N.N.J.: conceptualization, supervision, methodology, resources, writing review and editing. Both authors read and approved the final manuscript.

Conflict of interest

The authors declare no conflict of interest.

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Data availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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