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NEUROPROTECTIVE POTENTIAL OF *CNIDOSCOLUS ACONITIFOLIUS* AGAINST DOPAMINERGIC NEUROTOXICITY: A REVIEW OF PHYTOCHEMICAL EVIDENCE AND IN VITRO PARKINSON'S DISEASE MODELS

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ABSTRACT

Parkinson's disease is the second most common progressive neurodegenerative disorder worldwide and is defined by the gradual loss of dopamine-producing neurons in the substantia nigra pars compacta, which causes both motor and non-motor disability. Available dopamine-replacement drugs relieve symptoms without altering the course of the disease and often cause long-term complications, so disease-modifying agents of natural origin are increasingly sought. Cell-culture systems in which neuronal cells, most often human SH-SY5Y neuroblastoma cells, are injured with 1-methyl-4-phenylpyridinium, 6-hydroxydopamine or rotenone serve as first-line platforms for screening such agents. *Cnidoscolus aconitifolius* (Euphorbiaceae), a leafy shrub eaten as a vegetable and used in the folk medicine of West Africa, Mexico and Central America, contains flavonoids, phenolic acids, alkaloids, saponins and tannins, and has been reported to show antioxidant, anti-inflammatory, cholinesterase-inhibitory and memory-enhancing effects, mainly in rodent studies and cell-free assays. This review brings together published information on neurotoxin-based *in vitro* models of Parkinson's disease, on the tetrazolium-based cell-viability assay and its pitfalls with polyphenol-rich extracts, and on the phytochemistry and neuropharmacology of the plant. On this basis, a mechanistic case is outlined for testing its ethanolic leaf extract against toxin-induced neuronal injury through radical scavenging, protection of mitochondrial function, modulation of apoptosis, reduction of inflammatory mediators and inhibition of monoamine oxidase and acetylcholinesterase. No study testing this plant directly in a Parkinson's disease cell model was found, which underlines the need for such an investigation.

KEYWORDS: *Cnidoscolus aconitifolius*; Parkinson's disease; SH-SY5Y; neuroprotection; oxidative stress.

1. INTRODUCTION

Parkinson's disease (PD) is a chronic, progressive disorder in which the nigrostriatal dopaminergic pathway deteriorates. Its defining motor signs are resting tremor, muscle rigidity, slowness of movement and impaired postural balance, and these are accompanied by non-motor problems such as cognitive decline, low mood and autonomic disturbance.[1,2] Prevalence and disability attributable to PD have climbed steeply in recent decades, particularly among ageing populations.[2]

The cause of PD is still only partly understood. Current evidence points to a set of interacting processes, namely mitochondrial impairment, oxidative stress, misfolding and aggregation of α-synuclein, and persistent neuroinflammation, which together drive the loss of dopaminergic neurons.[1] Levodopa and dopamine agonists remain the mainstay of treatment, yet they only ease symptoms; they neither stop nor reverse neuronal degeneration, and long-term use often brings motor fluctuations, dyskinesia and neuropsychiatric adverse effects.[1] Attention has therefore turned to agents that can interrupt the oxidative and inflammatory chain of events before neuronal death becomes irreversible.

Plant-derived compounds, polyphenols in particular, are attractive candidates because they can neutralise reactive oxygen species, switch on endogenous antioxidant defences such as the nuclear factor erythroid 2-related factor 2/antioxidant response element (Nrf2/ARE) pathway, and influence the apoptotic and inflammatory signalling that is relevant to PD.[3,4] Before committing to costly animal experiments, such candidates are usually examined in neurotoxin-based cell-culture models, which reproduce selected features of PD under controlled and repeatable conditions.

Cnidoscolus aconitifolius (Mill.) I.M. Johnst., known as chaya or tree spinach, is a perennial shrub of the family Euphorbiaceae that is eaten as a cooked leafy vegetable and widely employed in folk medicine in West Africa, Mexico and Central America.[5,6] Its leaves contain flavonoids, phenolic acids, alkaloids, saponins, tannins and cyanogenic glycosides, and the reported pharmacological activities include antidiabetic, hepatoprotective, gastroprotective, antimicrobial, anti-inflammatory and antioxidant effects.[5,7,8] Recent studies have also pointed to neuropharmacological actions: leaf extracts counteracted lipopolysaccharide-induced neuroinflammation and memory loss in rats, improved cholinergic function, and inhibited monoamine oxidase and acetylcholinesterase.[9-11]

Nevertheless, no published work was found that tests *C. aconitifolius* extracts in neurotoxin-based *in vitro* PD models. Accordingly, this article outlines the main cell-culture models, discusses the measurement of cell viability with the MTT assay, and collates the phytochemical and pharmacological findings that justify examining an ethanolic leaf extract against dopaminergic neurotoxicity.

2. PATHOPHYSIOLOGY AND MOLECULAR BASIS OF PARKINSON'S DISEASE

The key neuropathological feature of PD is the steady loss of dopaminergic neurons in the substantia nigra pars compacta, together with intracellular deposits of misfolded α-synuclein known as Lewy bodies and Lewy neurites.[1] Several linked mechanisms, summarised in Fig. 1, are thought to converge on this outcome.

2.1 Mitochondrial dysfunction and oxidative stress

Nigral dopaminergic neurons are especially exposed to oxidative damage, because dopamine metabolism itself yields reactive oxygen species (ROS), both through spontaneous auto-oxidation and through degradation by monoamine oxidase. When the activity of mitochondrial complex I falls, adenosine triphosphate (ATP) production declines and ROS formation rises further, setting up a self-reinforcing loop that injures lipids, proteins and DNA and eventually triggers apoptosis.[1,3]

2.2 Neuroinflammation

Activated microglia and astrocytes release pro-inflammatory cytokines, including tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6), which aggravate neuronal injury. Inflammation is considered both a result and a cause of dopaminergic degeneration, so anti-inflammatory activity is a useful criterion when screening potential neuroprotective agents.[3,4]

2.3 Protein aggregation and apoptosis

Misfolded α-synuclein oligomers are toxic in their own right and impair proteasomal and autophagic clearance. This failure of protein handling, combined with oxidative and mitochondrial stress, activates the intrinsic apoptotic pathway, seen experimentally as a higher Bcl-2-associated X protein/B-cell lymphoma 2 (Bax/Bcl-2) ratio and caspase activation.[12]

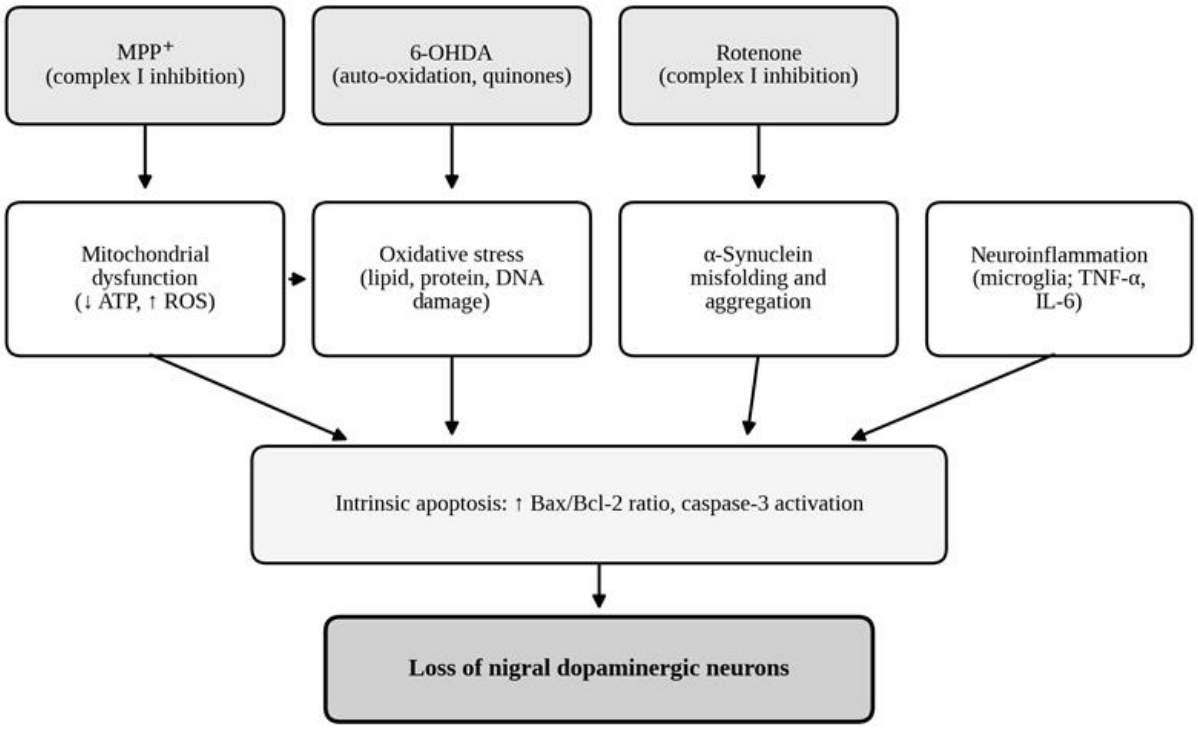

Fig. 1: schematic overview of the neurotoxins used to model Parkinson's disease *in vitro* and the principal mechanisms that converge on loss of dopaminergic neurons.

3. IN VITRO NEUROTOXIC CELL CULTURE MODELS FOR ANTIPARKINSONIAN SCREENING

Human dopaminergic tissue is hard to obtain, so cell-culture models have become essential for studying PD mechanisms and for first-pass screening of candidate neuroprotectants, including plant extracts. In these systems neuronal or neuron-like cells are exposed to defined toxins that mimic particular aspects of PD pathology, permitting concentration-dependent, mechanistic evaluation of protective agents under reproducible conditions.[13,14] The models discussed below are compared in Table 1.

3.1 SH-SY5Y human neuroblastoma cells

SH-SY5Y, a human neuroblastoma line, is the most frequently used platform in PD research because it is inexpensive, easy to maintain and can be differentiated towards a dopaminergic-like phenotype with retinoic acid and phorbol ester protocols. Differentiated cells express mature neuronal markers and, after exposure to suitable toxicants, show PD-relevant changes such as apoptosis and α-synuclein accumulation.[13,14]

3.2 1-Methyl-4-phenylpyridinium (MPP+)-induced toxicity

1-Methyl-4-phenylpyridinium (MPP+) is the toxic metabolite of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a meperidine analogue that caused severe parkinsonism in people who used contaminated synthetic drug preparations.[15] In culture, MPP+ is added directly, since most neuronal cell lines lack the monoamine oxidase-B activity needed to convert MPTP. MPP+ blocks mitochondrial complex I, thereby disturbing oxidative phosphorylation, increasing ROS and shifting cytosolic dopamine towards oxidative breakdown, which ends in apoptosis.[14]

3.3 6-Hydroxydopamine (6-OHDA)-induced toxicity

6-OHDA is a hydroxylated dopamine analogue taken up preferentially by dopaminergic and noradrenergic neurons through catecholamine transporters. Inside the cell it auto-oxidises, producing hydrogen peroxide, superoxide and quinones; the resulting oxidative and mitochondrial damage closely resembles the biochemical profile of nigral degeneration in PD.[14]

3.4 Rotenone-induced toxicity

Rotenone, a naturally derived pesticide, crosses membranes freely and inhibits complex I without needing the dopamine transporter. Prolonged low-dose exposure in culture reproduces α-synuclein aggregation, cytoskeletal disruption and selective vulnerability of dopaminergic cells, so this model captures both the oxidative and the proteostatic aspects of PD.[13]

3.5 Complementary and emerging models

PC12 pheochromocytoma cells and Lund human mesencephalic (LUHMES) neurons are increasingly used alongside SH-SY5Y cells. LUHMES cells have a more uniform dopaminergic phenotype and respond more consistently and strongly to 6-OHDA and MPP+, and some investigators therefore recommend wider use of them in preclinical antiparkinsonian screening.[16]

Table 1: Neurotoxin-based *in vitro* models commonly used in Parkinson's disease research.

Sr. No.	Neurotoxic agent	Primary mechanism	Typical cell model	Relevance to Parkinson's disease pathology
1	MPP+	Complex I inhibition; ROS generation; oxidation of cytosolic dopamine	SH-SY5Y, PC12	Reproduces the biochemical insult of MPTP-induced human parkinsonism
2	6-OHDA	Selective catecholaminergic uptake; auto-oxidation producing H_2O_2 and quinones	SH-SY5Y, LUHMES, PC12	Mimics oxidative, catecholamine-selective nigral injury
3	Rotenone	Direct complex I inhibition, independent of the dopamine transporter	SH-SY5Y, primary neurons	Reproduces α-synuclein aggregation and chronic mitochondrial stress

Abbreviations: MPP+, 1-methyl-4-phenylpyridinium; 6-OHDA, 6-hydroxydopamine; PC12, pheochromocytoma cell line; LUHMES, Lund human mesencephalic cells; ROS, reactive oxygen species; H_2O_2, hydrogen peroxide.

4. ASSESSMENT OF CELL VIABILITY IN NEUROTOXIN-CHALLENGED CULTURES: THE TETRAZOLIUM REDUCTION (MTT) ASSAY

Whatever toxin is chosen, the verdict on whether an agent is neuroprotective rests on a quantitative readout of cell survival. For this purpose the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay is one of the most commonly applied endpoints in PD cell models.[13,14] It was introduced by Mosmann as a quick, non-radioactive colorimetric alternative to isotope-incorporation methods for measuring cell growth and survival,[17] and its low cost, simplicity and suitability for 96-well high-throughput formats have kept it in use for four decades.

4.1 Principle of the assay

MTT is a water-soluble, positively charged tetrazolium salt that readily enters intact living cells. Inside the cell it is reduced, mainly by mitochondrial succinate dehydrogenase and other NAD(P)H-dependent oxidoreductases, to an insoluble purple formazan, although the exact subcellular sites of reduction are still debated.[18,19] Because this conversion requires active cellular dehydrogenases, formazan accumulates essentially in metabolically active cells and is negligible in dead cells. After a set incubation time the crystals are dissolved, typically in dimethyl sulfoxide or acidified isopropanol, and absorbance is read at roughly 550-590 nm; absorbance is proportional to the number of metabolically active cells, and viability is expressed as a percentage of the untreated control.[17,18]

4.2 Application in neurotoxin-based Parkinson's disease models

In SH-SY5Y-based PD models the assay serves two purposes. First, it defines the concentration-response and time-course of MPP+, 6-OHDA or rotenone toxicity, so that a concentration producing a moderate and reproducible decline in viability can be adopted as the standard insult.[12,14] Second, it is used to test whether pre-treatment or co-treatment with an extract or compound limits the toxin-induced loss of viability; a concentration-dependent improvement in survival is taken as primary evidence of neuroprotection.[3,20] Agents ranging from purified flavonoids to crude ethanolic or methanolic extracts have been evaluated in this manner, and the viability data are usually backed up by parallel measures of ROS, lipid peroxidation, glutathione, superoxide dismutase activity or apoptotic markers such as the Bax/Bcl-2 ratio and caspase-3.[3,21] This two-step design, toxin optimisation followed by extract-mediated rescue, is the methodological template that a study of ethanolic *C. aconitifolius* extract would be expected to follow.

4.3 Interpretive value and limitations for plant extracts

The MTT assay has a documented weakness that matters greatly for phenolic- and flavonoid-rich material such as *C. aconitifolius*. Several groups have shown that some plant extracts and polyphenols, including kaempferol and resveratrol, as well as antioxidants such as ascorbic acid and vitamin E, can reduce MTT to formazan directly under cell-free conditions, independently of mitochondrial dehydrogenase activity.[22-24] This chemical reduction can inflate apparent viability; in one comparison with an ATP-based assay, methanolic plant extracts gave strikingly high MTT "viability" even where the cells had been killed.[25]

Because ethanolic extracts are expected to be rich in redox-active phenolics, any MTT-based study of *C. aconitifolius* should include cell-free control wells containing extract and MTT only, and should confirm the results with an orthogonal, non-tetrazolium method, such as lactate dehydrogenase (LDH) release, trypan blue exclusion, ATP luminescence or Hoechst/propidium iodide staining, before attributing higher formazan formation to genuine cytoprotection.[19,25] With these precautions, MTT remains a quick, reproducible and economical first-line tool for defining the toxic range of MPP+, 6-OHDA and rotenone and for preliminary screening of candidate agents.

5. RATIONALE FOR PLANT-DERIVED NEUROPROTECTIVE AGENTS IN PARKINSON'S DISEASE

Since oxidative stress and neuroinflammation are central to dopaminergic degeneration, compounds that neutralise free radicals and dampen inflammatory signalling are of obvious therapeutic interest. Plant polyphenols, flavonoids and alkaloids act through several overlapping routes: direct radical scavenging, chelation of redox-active metals, activation of the Kelch-like ECH-associated protein 1 (Keap1)/Nrf2/ARE antioxidant response, inhibition of pro-inflammatory transcription factors such as nuclear factor kappa B (NF-κB), and modulation of mitochondrial apoptotic signalling.[3,4] Curcumin, resveratrol, quercetin, baicalein and the isoflavones of soy and red clover are well-studied examples that protect in MPP+, 6-OHDA or rotenone cell models and in MPTP- or rotenone-treated rodents,[20,21,26] and the flavonoid phloretin reduced behavioural deficits and neuroinflammation in MPTP-treated mice.[27]

A semi-systematic review further indicated that traditional medicinal plants such as *Curcuma longa*, *Withania somnifera*, *Ginkgo biloba* and *Pueraria lobata* slow markers of dopaminergic degeneration through antioxidant and anti-apoptotic actions.[28] Together, this body of work justifies systematic screening of further phenolic-rich traditional plants and positions *C. aconitifolius* as a plausible candidate for direct testing in neurotoxin-challenged neuronal cultures.

6. *CNIDOSCOLUS ACONITIFOLIUS*: BOTANICAL PROFILE AND TRADITIONAL SIGNIFICANCE

C. aconitifolius is a fast-growing, perennial, semi-woody shrub of Mexican and Central American origin that is now naturalised and cultivated in tropical West Africa and parts of Asia.[5,6] Known as chaya or tree spinach, it is grown mainly for its palmately lobed leaves, which are eaten as a nutritious vegetable after cooking, a step that destroys cyanogenic glycosides such as linamarin.[5,29]

Ethnobotanical surveys document the traditional use of leaf preparations against diabetes, hypertension, inflammatory conditions, insomnia and alcoholism, as a general tonic, and to support memory and cognition.[6,11] The last indication is notable because it foreshadows the neuropharmacological properties that have since been demonstrated experimentally.

7. PHYTOCHEMICAL CONSTITUENTS OF *CNIDOSCOLUS ACONITIFOLIUS*

Phytochemical screening of leaf extracts has repeatedly revealed flavonoids, phenolic acids, tannins, saponins, alkaloids, terpenoids, coumarins, steroids and cyanogenic glycosides, with relative amounts depending on the solvent, plant part and geographical origin.[5,7,29,30] Ethanolic and aqueous extracts generally give the highest phenolic and flavonoid yields among common solvents, and this corresponds with stronger 2,2-diphenyl-1-picrylhydrazyl (DPPH) and 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) radical-scavenging activity.[30,31] Profiling has identified phenolic acids and flavonoids including p-coumaric acid, quercetin, rutin and kaempferol derivatives, and more recent isolation work has reported several kaempferol glycosides and megastigmane glycosides from the leaves.[6,32] The main classes and their possible relevance to neuroprotection are listed in Table 2.

Table 2: Principal phytochemical classes reported in *C. aconitifolius* leaves and their relevance to neuroprotection.

Sr. No.	Phytochemical class	Representative constituents	Potential relevance
1	Flavonoids	Kaempferol derivatives, quercetin-type glycosides	Free-radical scavenging; Nrf2/ARE activation; anti-apoptotic signalling
2	Phenolic acids	Coumaric acid, caffeic acid-related compounds	Metal chelation; inhibition of lipid peroxidation
3	Alkaloids	Miscellaneous leaf alkaloids	Cholinesterase and monoamine oxidase inhibitory activity
4	Tannins and saponins	Condensed tannins, triterpene saponins	Anti-inflammatory and membrane-stabilising activity
5	Cyanogenic glycosides	Linamarin	Low levels after cooking; not linked to the neuroprotective fraction

Nrf2/ARE, nuclear factor erythroid 2-related factor 2/antioxidant response element.

8. REPORTED PHARMACOLOGICAL AND NEUROPHARMACOLOGICAL ACTIVITIES

8.1 Antioxidant and anti-inflammatory activity

In vitro tests have repeatedly confirmed the radical-scavenging capacity of leaf extracts, with ethanolic and acetone fractions giving the strongest DPPH and ABTS inhibition among the solvents compared. Ethanolic extracts have also markedly reduced TNF-α and IL-6 gene expression and release in lipopolysaccharide (LPS)-stimulated macrophages, indicating an anti-inflammatory action consistent with the antioxidant findings.[30,31]

8.2 Neuroprotective and cognitive effects

A methanolic leaf extract protected rats against lipopolysaccharide-induced cortico-hippocampal neuroinflammation, oxidative stress and memory impairment, with better scores in the Y-maze and novel-object-recognition tests.[9] In another study, feeding Wistar rats a *C. aconitifolius*-supplemented diet for several weeks improved spatial memory in the Morris water maze, raised endogenous antioxidants (glutathione and catalase), lowered malondialdehyde and preserved hippocampal neuronal structure, effects ascribed to combined antioxidant and cholinergic actions.[10] An ethyl acetate leaf fraction was also found to be antioxidant and to inhibit cholinergic and monoaminergic enzymes *in vitro*.[11]

Extracts have additionally shown hepatoprotective, gastroprotective and hypoglycaemic effects in experimental models.[5,6] Although unrelated to PD, these findings point to broader pharmacological potential and provide background information for later safety evaluation.

9. MECHANISTIC RATIONALE FOR ANTIPARKINSONIAN POTENTIAL IN NEUROTOXIC MODELS

Drawing the above evidence together, several lines of reasoning support the hypothesis that an ethanolic extract of *C. aconitifolius* leaves could protect neuronal cells in MPP+, 6-OHDA or rotenone-based PD models:

- The high flavonoid and phenolic content offers a plausible basis for direct scavenging of the ROS produced by complex I inhibition and dopamine auto-oxidation, the central toxic mechanism shared by the three neurotoxins.
- Documented suppression of pro-inflammatory cytokine expression suggests that the extract could limit the inflammatory amplification loop that adds to direct neurotoxic injury.
- Reported cholinergic and monoamine oxidase inhibitory activity raises the possibility of less enzymatic production of peroxide by-products from dopamine catabolism, complementing the antioxidant action.
- Preserved hippocampal neuronal integrity and reduced oxidative markers (malondialdehyde, glutathione, catalase) in an unrelated neurotoxic (LPS) rodent paradigm indicate a protective phenotype that may carry over to dopaminergic cell cultures.
- The lack, to date, of any published study testing *C. aconitifolius* extracts against MPP+-, 6-OHDA- or rotenone-induced toxicity is a clear and addressable knowledge gap.

Ethanol is expected to concentrate the moderately polar and lipophilic phenolic and flavonoid constituents most closely linked to antioxidant and enzyme-inhibitory activity in solvent-comparison studies, which gives a rational basis for choosing this extract for cell-based screening.[30,31]

10. COMPARISON WITH OTHER PLANT-DERIVED NEUROPROTECTANTS

Beside better-characterised antiparkinsonian phytochemicals such as curcumin, resveratrol and baicalein, *C. aconitifolius* shares the same broad mechanistic themes of antioxidant defence, anti-inflammatory modulation and anti-apoptotic signalling, but its efficacy in dopaminergic neurotoxicity models has not yet been established experimentally.[20,26] In contrast to single isolated compounds, its extracts contain a complex matrix of flavonoids, phenolics and alkaloids that may act synergistically, a feature increasingly regarded as advantageous in multi-target neurodegenerative disease therapy, although it also complicates standardisation and mechanistic attribution.[3,28] The plant is therefore a scientifically justified but comparatively underexplored candidate that merits direct experimental evaluation.

11. RESEARCH GAPS AND FUTURE DIRECTIONS

- No direct *in vitro* study of *C. aconitifolius* extracts against MPP+-, 6-OHDA- or rotenone-induced dopaminergic neurotoxicity was identified in the literature reviewed here.
- The constituents responsible for any neuroprotective effect have not been isolated or mechanistically confirmed for this plant in the context of PD.
- Concentration-response and time-course relationships between extract dose and protection against toxin-induced cell death remain uncharacterised.
- Endpoints of interest for future work include MTT viability together with an orthogonal assay (LDH release, ATP luminescence or trypan blue exclusion), ROS quantification, mitochondrial membrane potential, Bax/Bcl-2 and caspase-3 expression, and Nrf2/haem oxygenase-1 (HO-1) pathway activation.
- Translation from cell culture to *in vivo* rotenone or MPTP rodent models, followed by standardisation and bioavailability assessment of the active fraction, will be needed before clinical relevance can be judged.

12. CONCLUSION

Neurotoxin-induced cell-culture models, particularly SH-SY5Y cells challenged with MPP+, 6-OHDA or rotenone, form a well-validated and mechanistically informative platform for preliminary screening of candidate antiparkinsonian agents. *Cnidoscolus aconitifolius* is a phenolic- and flavonoid-rich medicinal plant with documented antioxidant, anti-inflammatory, cholinesterase-inhibitory and neuroprotective activity in non-parkinsonian paradigms, yet its potential in dopaminergic neurotoxicity models remains untested. The match between its phytochemical profile and the pathological mechanisms reproduced by these models provides a coherent scientific rationale for evaluating its ethanolic leaf extract in neurotoxin-challenged neuronal cultures, and such work would be a novel, evidence-based contribution to the search for plant-derived antiparkinsonian therapies.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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