



Prodigiosin in Neurodegeneration: A Critical Review, Comparative Analysis and Translational Gap Assessment

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ABSTRACT

Neurodegenerative diseases, including alzheimer's disease (AD), parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS), share interconnected pathogenic mechanisms-oxidative stress, mitochondrial dysfunction, neuroinflammation and progressive neuronal loss-for which available interventions remain largely symptomatic, sustaining interest in pleiotropic natural compounds. This critical narrative review evaluates prodigiosin-a bacterial tripyrrole pigment produced by *Serratia marcescens*-as a candidate neuroprotective compound, situates its evidence against established natural antioxidants (Curcumin, quercetin and resveratrol) and identifies translational gaps through a structured gap analysis. A structured narrative search was conducted across PubMed, Scopus, Web of Science and Google Scholar (2010-2025), combining prodigiosin with neurodegeneration-related descriptors. Given the sparse and heterogeneous evidence base, a critical narrative rather than systematic review framework was applied. Prodigiosin may modulate multiple neuroprotective pathways: (1) Nrf2/HO-1 antioxidant activation (enhanced SOD, CAT, GPx; reduced MDA and nitric oxide); (2) NF-κB suppression (downregulated IL-1β, TNF-α, COX-2, iNOS); (3) apoptosis attenuation via Bcl-2/Bax modulation and caspase-3 reduction and (4) partial restoration of neurotransmitter and neurotrophic (BDNF) indices. However, the evidence derives predominantly from a single research cluster using aluminum chloride models and lacks pharmacokinetic characterization, blood-brain barrier penetration data, independent replication and transgenic model validation.

Key words: Natural antioxidants, Neurodegeneration, NF-κB, Nrf2/HO-1, Oxidative stress, Prodigiosin.

Neurodegenerative diseases represent a heterogeneous group of chronic disorders characterized by selective neuronal vulnerability, progressive functional decline and ultimately irreversible tissue loss. Alzheimer's disease (AD), parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS) remain the most widely studied examples, shared/overlapping mechanistic features: redox imbalance, mitochondrial dysfunction, defective proteostasis, synaptic failure and chronic innate immune activation (Olufunmilayo *et al.*, 2023; Singh *et al.*, 2019). The global burden continues to expand, with neurological disorders affecting approximately 15% of the global population and projections estimating a rise to 4.9 billion cases of brain disorders (Van Schependom and D'Haeseleer, 2023).

Current therapeutic strategies remain largely palliative. In AD, cholinesterase inhibitors and memantine provide modest symptomatic relief, while recently approved monoclonal antibodies such as lecanemab show limited clinical benefits with notable side effects (Armstrong and Okun, 2020). PD management relies on dopaminergic therapy with progressive motor complications (Armstrong and Okun, 2020) and ALS treatment with riluzole and edaravone offers only modest survival benefits (Choi *et al.*, 2023). The multifactorial etiology of these diseases has driven increasing interest in multi-target therapeutic strategies capable of modulating multiple pathological processes simultaneously (Lustoza *et al.*, 2023).

Natural compounds have been proposed repeatedly as candidate multi-target neuroprotectants because many combine antioxidant, anti-inflammatory, anti-apoptotic and

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signaling-modulatory properties. Curcumin, quercetin and resveratrol are among the most intensively investigated and provide a useful translational benchmark. Prodigiosin a bacterial tripyrrole pigment primarily produced by *Serratia marcescens*, has emerged as a mechanistically intriguing but still underdeveloped candidate, with reported activities extending to antimicrobial, anticancer and anti-inflammatory domains (Lu *et al.*, 2024).

That mechanistic interest, however, should not be mistaken for evidentiary maturity. The current prodigiosin literature in neurobiology remains limited, model-restricted and uneven in translational depth. Previous reviews have discussed prodigiosin's biological activities without adequately distinguishing between plausible activity, reproducible efficacy and realistic translational readiness. The present manuscript therefore adopts an explicitly critical stance with four objectives: (1) to evaluate the current

evidence linking prodigiosin to oxidative stress-related neuroprotection with full molecular mechanistic detail; (2) to compare that evidence qualitatively with the established literatures of curcumin, quercetin and resveratrol; (3) to identify the principal methodological and translational gaps through a structured analysis; and (4) to outline a prioritized research roadmap for credible translational advancement.

Review scope and search strategy

This manuscript is a critical narrative review of heterogeneous evidence unsuitable for systematic synthesis. Although the literature search was structured and multi-database, the available prodigiosin evidence base is too limited and heterogeneous to justify systematic-review claims without a formal screening registry, duplicate study selection workflow, risk-of-bias assessment and PRISMA-compliant documentation.

The literature survey covered publications from 2010 through 2025 in PubMed, Scopus, Web of Science and Google Scholar. The primary search strategy combined “prodigiosin” with neurodegeneration-related descriptors using Boolean operators: (prodigiosin) and (neurodegeneration OR neurotoxicity OR neuroprotection OR “oxidative stress” OR neuroinflammation OR mitochondria OR apoptosis OR “Alzheimer’s disease” OR “Parkinson’s disease” OR ALS OR stroke OR epilepsy OR depression). Comparator searches for curcumin, quercetin and resveratrol used analogous concepts to support contextual benchmarking.

Eligible sources included peer-reviewed original experimental studies (both *in vitro* and *in vivo*), mechanistic investigations and selected reviews clarifying biological pathways or translational context. Exclusions encompassed non-peer-reviewed material, conference abstracts without full-text availability and publications that did not contribute meaningfully to neurodegeneration, oxidative stress, or prodigiosin pharmacology. Because this manuscript does not claim systematic-review status, exact study flow counts are not reported. The search was designed to maximize conceptual coverage of mechanistic and translational themes rather than to produce an exhaustive count-based synthesis suitable for meta-analysis; screening proceeded iteratively and conceptually, prioritizing relevance to the review’s critical objectives. Authors wishing to convert this work to a systematic or scoping review should rerun the search prospectively, document screening decisions and generate a PRISMA-compliant flow diagram.

Oxidative stress in neurodegeneration: Pathological mechanisms and therapeutic targets

ROS/RNS generation and neuronal vulnerability

Oxidative stress is best understood not as an isolated biochemical abnormality but as a systems-level amplifier of neuronal vulnerability (Albaqami, 2026; Long *et al.*, 2022; Mohammed *et al.*, 2025; Mohammed *et al.*, 2024). Neurons operate under high metabolic demand, consuming

approximately 20% of total body oxygen, possess lipid-rich membranes with abundant polyunsaturated fatty acids susceptible to peroxidation and display limited regenerative reserve (Singh *et al.*, 2019). Reactive oxygen species (ROS) including superoxide anion (O_2^-), hydrogen peroxide (H_2O_2) and hydroxyl radical ($\bullet OH$) and reactive nitrogen species (RNS) encompassing nitric oxide ($\bullet NO$) and peroxynitrite ($ONOO^-$) emerge from mitochondrial electron transport chain complexes I and III, NADPH oxidases, xanthine oxidase and cytochrome P450 enzymes (Olufunmilayo *et al.*, 2023; Singh *et al.*, 2019; Zhao *et al.*, 2019).

The detrimental effects manifest through multiple cellular damage mechanisms. Lipid peroxidation produces toxic aldehydes malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE)-compromising membrane fluidity and facilitating calcium dysregulation (Ayala *et al.*, 2014). Protein oxidation leads to carbonyl formation and altered enzyme function, with peroxynitrite-mediated tyrosine nitration promoting misfolding and aggregation of disease-specific proteins: nitrated tau promotes filamentous inclusions in AD, while α -synuclein nitration at Tyr39 enhances toxic oligomer formation in PD (Nakamura *et al.*, 2021). DNA damage, notably 8-hydroxy-2'-deoxyguanosine (8-OHdG) formation, compromises genomic integrity in post-mitotic neurons with limited repair capacity, activating p53-mediated apoptosis (Caldecott, 2024).

The oxidative stress-neuroinflammation axis

The relationship between oxidative stress and neuroinflammation forms a destructive self-amplifying loop of particular therapeutic relevance. Activated microglia and reactive astrocytes responding to protein aggregates upregulate ROS-producing enzymes and activate NF- κ B, promoting release of pro-inflammatory cytokines (IL-1 β , TNF- α , IL-6) and additional oxidative injury (Heneka *et al.*, 2014). Initially neuroprotective, microglial activity becomes maladaptive through sustained activation, impairing protein clearance and amplifying inflammatory responses. These cascading events trigger the intrinsic mitochondrial apoptotic pathway through Bax/Bcl-2 ratio dysregulation, mitochondrial membrane permeabilization, cytochrome c release and caspase-9/caspase-3 activation (Bonora *et al.*, 2022). This dual-pathway mechanism represents a critical therapeutic target, requiring multi-pathway interventions.

Key molecular targets for neuroprotective intervention

The Nrf2/ARE pathway serves as the master regulator of antioxidant gene expression, inducing cytoprotective enzymes including heme oxygenase-1 (HO-1), NAD(P)H: quinone oxidoreductase 1 (NQO1), superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and glutathione reductase (GR). Under homeostatic conditions, Nrf2 is sequestered by Keap1 in the cytoplasm and targeted for proteasomal degradation. Under oxidative stress, Keap1 modification releases Nrf2 for nuclear translocation and ARE-dependent transcription. Concurrently, NF- κ B acts as

the central inflammatory transcription factor and mounting evidence suggests reciprocal cross-talk between Nrf2 activation and NF- κ B suppression (Katselou *et al.*, 2014). Compounds capable of simultaneously activating Nrf2 while suppressing NF- κ B are therefore of particular interest, a framework within which prodigiosin has been evaluated.

Prodigiosin: Source, structure and pharmacological profile

Natural origin and chemical structure

Prodigiosin is a vivid red pigment belonging to the prodiginine family of tripyrrole alkaloids, primarily produced by *Serratia marcescens* and some *Streptomyces* and marine bacteria (Hu *et al.*, 2016). Its biosynthesis is controlled by the pig gene cluster comprising 13-15 genes encoding a hybrid NRPS/PKS pathway. The molecular structure consists of three pyrrole rings (A, B and C) connected *via* methylene bridges forming a linear framework with molecular formula $C_{20}H_{25}N_3O$ and molecular weight 323.44 Da. Ring A derives from L-proline through NRPS activity, ring B arises from malonyl-ACP condensation (containing a methoxy group crucial for electronic properties) and ring C forms from pyruvate and 2-octenal with a hydrophobic pentyl side chain contributing to lipophilicity (Hu *et al.*, 2016). This unique structure enables strong π - π stacking, hydrogen bonding and characteristic red pigmentation with absorption near 535 nm.

The chemical scaffold differs substantially from the polyphenolic structures of curcumin, quercetin and resveratrol, which is relevant because scaffold novelty may confer distinct target engagement, redox behavior and medicinal-chemistry opportunities. The prodiginine family includes over 30 analogs such as undecylprodigiosin and cycloprodigiosin differing in side-chain modifications that significantly affect biological potency and selectivity (Stankovic *et al.*, 2014). Due to hydrophobicity, prodigiosin is poorly water-soluble but dissolves well in organic solvents, significantly affecting pharmacokinetics and bioavailability (Darshan and Manonmani, 2015).

Antioxidant activity and Nrf2 pathway modulation

Prodigiosin demonstrates both direct and indirect antioxidant activities. *In vitro* assays using DPPH and ABTS radical scavenging revealed the complete neutralization of free radicals at 10 mg/L, while electron spin resonance (ESR) spectroscopy confirmed electron donation capacity and direct radical quenching (Arivizhivendhan *et al.*, 2018). *In vivo* studies using aluminum chloride-induced neurodegeneration models reported that prodigiosin (300 mg/kg, oral gavage, 42 days) significantly enhanced hippocampal antioxidant enzyme activities SOD, CAT, GPx and GR while reducing MDA and nitric oxide levels (Alsharif *et al.*, 2023). These effects were associated with Nrf2 nuclear translocation and HO-1 upregulation. Additionally, prodigiosin elevated total glutathione levels and GR activity,

suggesting restoration of the glutathione redox cycle-a critical defense system given that reduced glutathione serves as the brain's primary non-enzymatic antioxidant.

However, it is important to note that the upstream molecular mechanism through which prodigiosin activates Nrf2 remains uncharacterized. Whether this occurs through direct Keap1 modification, PI3K/Akt signaling, or other mechanisms has not been determined, representing a significant knowledge gap for mechanism-based optimization.

Anti-inflammatory properties

Prodigiosin exerts anti-inflammatory effects primarily through suppression of NF- κ B signaling and its downstream mediators. In the $AlCl_3$ model, prodigiosin reduced hippocampal levels of IL-1 β , TNF- α and COX-2 while decreasing iNOS gene expression (Alsharif *et al.*, 2023). Molecular docking studies indicate preferential binding to COX-2 over COX-1, suggesting selective anti-inflammatory action that may minimize disruption of physiological prostaglandin synthesis (Krishna *et al.*, 2013). In lipopolysaccharide-challenged models, prodigiosin suppressed nitric oxide, IL-6 and IL-8 production, reinforcing its modulation of innate immune responses. These findings are biologically plausible and mechanistically coherent, but should be interpreted with caution given the limited number of independent studies and the known promiscuity of NF- κ B modulation across many natural compounds.

Anti-apoptotic and neuromodulatory effects

Prodigiosin demonstrates anti-apoptotic properties through modulation of the intrinsic mitochondrial pathway. In preclinical models, the compound decreased pro-apoptotic Bax and caspase-3 levels while increasing anti-apoptotic Bcl-2 expression, indicating preservation of mitochondrial membrane potential ($\Delta\Psi$ m) and prevention of cytochrome c release (Albrakati *et al.*, 2021; Alsharif *et al.*, 2023). At the neuromodulatory level, prodigiosin treatment restored neurotransmitter levels-dopamine, norepinephrine and serotonin, enhanced BDNF expression, normalized Na^+ /K $^+$ -ATPase activity and reduced acetylcholinesterase activity. This simultaneous restoration of multiple monoamine pathways alongside neurotrophic support and transmembrane protein functionality represents a potentially interesting pharmacological profile, although it requires confirmation in independent studies and disease-relevant models.

Pharmacokinetic and safety considerations

Pharmacokinetic data for prodigiosin remain limited and primarily computational. *In silico* analyses classify the compound within toxicity class V (predicted LD_{50} : 2000-5000 mg/kg), indicating relatively low acute toxicity (Darshan and Manonmani, 2015). Selective cytotoxicity toward cancer cells (IC_{50} : 1.5-7 μ M) with lower toxicity in non-malignant cells has been reported and *in vivo* rodent studies revealed no significant abnormalities at doses up to 5000 mg/kg (Islan *et al.*, 2022). Nanoparticle-based delivery systems

particularly chitosan-based microspheres achieving ~96% entrapment efficiency have been developed to address solubility limitations.

Critically, direct blood-brain barrier (BBB) penetration studies are entirely absent. While prodigosin's lipophilicity may theoretically favor passive BBB penetration, lipophilicity alone is neither sufficient nor reliable as a predictor of CNS exposure. Without transport studies, brain-to-plasma ratios, or tissue distribution analyses, assertions regarding CNS therapeutic relevance remain speculative. This constitutes perhaps the single most important translational gap for prodigosin's neurotherapeutic development.

Neuroprotective evidence from experimental models

The experimental literature on prodigosin's neuroprotective effects derives from a limited but internally consistent set of preclinical studies, summarized in Table 1. A critical interpretive consideration is that the majority of these studies originate from the same collaborative research cluster, which provides methodological consistency but limits confidence in generalizability and independent reproducibility. The present review was conducted at the Department of Human Anatomy, School of Medicine, Taif University, Taif, Saudi Arabia, during the period from January 2025 to March 2026.

A notable observation requiring comment is the dose discrepancy across models. Chronic neurodegeneration paradigms employ 300 mg/kg orally over weeks, while acute ischemic models achieved efficacy at 10-100 µg/kg intravenously, a three-order-of-magnitude difference likely reflecting route-dependent bioavailability rather than differential pharmacodynamics. Without pharmacokinetic data, brain exposure measurements, or route-adjusted dose normalization, these differences should be treated as unresolved rather than informative.

Additionally, several studies employed selenium nanoparticle-conjugated formulations (SeNPs-PDG), complicating attribution of observed effects to prodigosin itself versus the formulation platform, selenium contribution, or synergistic interactions. This confounding factor must be acknowledged when interpreting the evidence base.

Distinguishing mechanistic signals from evidence strength

One of the most important analytical distinctions in evaluating prodigosin's neuroprotective potential is the difference between mechanistic signals and evidence strength. It is reasonable to state that the current literature suggests prodigosin may influence Nrf2/HO-1 antioxidant responses, NF-κB-related inflammation, mitochondrial membrane integrity, Bcl-2 family protein balance and selected neurotransmitter and trophic indices. It is not reasonable to conclude that these findings establish prodigosin as a validated multi-target neurotherapeutic agent.

This distinction matters because pathway-centric narratives in neurodegeneration research frequently overstate translational significance. Many compounds modulate common stress-responsive pathways (Nrf2, NF-κB, Bcl-2) in simplified or model-specific systems without demonstrating clinically meaningful CNS exposure, reproducible target engagement, or disease-modifying capacity. Table 2 explicitly separates the evidence level for each reported mechanism. The currently proposed neuroprotective mechanisms of prodigosin and the major translational barriers limiting its clinical advancement are summarized schematically in Fig 1.

Comparative positioning against established natural antioxidants

A comparative section is valuable only if it remains transparent about the asymmetry in evidence maturity. Curcumin, quercetin and resveratrol have each accumulated extensive literatures spanning numerous independent laboratories worldwide, diverse disease models, formulation studies, pharmacokinetic investigations and varying degrees of clinical evaluation. Prodigosin has not. Therefore, the comparison presented here is explicitly conceptual and translational not evidentially balanced and should be interpreted accordingly (Table 3).

Despite this substantial translational gap, prodigosin retains strategic interest for two reasons. First, its tripyrrole scaffold is chemically distinct from the polyphenolic structures shared by the comparator compounds, potentially conferring access to different binding pockets and structure-activity relationships. Second, its bacterial origin allows scalable fermentation-based production with derivatization flexibility. The existence of over 30 prodiginine analogs provides a rich but unexploited structure-activity space for neuroprotective optimization. However, these remain developmental possibilities rather than demonstrated translational strengths and should not be confused with evidentiary equivalence.

Major methodological and translational limitations

The current prodigosin literature in neuroprotection is constrained by several major limitations that should be stated explicitly rather than buried in qualifying clauses.

Model limitations

The reliance on aluminum chloride-induced neurotoxicity models represents a major translational limitation rather than a minor methodological inconvenience. While $AlCl_3$ models recapitulate oxidative stress and inflammatory components, they do not adequately reproduce the progressive proteinopathies (amyloid-β accumulation, tau hyperphosphorylation, α-synuclein aggregation, TDP-43 inclusions) that define human neurodegenerative diseases. The absence of evidence from established transgenic models (APP/PS1, 5xFAD, MPTP, SOD1-G93A) significantly weakens translational claims.

Table 1: Qualitative summary of representative preclinical studies on prodigiosin. Neuroprotection.

Study	Model	Dose/route	Reported observations	Principal caution
Alsharif <i>et al.</i> (2023)	Rat-AICl ₃ -induced neurotoxicity	300 mg/kg, oral, 42 d	↑SOD, CAT, GPx, GR, GSH; ↓MDA, NO; ↑Nrf2/HO-1; ↓IL-1β, TNF-α, COX-2, NF-κB; ↓Bax, caspase-3; ↑Bcl-2; ↑DA, NE, 5-HT, BDNF; ↓AChE ↓Infarct volume; ↑survival; ↓ROS/NO via gp91phox and iNOS inhibition	AICl ₃ model has limited fidelity to human AD proteinopathy; indepe- -ndent replication lacking.
Chang <i>et al.</i> (2011)	Mouse-MCAo/r ischemic stroke	10-100 µg/kg, IV		Acute ischemic model; not directly comparable with chronic neurodegeneration.
Al Omairi <i>et al.</i> (2022)	Rat-PTZ-induced epilepsy	SeNPs-PDG 0.5 mg/kg; PDG 300 mg/kg, oral	Delayed seizure onset; ↓duration; ↑Nrf2/antioxidants; ↓inflammation; ↓apoptosis	Attribution confounded by SeNP formulation platform; epilepsy model≠neurodegeneration.
Albrakati <i>et al.</i> (2021)	Rat-CUMS depression model	PDGs-SeNPs 200 mg/kg; PDG 300 mg/kg, oral	↑Hippocampal antioxidants; ↓TNF-α, IL-1β, IL-6; ↑Bcl-2; ↓caspase-3, Bax; ↑BDNF, monoamines	Depression model does not validate neurodegenerative disease modification; nanoparticle confounding.
Arivizhivendhan <i>et al.</i> (2018)	<i>In vitro</i> -DPPH/ABTS assays	10 mg/L	99% radical neutralization; ESR-confirmed electron donation	<i>In vitro</i> only; no cellular or <i>in vivo</i> correlation.

AICl₃: Aluminum chloride; AChE: Acetylcholinesterase; BDNF: Brain-derived neurotrophic factor; CAT: Catalase; COX-2: Cyclooxygenase-2; CUMS: Chronic unpredictable mild stress; DA: Dopamine; GPx: Glutathione peroxidase; GR: Glutathione reductase; GSH: Glutathione; HO-1: Heme oxygenase-1; MCAo/r: Middle cerebral artery occlusion/reperfusion; MDA: Malondialdehyde; NE: Norepinephrine; NF-κB: Nuclear factor kappa B; NO: Nitric oxide; Nrf2: Nuclear factor erythroid 2-related factor 2; PDG: Prodigiosin; PTZ: Pentylenetetrazole; SeNPs: Selenium nanoparticles; SOD: Superoxide dismutase; 5-HT: Serotonin.

Pharmacokinetic void

There are no robust data establishing oral bioavailability, plasma half-life, metabolic fate (cytochrome P450 interactions), brain exposure, or pharmacologically relevant CNS concentrations after systemic dosing. Without ADME characterization, dose-response relationships cannot be interpreted meaningfully.

BBB penetration gap

Direct blood-brain barrier penetration has not been assessed by any method, neither *in vitro* (MDCK-MDR1, PAMPA, human brain microvascular endothelial cell monolayers) nor *in vivo* (brain-to-plasma ratios, microdialysis). Lipophilicity-based predictions are insufficient for a putative CNS therapeutic.

Reproducibility concerns

The concentration of neuroprotective evidence within a single collaborative research cluster, while not invalidating the findings, limits confidence in robustness and generalizability. In the broader context of the reproducibility crisis in preclinical neuroscience, independent replication is not an optional refinement but a scientific requirement.

Formulation confounding

Several studies employed selenium nanoparticle-conjugated prodigiosin formulations, making it difficult to attribute

observed effects specifically to prodigiosin versus selenium, the nanoparticle platform, or synergistic interactions.

The current body of evidence should be interpreted with caution due to limited replication and model constraints. The combination of these limitations means that prodigiosin should not presently be portrayed as a near-clinical neuroprotective candidate. The principal translational deficiencies are summarized in Table 4.

Research priorities and translational roadmap

Immediate priorities (1-3 years)

The most urgent requirement is not another mechanistic study but a foundation-building program. Comprehensive pharmacokinetic characterization should establish oral bioavailability, plasma half-life, volume of distribution and metabolic fate *via* cytochrome P450 profiling. In parallel, BBB penetration must be assessed using complementary approaches: *in vitro* models (MDCK-MDR1, human brain microvascular endothelial cell monolayers) and *in vivo* brain-to-plasma ratio determination following systemic administration. These studies should proceed alongside independent replication of key neuroprotective findings by unaffiliated laboratories using standardized protocols.

Expansion to established transgenic models is essential: APP/PS1 or 5xFAD mice for AD, MPTP or 6-OHDA models for PD and SOD1-G93A mice for ALS. These studies should incorporate systematic dose-response designs

Table 2: Prodigiosin neuroprotective mechanisms stratified by evidence level.

Mechanism	Molecular detail	Evidence level	Key limitation
Nrf2/HO-1 activation	↑Nrf2 nuclear translocation; ↑HO-1; ↑SOD, CAT, GPx, GR, GSH; ↓MDA, NO	<i>In vivo</i> (rodent, AICl ₃ model)	Upstream target unknown; single model type; one research cluster
NF-κB suppression	↓IL-1β, TNF-α, COX-2, iNOS gene expression; ↓NF-κB protein levels	<i>In vivo</i> (rodent) + <i>in silico</i> (docking)	NF-κB modulation is common across natural compounds; specificity unclear.
Anti-apoptotic signaling	↑Bcl-2; ↓Bax, caspase-3; preserved ΔΨ _m ; ↓cytochrome c release	<i>In vivo</i> (rodent, multiple models)	Apoptosis markers are downstream; may reflect reduced injury rather than direct anti-apoptotic action.
Neurotransmitter restoration	↑DA, NE, 5-HT; ↑BDNF; ↑Na ⁺ /K ⁺ -ATPase; ↓AChE	<i>In vivo</i> (rodent, AICl ₃ model)	May be secondary to reduced neuronal injury; no receptor-level studies.
Direct radical scavenging	DPPH/ABTS neutralization; ESR-confirmed electron donation	<i>In vitro</i> only	No cellular or <i>in vivo</i> confirmation of direct scavenging contribution.
COX-2 selective binding	Preferential COX-2 over COX-1 docking scores	<i>In silico</i> only	Computational prediction only; no enzymatic validation.
BBB penetration	Lipophilicity-based theoretical prediction	Inferential only	No transport, distribution, or brain exposure studies.

AICl₃: Aluminum chloride; AChE: Acetylcholinesterase; ARE: Antioxidant response element; BBB: Blood-brain barrier; BDNF: Brain-derived neurotrophic factor; CAT: Catalase; COX: Cyclooxygenase; DA: Dopamine; DPPH: 2,2-diphenyl-1-picrylhydrazyl; ESR: Electron spin resonance; GPx: Glutathione peroxidase; GR: Glutathione reductase; GSH: Glutathione; HO-1, heme oxygenase-1; iNOS: Inducible nitric oxide synthase; MDA: Malondialdehyde; NE: Norepinephrine; NF-κB: Nuclear factor kappa B; NO: Nitric oxide; Nrf2: Nuclear factor erythroid 2-related factor 2; SOD: Superoxide dismutase; 5-HT: Serotonin; ΔΨ_m: Mitochondrial membrane potential.

with at least four dose levels, multiple time points, pre-specified behavioral, biochemical and histopathological endpoints and adequate sample sizes with statistical power calculations.

Medium-term priorities (3-5 years)

Structure-activity relationship studies exploring the prodiginine analog library should identify derivatives with optimized BBB penetration, oral bioavailability and neuroprotective potency. Advanced delivery systems, including liposomal formulations, polymeric nanoparticles and brain-targeted nanocarriers, should be evaluated with clear attribution protocols separating vehicle effects from compound effects. Multi-omics characterization (transcriptomics, proteomics, metabolomics) should map prodigiosin's

molecular mechanism comprehensively, particularly identifying the direct upstream target mediating Nrf2 activation.

The gut-brain axis interaction represents an unexplored but potentially significant mechanism. Given prodigiosin's known antimicrobial properties, its effects on gut microbiome composition and consequent neuroinflammatory modulation through the microbiota-gut-brain axis warrant systematic investigation. Comprehensive GLP-standard chronic toxicology studies-including hepatic, renal, cardiovascular and reproductive safety assessments-are prerequisites for regulatory advancement.

Long-term goals (5-10 years)

Conditional upon successful preclinical milestones, Phase 0 microdosing studies to assess human pharmacokinetics

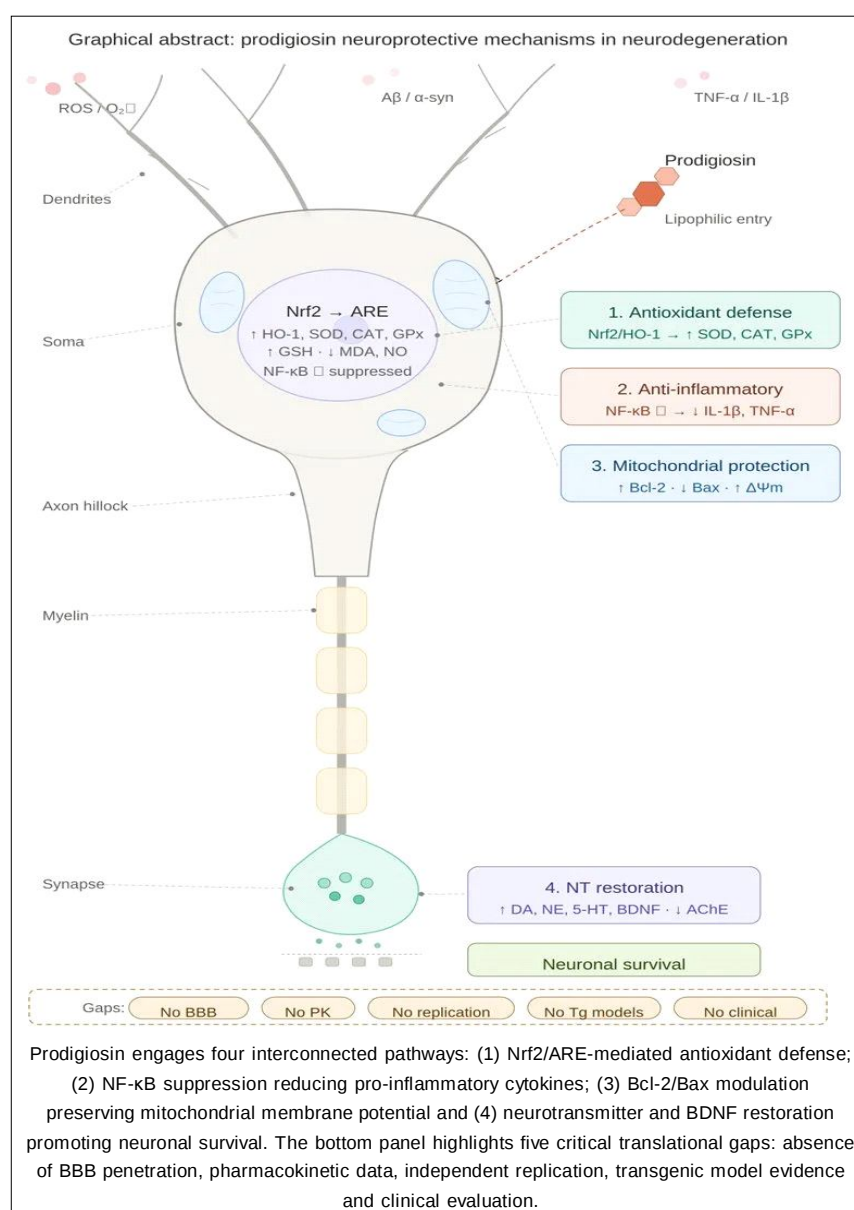


Fig 1: Proposed multi-pathway neuroprotective mechanisms of prodigiosin.

Table 3: Translational comparison of prodigiosin with selected natural neuroprotective compounds.

Parameter	Prodigiosin	Curcumin	Quercetin	Resveratrol	Interpretive note
Chemical class	Tripyrrole alkaloid	Curcuminoid	Flavonoid	Stilbenoid	Scaffold novelty may offer distinct targets.
Nrf2/HO-1 activation	Reported (<i>in vivo</i>)	Extensively supported preclinically; limited clinical exploration	Extensively supported preclinically; limited clinical exploration	Extensively supported preclinically; limited clinical exploration	Prodigiosin lacks upstream target identification.
NF-κB suppression	Reported (<i>in vivo</i>)	Broadly supported preclinically	Broadly supported preclinically	Broadly supported preclinically	Common across many natural compounds.
Transgenic model evidence	Absent	APP/PS1, 5xFAD, MPTP	APP/PS1, 6-OHDA	APP/PS1, SAMP8, MPTP	Critical translational gap for prodigiosin.
BBB penetration data	Inferential only	Limited; nanoformulation -dependent	Limited; nanoformulation -improved	Limited to moderate preclinical evidence; variability across formulations	Foundational gap for prodigiosin.
Clinical neuro trials	None	Early- to mid-phase clinical investigations in cognitive disorders reported	Early-phase clinical studies in cerebrovascular settings reported	Early- to mid-phase clinical investigations in cognitive aging reported	No clinical anchor for prodigiosin.
Independent replication	Limited; predominantly one collaborator cluster	Broad multi-laboratory replication across the literature	Broad	Broad	Major weakness for prodigiosin.
Oral bioavailability	Uncharacterized	Poor (<1%)	Poor (~2%)	Low (~1%)	Shared challenge; nanoformulations under investigation.
Overall translational maturity	Early-stage preclinical	Late preclinical with early clinical exploration	Moderate preclinical with limited clinical data	Moderate preclinical with limited clinical data	Comparison is conceptual, not parity-based.

AD: Alzheimer's disease; APP: Amyloid precursor protein; BBB: Blood-brain barrier; MCI: Mild cognitive impairment; MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; 6-OHDA: 6-hydroxydopamine; PS1: Presenilin-1; SAMP8: Senescence-accelerated mouse prone 8.

Table 4: Structured translational gap analysis.

Domain	Current status	Critical gap	Priority
Pharmacokinetics/ADME	Insufficiently characterized	No oral bioavailability, half-life, metabolite, or exposure data.	Highest-prerequisite for all dose-response interpretation.
BBB penetration	Theoretical prediction only	No <i>in vitro</i> or <i>in vivo</i> transport/distribution studies.	Highest-foundational for CNS drug development.
Disease model diversity	Primarily AlCl ₃ model	No transgenic AD/PD/ALS models tested.	High-essential for translational relevance.
Independent replication	Single research cluster predominates	No unaffiliated laboratory confirmation.	High-essential for confidence in robustness.
Dose-response characterization	2-3 dose levels tested	No systematic dose-response with ≥ 4 levels.	High-required for therapeutic window definition.
Upstream molecular target	Nrf2 activation demonstrated	Direct binding target and Keap1 interaction unknown.	Moderate-important for rational optimization.
Chronic toxicology	Low acute toxicity (LD ₅₀ >2000 mg/kg)	No GLP chronic hepatic, renal, or cardiac safety data.	Moderate-required before chronic dosing.
Gut-brain axis interaction	Unexplored	Antimicrobial properties may affect microbiome-brain signaling.	Emerging-potential novel mechanism.
Clinical translation	Absent	No phase 0/I studies in any indication.	Long-term-dependent on preclinical milestones.

ADME: Absorption, distribution, metabolism, excretion; AlCl₃: Aluminum chloride; BBB: Blood-brain barrier; CNS: Central nervous system; GLP: Good laboratory practice.

and biodistribution represent the logical next step, followed by Phase I dose-escalation studies. Combination therapy approaches integrating prodigiosin with established neuroprotective agents may reveal synergistic interactions. Integration of computational approaches for patient stratification may enable targeted clinical investigation. However, these long-term goals are entirely contingent upon the foundational work outlined above; progressing to clinical investigation without adequate pharmacokinetic, BBB and safety data would be scientifically premature and ethically questionable.

CONCLUSION

This critical review indicates that the available literature supports a mechanistically coherent but still preliminary multi-pathway neuroprotective profile for prodigiosin, which simultaneously engages Nrf2/HO-1 antioxidant defense, NF- κ B inflammatory suppression, mitochondrial protection through Bcl-2 family modulation and neurotransmitter/neurotrophic restoration. This mechanistic breadth, if validated, would position prodigiosin among a limited number of natural compounds capable of addressing the interconnected pathological pillars of neurodegenerative disease. However, the comparative analysis presented herein reveals a substantial translational maturity gap between prodigiosin and established neuroprotective natural products. While curcumin, quercetin and resveratrol have accumulated decades of evidence across numerous

independent laboratories worldwide, diverse transgenic disease models and multiple clinical trials, prodigiosin's evidence derives predominantly from a single collaborative research cluster using models of limited translational fidelity. The complete absence of BBB penetration data, pharmacokinetic characterization, independent replication and transgenic model evidence represents not minor gaps but foundational deficiencies that prevent meaningful translational claims.

Accordingly, prodigiosin is best positioned not as an established multi-target neuroprotective agent, but as an emerging, hypothesis-generating scaffold whose mechanistic signals warrant systematic investigation. The structured gap analysis and translational roadmap presented here provide a clear framework for credible advancement from pharmacokinetic foundation-building and BBB assessment through independent validation and model diversification. The ultimate determination of prodigiosin's therapeutic relevance will depend not on the strength of mechanistic narratives but on the rigor of the translational evidence generated in the coming years.

This cautious, evidence-weighted framing is more likely to withstand critical peer review and contribute meaningfully to the field than promotional language that outruns the available data. Importantly, any advancement toward clinical translation without prior resolution of pharmacokinetic and blood-brain barrier uncertainties would be scientifically unjustified.

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Author contributions

The principal author completed all research work items in this study.

Data availability statement

Data is contained within the article.

Conflict of interest

The authors declare no conflict of interest.

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