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Elucidating the multitarget neuroprotective mechanisms of protocatechuic acid in neurological disorders (Review)

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Abstract. Neurological disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), cerebral ischemia, anxiety and depression pose significant global public health challenges due to their high prevalence and complex pathological mechanisms. Current therapeutic strategies primarily offer symptomatic relief, with limited efficacy in mitigating disease progression. Neuroprotection involves interventions aimed at preserving neuronal structure and function through mechanisms such as reducing oxidative stress, modulating inflammation and inhibiting apoptosis, presenting a promising avenue for treating these conditions. Protocatechuic acid (PCA), a natural phenolic acid compound prevalent in a variety of foods and herbal medicines, has received considerable attention for its notable antioxidant, anti-inflammatory and neuroprotective properties. The present study systematically reviews the neuroprotective effects and molecular mechanisms of PCA in various neurological disorders (including AD, PD and cerebral ischemia). The present review highlights the multi-target mechanisms of PCA, which act by mitigating oxidative stress, neuroinflammation, mitochondrial dysfunction and apoptosis, while promoting neuronal regeneration. Furthermore, the present review integrates the body of evidence across neurological contexts to identify conserved protective pathways and discusses the translational potential of PCA, providing a foundation for its clinical application in treating neurological diseases.

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Abbreviations: PCA, protocatechuic acid; ND, neurodegenerative disease; AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; HD, Huntington's disease; PD, Parkinson's disease; α-syn, α-synuclein; Aβ, amyloid-β; APP, amyloid precursor protein; PS1, presenilin 1; ROS, reactive oxygen species; BBB, blood-brain barrier; CNS, central nervous system; NSC, neural stem cell; MSC, mesenchymal stem cell; BDNF, brain-derived neurotrophic factor; NGF, nerve neurotrophic factor; 5-HT, 5-hydroxytryptamine; DA, dopamine; NE, norepinephrine; CIRI, cerebral ischemia-reperfusion injury; DAMP, damage-associated molecular pattern; GSK-3β, glycogen synthase kinase-3β; MDA, malondialdehyde; NRF2, nuclear factor erythroid 2-related factor 2; SIRT, sirtuin; HO-1, heme oxygenase-1

Key words: PCA, neuroprotection, antioxidant, neurological disorders, nerve regeneration

Contents

1. Introduction

Neuroprotection is a strategy that actively protects the brain, spinal cord and peripheral nervous system from acute and progressive neurodegenerative diseases (NDs) by preventing or limiting damage to neurons and other components (1). NDs are a group of disorders characterized by the progressive loss of neurons in the brain and spinal cord. Their manifestations fall into two main categories: One affects movement (for example, cerebellar ataxia) and the other affects memory (for example, dementias) (2). NDs include Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), multiple sclerosis, Parkinson's disease (PD) and spinal muscular atrophy (3,4). The nervous system is characterized by high oxygen consumption, a high content of unsaturated fatty acids and vulnerability to lipid peroxidation (5). Oxidative stress, resulting from an imbalance between reactive oxygen species (ROS) and antioxidant defenses, damages cellular structures and contributes to the pathogenesis of NDs such as AD and PD (6). Oxidative stress also disrupts the blood-brain barrier (BBB), permitting entry of neurotoxic plasma components, blood cells and pathogens into the brain, leading to amplified

ROS production, mitochondrial dysfunction and inflammation, ultimately driving neuronal apoptosis and the progression of NDs (7). Neuroprotection employs targeted biological and pharmacological interventions to preserve neuronal function and network integrity by mitigating neuronal damage, preventing cell death and maintaining central nervous system (CNS) functionality (8).

Protocatechuic acid (PCA) is a natural phenolic acid, widely found in plants and chemically defined as 3,4dihydroxybenzoic acid (9). PCA occurs mainly in vegetables (10-12), fruits (13), green tea (14) and walnuts (15), and is an active compound found in several traditional Chinese medicines (such as *Alpiniae oxyphyllae* Fructus) (16). PCA shows a good neuroprotective effect by inhibiting oxidative stress, regulating inflammatory response and promoting neuronal survival. For instance, PCA reduces cyclophosphamide-induced neuronal degeneration by regulating the NOD-, LRR- and pyrin domain-containing protein 3 inflammasome, and sirtuin (SIRT)1, thereby reducing the production of pro-inflammatory cytokines (17). In addition, PCA enhances the antioxidant capacity of nerve cells, promotes cell survival and significantly improves scopolamine-induced learning and memory impairment (10). PCA, melatonin and hydroxytyrosol confer neuroprotection by inhibiting abnormal α-synuclein (α-syn) assembly, reducing its toxicity, and upregulating SIRT-2, Heme oxygenase-1 (HO-1) and 70-kDa heat shock protein expression (18). The present study provides a systematic summary of the role of PCA in neuroprotection to offer novel mechanistic insights and a theoretical foundation for developing novel therapeutic strategies.

2. Neural injury and repair mechanisms

Neuroprotection after neural injury, which is pivotal in neuroscience, involves mechanisms such as anti-inflammation, antioxidation and anti-apoptosis, and is linked to disorders such as neurodegenerative diseases, anxiety, depression, ischemic/hemorrhagic stroke and drug-induced neurotoxicity (19). Due to the depletion of endogenous neurotrophic factors in neural injury, neuronal repair requires sustained exogenous neurotrophic factor supplementation to meet neuronal metabolic demands (20). Neuroprotective agents [such as saffron, coenzyme Q10 and nerve growth factor (NGF)] may offer new therapeutic benefits through anti-apoptotic mechanisms (21). In fact, NGF has been used clinically to treat optic nerve-related diseases, but its short half-life and poor bioavailability limit its efficacy (22).

The neurotransmitter system regulates the functions of target organs by transmitting nerve impulses based on the types of neurotransmitters it releases (including cholinergic, glutamatergic, γ-aminobutyric acidergic, dopaminergic, serotonergic and aminergic systems) (23). The imbalance of neurotransmitters is closely associated with the occurrence of various neurological disorders, especially in NDs, where the abnormal metabolism of neurotransmitters and oxidative stress are considered as important pathological mechanisms (24). For instance, the gradual reduction of dopaminergic neurons in the substantia nigra compacta of the brain and the decrease in dopamine (DA) content are important pathological features of PD (25). The addition of partial agonists of DA and 5-hydroxytryptamine (5-HT) on top of norepinephrine (NE)/5-HT reuptake inhibitors is often used to enhance the antidepressant effect (26). Moreover, the levels of acetylcholine and glutamate excitotoxicity are related to AD (27).

Neural stem cells (NSCs)/precursor cells have long-term potential for neural function recovery (28). Mesenchymal stem cell (MSC) secretions exhibit neuroprotective effects in traumatic brain injury (29). Through their interaction with neuropeptides, MSC-derived extracellular vesicles promote brain-derived neurotrophic factor (BDNF) expression and neural repair, making them a promising therapeutic agent for alleviating brain stroke damage (30). Recently, a growing amount of research has highlighted the non-motor functions of the cerebellum, such as cognitive, behavioural and emotional processing, which are increasingly associated with mechanisms such as neurodegeneration, neuroinflammation, oxidative stress and metabolic dysregulation via multiple pathways (31-33).

Overall, neuroprotective strategies target neuroinflammation, oxidative stress and impaired neural repair to promote functional recovery through pathways involving abnormal protein aggregation, toxin-induced injury via redox modulation, neurotrophic/TrkB/PI3K/Akt signaling, microglial activation and mitochondrial dysfunction (Fig. 1) (34). Neuroprotective agents function through multifaceted mechanisms, including antioxidant activity, anti-inflammatory effects via microglial suppression and NF-κB inhibition, enhanced energy metabolism, mitochondrial stabilization, apoptosis suppression through PI3K/Akt signaling, clearance of pathological protein aggregates, and promotion of neuronal repair and stem cell differentiation (35). In addition, various neuroprotective or neurological disorders-related agents were summarized in Table I (35-47).

3. PCA and neuroprotection

Sources and absorption characteristics of PCA. Date palm fruits, rich in polyphenolic antioxidants, including PCA, demonstrate neuroprotective properties in model systems, suggesting potential to reduce AD risk, delay onset or slow progression (48). PCA could be responsible for the beneficial health effects of polyphenol-rich foods, as they can easily cross the BBB (49). Bioavailable PCA extracted from edible chicory has been shown to undergo partial glucosylation and sulfation in human adults (50). Among the four primary active components of Alpiniae oxyphyllae fructus (nootkatone, tectochrysin, chrysin and PCA), PCA exhibits high BBB permeability via passive diffusion, whereas lactoferrin demonstrates relatively poor permeability (51).

PCA exhibits diverse pharmacological activities, including antioxidant, anti-inflammatory, neuroprotective, antibacterial, antiviral, anticancer, anti-osteoporotic, analgesic and anti-aging effects, metabolic syndrome prevention, and protection of liver, kidney and reproductive functions (52,53). PCA also modulates neuroprotective factor expression, suppresses apoptosis, activates the autophagy-lysosomal pathway, reduces oxidative stress and inflammation, enhances synaptic plasticity, inhibits amyloid-β (Aβ) accumulation, decreases amyloid precursor protein (APP) processing, strengthens the cholinergic system and mitigates neuronal excitotoxicity (54).

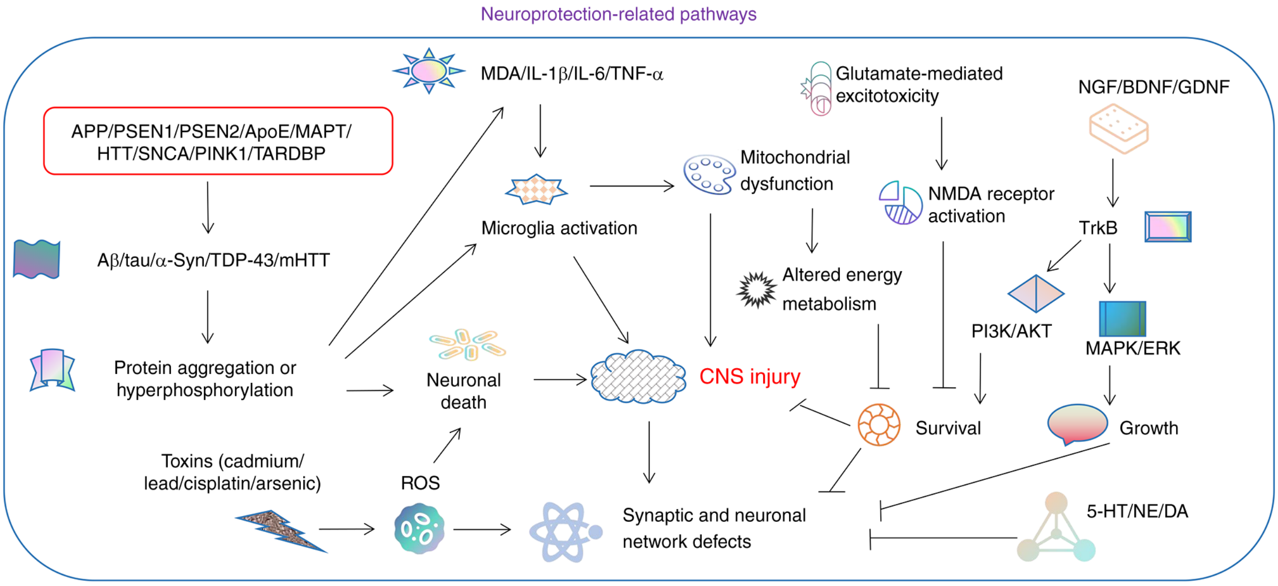

Figure 1. Interaction among neuroprotection-related pathways. Abnormal protein aggregation, toxin-induced nerve injury through REDOX homeostasis modulation, the neurotrophic factor/TrkB/PI3K/Akt pathway, glutamate-mediated excitotoxicity, microglia activation and mitochondrial dysfunction are the basis of the crosstalk among CNS injury-related molecules. CNS, central nervous system; α-syn, α-synuclein; Aβ, amyloid-β; mHTT, mutant huntingtin; TDP-43, TAR DNA-binding protein 43; ROS, reactive oxygen species; TrkB, tropomyosin receptor kinase B; GDNF, glial cell line-derived neurotrophic factor; MDA, malondialdehyde; BBB, blood-brain barrier; BDNF, brain-derived neurotrophic factor; NGF, nerve neurotrophic factor; 5-HT, 5-hydroxytryptamine; DA, dopamine; NE, norepinephrine; TNF-α, tumor necrosis factor-α; IL, interleukin-6.

Consequently, PCA, present in various fruits, vegetables and grains, shows promise as a dietary supplement for alleviating cognitive deficits associated with NDs.

Neuroprotective mechanism of PCA

Antioxidant effect of PCA and its mechanisms. Oxidative stress, characterized by a systemic oxidant/antioxidant imbalance, leads to excessive ROS production that damages critical biomolecules (such as lipids, proteins and DNA), resulting in neuronal dysfunction and ultimately cell death in brain tissue (55,56). Due to its high metabolic oxygen consumption characteristic, the brain is extremely sensitive to oxidative stress, which is a key pathogenic factor for NDs (57). Consequently, antioxidant strategies, including phytochemical-rich dietary supplements, combined with moderate exercise, may mitigate oxidative stress-induced neurodegeneration (1).

As a natural antioxidant, PCA demonstrates broad potential for neuroprotection and antioxidant therapy. Pretreatment with *Lycium barbarum* polyphenols, such as PCA, attenuated hydrogen peroxide (H_2O_2)-induced toxicity in PC12 cells, a rat adrenal pheochromocytoma-derived neuroendocrine cell line, by reducing ROS production, restoring mitochondrial membrane potential and inhibiting apoptosis (58). In a global ischemia model in rats, PCA significantly reduced cell death, oxidative stress, microglial and astrocyte activation, and BBB disruption in degenerative neurons, and increased glutathione concentration in hippocampal neurons (59). PCA and chrysin exerted synergistic neuroprotection in 6-hydroxydopamine-treated PC12 cells by enhancing viability, reducing lactate dehydrogenase release and modulating cellular redox status through upregulation of key antioxidant enzymes (60). Pre-treatment with PCA significantly reduced apoptosis, inflammation and oxidative stress in the neonatal mouse hippocampus following sevoflurane exposure (61).

Although both PCA and 4-hydroxybenzoic acid alleviated H_2O_2-induced oxidative stress in primary cultured cerebellar granule neurons, only PCA provided neuroprotection during CNS inflammation with nitrosative stress by specifically reducing nitric oxide production (62). PCA enhanced PC12 cell viability and dose-dependently attenuated H_2O_2- and sodium nitroprusside-induced cell death (63,64). Ethyl PCA showed an acute concentration-dependent and reversible inhibitory effect on synaptic transmission in the dentate gyrus of rats, which may involve a novel postsynaptic mechanism and be related to the activation of N-methyl-D-aspartate and type-A γ-aminobutyric receptors (65).

Anti-inflammatory effects of PCA and its mechanisms. In protein-misfolding disorders such as AD and PD, neuroinflammatory pathway activation triggers concomitant oxidative and nitrosative stress (66). Inhibition of neuroinflammatory nitric oxide signaling can mitigate functional neurodegeneration and reduce cellular stress associated with aberrant nitrogen metabolism and protein glycosylation (67). The neuroimmune axis exhibits complex interdependencies, serving as the primary pathogenic driver in multiple sclerosis with similarly amplified involvement in other NDs, including AD, ALS and PD (68). Chronic innate immune cell activation, a hallmark of age-related NDs, exacerbates neurodegeneration by promoting Aβ plaque formation and τ hyperphosphorylation, as exemplified in AD (69). A range of neurological conditions, including NDs and COVID-19 neurological sequelae, share persistent neuroinflammation, with mounting evidence implicating inflammasome activation in driving their pathogenesis (70). Aggregated proteins linked to NDs, such as Aβ, τ, α-syn and TAR DNA-binding protein 43, function as damage-associated molecular patterns (DAMPs), activating innate immune responses via multiple pattern recognition

Table I. Neuroprotection-related diseases and drugs.

Disease category	Key pathological molecules	Representative drugs or compounds	Targets	Mechanisms
Alzheimer's disease	Aβ deposition and neuronal toxicity, tau hyperphosphorylation and neurofibrillary tangles, APOE4 gene mutation	Donepezil, huperzine A, galantamine, memantine, lecanemab (36)	AChE, NMDA receptors, Aβ aggregation	Improves cognition; delays functional decline; monoclonal antibody binding to Aβ protofibrils
Parkinson's disease	α-synuclein aggregation and Lewy bodies, LRKK2 mutation, loss of dopaminergic neurons	Levodopa/carbidopa, pramipexole, ropinirole (37)	Dopamine receptors, MAO-B enzyme	Dopamine replacement; inhibits the degradation of dopamine
Amyotrophic lateral sclerosis	SOD1 mutation, TDP-43 aggregation, C9orf72 gene amplification, FUS mutation or abnormal positioning	Riluzole, edaravone, tofersen (38)	Glutamate release, ROS scavenging, SOD1	Blocks excitotoxicity; free radical scavenging slows progression; reduces mutant SOD1 synthesis
Huntington's disease	Mutant HTT aggregates, decreased BDNF	Deutetrabenazine (39)	VMAT2, mutant HTT	Reduces dopamine release for chorea control
Multiple sclerosis	MBP/MOG/MAG, NF-κB, IL-1β, $CD20^+$ B cells, S1P receptors	IFN-β, ocrelizumab, siponimod (40)	Immune modulation, CD20 antigen	B-cell depletion; traps lymphocytes in lymph nodes
Ischemic stroke	ROS, glutamate excitotoxicity, inflammatory mediator	Alteplase, clopidogrel, butylphthalide, edaravone (41)	tPA, free radicals, platelets, mitochondrial function	Thrombolysis reperfusion; antiplatelet activity; ROS scavenger; reduces reperfusion injury
Intracerebral hemorrhage	Damage to the BBB; inflammatory factor; hemoglobin toxicity, iron overload, thrombin	Tranexamic acid (42), deferoxamine (43)	Plasminogen, iron chelation	Limits hematoma expansion; mitigates iron-mediated neurotoxicity
Neuropathic pain	Nav1.7/1.8 activation, substance P, TRPV1	Pregabalin, gabapentin, duloxetine (44)	α2δ subunit of VGCC, SERT/NET	Suppresses hyperalgesia; augments descending inhibitory pathways
Anxiety	5-HT1A decline, CRH upregulation	Venlafaxine, escitalopram, paroxetine (45)	SERT, NET	SSRIs/SNRIs potentiate 5-HT and NE signaling
Depression	BDNF deficiency, NE/5-HT/DA imbalance, HPA axis excessive activation, inflammation	Sertraline, mirtazapine, vortioxetine (46)	SERT, MAO, 5-HT3 receptor	Neurotransmitter reuptake or BDNF elevation; inhibits MAO activity
Drug-induced neurological damage	Pt-DNA adducts, TRPA1/V1 activation, mitochondrial damage	Duloxetine, pregabalin (47)	NET, mitochondrial membranes	Improves sensory abnormalities; restores energy metabolism

Aβ, amyloid-β; AChE, acetylcholinesterase; NMDA, N-methyl-D-aspartate; BBB, blood-brain barrier; MAO, monoamine oxidase; DA, dopamine; BDNF, brain-derived neurotrophic factor; 5-HT, 5-hydroxytryptamine; NE, norepinephrine; VGCC, voltage-gated calcium channel; SERT, serotonin transporter; NET, noradrenaline transporter.

receptors, including Toll-like receptors, NOD-like receptors, cytosolic DNA sensors and other DAMP receptors (71). As resident immune cells of the CNS, microglia play a protective role by phagocytosing pathological protein aggregates, yet excessive phagocytosis can impair their function, induce neuroinflammation and ultimately promote neurodegeneration in various NDs (72).

PCA exerted anti-inflammatory effects in lipopolysaccharide (LPS)-stimulated BV2 microglia by inhibiting the Toll-like receptor 4-mediated NF-κB and MAPK signaling pathways (73). PCA also inhibited the immune response in LPS-activated BV2 microglia via the SIRT1/NF-κB pathway and suppressed PC12 cell apoptosis induced by microglial activation (74). In addition, PCA promoted the M1/M2 phenotypic shift via m-TOR pathway inhibition, thereby ameliorating inflammation in mouse models of brain haemorrhage (75). 3,4-Dihydroxyphenylacetic acid, PCA and dihydrocaffeic acid, and their conjugated forms, significantly attenuated neuroinflammation by scavenging ROS, thereby protecting neuronal cells. Notably, phenolic acid conjugates demonstrated superior efficacy in mitigating oxidative stress and inflammatory damage to neuronal SH-SY5Y cells stimulated by bacterial lipopolysaccharide and tert-butyl hydroperoxide compared with their free forms (76).

Neuroregenerative effects of PCA and its mechanisms. Neural regeneration refers to the restoration of neurological function through complex biological processes, including neuronal regrowth, proliferation or differentiation of NSCs, and participation of dual roles of glial cells (such as microglia and astrocytes) (77). Post-injury, damaged neurons release neurotrophic factors (including BDNF and NGF) and cytokines that promote axonal regeneration and synaptic reconnection (78). Neural regeneration also relies on signal transmission between cells and microenvironmental regulation, such as the influence of BDNF and NGF, which enhance neuronal survival and promote neuronal growth and differentiation (79). Concurrently, NSCs contribute to repair via their self-renewal capacity and multilineage differentiation potential, essential for maintaining CNS homeostasis (80). MSCs also play an important role in reconstructing neural networks and restoring their functions with burgeoning preclinical evidence (81-83).

PCA promotes neural regeneration, with its mechanism potentially involving the insulin-like growth factor 1 receptor/PI3K/Akt signaling pathway (84). PCA increased the survival of primary cultured cortical neurons in newborn rats and promoted neurite growth in these neurons (85), and this neurotrophic protective effect exerted by PCA was correlated to its regulation of phosphorylated AKT expression (86). In addition, PCA promoted RSC96 Schwann cell migration, regeneration and peripheral nerve repair by regulating MAPK, plasminogen activator and MMP signaling pathways (87). When combined with fetal bovine serum *in vitro*, PCA promoted neuronal differentiation, induced neuronal maturation and enhanced neurite growth in cultured neural stem and progenitor cells (88). PCA treatment significantly reduces ROS levels, caspase 3 activity and apoptosis in NSCs (89). Therefore, PCA has also gained increasing attention in neural regeneration and neurotrophic protective effects.

4. PCA and various neurological disorders

Neuroprotective effects of PCA in NDs. Despite clinical differences, NDs share fundamental pathological mechanisms, such as abnormal protein deposition, intracellular calcium overload, mitochondrial dysfunction, REDOX homeostasis imbalance and neuroinflammation (90). NDs are characterized by a suite of interconnected hallmark features, such as pathological protein aggregation, synaptic dysfunction, disrupted proteostasis, cytoskeletal defects, metabolic imbalance, nucleic acid alterations, neuroinflammation and neuronal loss, all of which collectively drive disease onset and progression through complex interactions modulated by genetic determinants and biochemical pathways (91).

The pathological mechanisms of AD mainly include the formation of amyloid plaques, abnormal phosphorylation of τ protein, neuroinflammation and oxidative stress. As a primary metabolite in blueberry extracts, PCA mitigates neuronal damage by enhancing autophagy, supporting its potential for dietary AD intervention (13). While okadaic acid induces AD-like pathology, including τ hyperphosphorylation, neurofibrillary tangle formation and Aβ deposition, PCA counteracted this cytotoxicity in PC12 cells by regulating Akt/glycogen synthase kinase-3β (GSK-3β)/myocyte-specific enhancer factor 2D signaling and modulating autophagic activity, thereby demonstrating neuroprotective efficacy (92). In a rat model of mild memory impairment induced by long-term intragastric administration of D-galactose, PCA improved learning and spatial memory abilities in the Morris water maze test and restored dysregulated serotonergic and dopaminergic activity (93).

The abnormal aggregation of Aβ and α-syn drives the formation of amyloid plaques in AD and Lewy bodies in PD, with the latter also characterized by progressive degeneration of dopaminergic neurons in the substantia nigra. Treatment of amyloid precursor protein (APP)/presenilin 1 (PS1) transgenic mice (a double-transgenic mouse model co-expressing mutant human APP/PS1, commonly used to model AD) with PCA significantly increased BDNF levels in the hippocampus and cerebral cortex, reduced Aβ deposition, decreased APP expression and inflammatory responses, and improved learning and memory abilities (94). High doses of PCA (50 mg/kg) alleviated symptoms in an AD mouse model induced by Aβ injection into the hippocampus, potentially via the cholinergic synaptic signaling pathway (95). By downregulating inflammatory mediators in the brain of $A\beta_{25\text{-}35}$-injected AD model mice, particularly inducible nitric oxide synthase and cyclooxygenase-2, PCA significantly alleviated neuroinflammation and inhibited lipid peroxidation in the brain, kidney and liver tissues (96). As the main metabolite of anthocyanins, PCA, also known as anthocyanin 3-glucoside, inhibited the aggregation of Aβ and α-syn, destabilizing their pre-formed fibrils and preventing the PC12 cell death mediated by the toxicity of the Aβ and α-syn (97).

PCA exerted neuroprotective effects in both 1-methyl-4-phenylpyridinium (MPP+)-treated PC12 cells and the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced PD mouse model, and was associated with the inhibition of α-syn oligomerization (98,99). Although PCA significantly increased dopamine turnover in the striatum and improved cognitive function in experimental memory impairment mice, it did not significantly affect memory performance in healthy rats (100). The combination of PCA with ginkgolide B significantly restored the motor ability of PD mice, alleviated neuronal damage, boosted the activity of antioxidant enzymes in brain tissue and increased the expression in the midbrain substantia nigra (101). The combination of honokiol with PCA reduced neuronal loss in 6-hydroxydopamine-treated zebrafish PD models (102). PCA demonstrated neuroprotective efficacy in ALS transgenic mice by extending survival time, suppressing spinal glial proliferation, preventing motor neuron apoptosis, alleviating pathological manifestations and preserving neuromuscular junction integrity, thereby countering key features of this severe disease (103).

PCA and drug-induced neurotoxicity. Arsenic and common heavy metals (including plumbum, hydrargyrum, cadmium and manganese) exhibit neurotoxic effects, with notable sex-specific differences observed in response to exposure (104). Neurotoxic compounds, such as rotenone, 6-hydroxydopamine, MPTP, MPP+, paraquat and maneb, are commonly used in preclinical models of PD (105). In anisodamine-induced amnesia models, PCA administered orally could protect against oxidative stress-related learning and memory deficits (10). PCA enhanced the antioxidant defense system, suppressed inflammation and apoptosis, and thereby counteracted cadmium-induced neurocortical toxicity (106). PCA could also exert protective effects against cisplatin-induced neurotoxicity by inhibiting neuroinflammation and restoring the oxidative/antioxidative balance (107). As a toxic metalloid, arsenic exposure increased pro-inflammatory cytokine levels (TNF-α and IL-1β), upregulated apoptosis-related molecules (caspase-3 and Bax), and reduced acetylcholinesterase activity and BDNF levels in the mouse cerebral cortex. PCA pretreatment attenuated arsenic-induced histopathological alterations in brain tissue (108). PCA also markedly reduced hippocampal neuronal death and microglial activation in a model of intraperitoneal injection of pilocarpine-induced epilepsy in adult male rats (109).

PCA prevented rotenone-induced apoptosis of PC12 cells by alleviating mitochondrial dysfunction (110). Additionally, PCA significantly alleviated MPP(+)-induced mitochondrial dysfunction in these cells (111). Although bromate, used as a food additive, was shown to disrupt the CNS, PCA protected the cells from bromate-induced gastric mucosal ulceration (112). PCA alleviated oxidative stress, elevated neurotransmitter levels, and improved learning and memory deficits in lead-exposed rats (113). Additionally, PCA prevented cadmium-induced neurotoxicity by altering the activities of key enzymes, such as Na^+/K^+-ATPase, acetylcholinesterase, butylcholinesterase and endogenous antioxidant enzymes (114).

PCA and anxiety/depression. Depression and anxiety are mental disorders characterized by persistent dysregulation of emotional and behavioral responses, which is associated with reduced levels of 5-HT, DA and NE in the CNS (115). Chronic corticosterone exposure induces depressive-like behavior in mice, accompanied by oxidative stress, neuroinflammation and medial prefrontal cortex synaptic plasticity impairment, further supporting the pivotal role of oxidative stress in depression pathogenesis (116).

Acute inhibitory stress triggers depression-like behavior via oxidative neuronal damage in mice. Ethyl PCA mitigates serum corticosterone elevation and lipid peroxidation induced by acute inhibitory stress while restoring enzymatic antioxidant levels in the cerebral cortex and hippocampus (117). In scopolamine-induced long-term memory impairment of mice, following acute treatment, PCA induced an anxiogenic effect, whereas repeated administration produced anxiolytic effects and enhanced cognitive function in both acute and chronic models, but their impact on long-term memory was greater than on short-term memory (118). PCA not only reduced the immobility time, serum corticosterone, cytokines TNF-α and IL-6, and malondialdehyde (MDA) levels in mice exposed to chronic unpredictable mild stress, but also improved sucrose preference and restored BDNF levels (119). PCA exhibited antidepressant-like effects by enhancing BDNF, 5-HT, DA and NE levels in the hippocampus and cerebral cortex, while reducing oxidative and inflammatory markers, including MDA, IL-6 and TNF-α (120).

PCA alleviated post-traumatic stress disorder-like symptoms in rats induced by single prolonged stress, through modulation of central monoaminergic systems, improved freezing behavior and demonstrated antidepressant and anxiolytic properties (121). PCA also markedly reduced the biomarkers of inflammation and oxidative stress in the hypothalamus, testis and epididymis (122). Furthermore, PCA improved the hypothalamic-pituitary-gonadal axis function defect in rats exposed to furan by inhibiting oxidative inflammatory stress and apoptosis (123). Both hyperoside and PCA, two polyphenolic compounds, were shown to mediate antidepressant-like effects in mice by modulating the monoamine system and upregulating BDNF levels (124).

PCA and cerebral ischemia-reperfusion injury (CIRI). CIRI, a major cause of adult disability and mortality, refers to the secondary brain damage that results following the restoration of blood flow to previously ischemic brain regions (125). The pathological mechanisms of ischemic stroke involve oxidative stress, apoptosis, ferroptosis and mitochondrial dysfunction, whereas N-butylphthalide with ligustrazine confer anti-ischemic effects via the Kelch-like ECH-associated protein 1-nuclear factor erythroid 2-related factor 2 (NRF2) pathway and isocitric rutinine provides neuroprotection in CIRI mice through *Nrf2* activation to alleviate oxidative stress and mitochondrial impairment (125,126).

The protective effects of PCA against CIRI are considered to be mediated by the upregulation of NRF2 expression (127). PCA may have the potential to prevent early reperfusion injury, restore the balance between survival and death proteins, and serve as a cost-effective adjunctive treatment for stroke (128). PCA could also reduce brain edema and BBB damage caused by intracerebral hemorrhage via the Nrf2/HO-1 signaling pathway (129). In a collagenase IV-induced mouse model of intracerebral hemorrhage, PCA attenuated oxidative stress, inflammation and apoptosis through downregulation of the p38/JNK-NF-κB pathway, thereby reducing third-stage brain edema, improving neurological function and decreasing TNF-α, IL-1β and IL-6 expression at both the protein and gene levels (130). In a rat model of global CIRI, both silymarin and ethyl PCA improved cognitive and motor function, and reduced histopathological damage, cerebral edema and infarct volume, with silymarin demonstrating superior efficacy compared with piracetam and ethyl PCA (131). In a mouse model of intestinal ischemia-reperfusion injury, PCA exerted protective effects on both the local intestine and remote liver damage, which were mediated through its anti-apoptotic and antioxidant properties (132).

Table II. Associations between the key mechanisms of PCA and specific diseases.

Core mechanism of PCA	Evidence in ND models	Evidence in drug-induced neurotoxicity and anxiety/depression	Evidence in CIRI, neuralgia and other conditions
Anti-protein aggregation	Inhibits Aβ and α-syn aggregation in APP/PS1 or MPTP models (94,97-99).	/	/
Anti-neuroinflammation	Downregulates iNOS and COX-2; reduces inflammatory response to Aβ (94,96); suppresses spinal glial proliferation in ALS mice (103).	Reduces cisplatin-induced neurotoxicity by inhibiting neuroinflammation (107); reduces the serum corticosterone, TNF-α, IL-6, and MDA levels (119).	Reduces inflammation in intracerebral hemorrhage by downregulating the p38/JNK-NF-κB pathway (130).
Antioxidant	Inhibits lipid peroxidation in brain tissue induced by Aβ (96); boosts antioxidant enzyme activity in brain tissue (101); preserves neuromuscular junction integrity in ALS (103); alleviates oxidative stress from D-galactose (93).	Alleviates oxidative stress in lead-exposed rats (113); reduces the biomarkers of inflammation and oxidative stress in the hypothalamus (105).	Against CIRI by upregulating NRF2 (127); reduces brain edema via the Nrf2/HO-1 (129); inhibits the JNK/CXCL1/CXCR2 to improve oxidative stress (137).
Promote cell survival	Counters toxicity via Akt/GSK-3β/MEF2D signaling (92); combined therapy reduces neuronal loss (102); extends survival and prevents motor neuron apoptosis in ALS (103).	Attenuates arsenic-induced upregulation of apoptosis-relatedmolecules (108).	Attenuates inflammation, and apoptosis by downregulating the p38/JNK-NF-κB pathway (130).
Neurotransmitter or neurotrophic regulation	Increases BDNF levels in hippocampus/cortex (94); may act via cholinergic pathways (95); increases dopamine turnover in striatum (100); combined therapy restores motor ability (101); restores serotonergic/dopaminergic activity in D-galactose impairment model (93).	Prevents lead- or cadmium-induced neurotoxicity by altering neurotransmitter levels (114); mediates antidepressant-like effects by modulating the monoamine system, BDNF, 5-HT, DA and NE levels (120,124).	Mitigates chronic intermittent hypoxia-induced cognitive dysfunction by upregulating BDNF and synapsin expression (143).

ALS, amyotrophic lateral sclerosis; Aβ, amyloid-β; α-syn, α-synuclein; BDNF, brain-derived neurotrophic factor; 5-HT, 5-hydroxytryptamine; DA, dopamine; NE, norepinephrine; PCA, protocatechuic acid; MDA, malonaldehyde; CIRI, cerebral ischemia-reperfusion injury; APP/PS1, amyloid precursor protein/presenilin 1; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; iNOS, inducible nitric oxide synthase; COX-2, cyclooxygenase-2; GSK, glycogen synthase kinase; ND, neurodegenerative disease.

PCA and neuralgia. Neuralgia, one of the most debilitating neurological disorders, poses a major therapeutic challenge due to the complex interplay of pathogenic mechanisms involving oxidative stress, neuroinflammation and mitochondrial dysfunction (133). Trigeminal neuralgia is a severe facial pain disorder primarily attributed to neurovascular compression and demyelination of afferent fibers leading to neuronal hyperexcitability, with carbamazepine and oxcarbazepine serving as first-line pharmacotherapy (134). Furthermore, a longer duration and a broader involvement of trigeminal neuralgia are associated with more severe depression, anxiety and insomnia, while these emotional disorders in turn can exacerbate the risk and manifestation of neuralgia (135).

In a chronic constriction injury-induced neuropathy rat model, PCA exhibited similar therapeutic effects as carbamazepine and mitigated the adverse effects caused by neurogenic pain drugs alone (136). PCA alleviated neuropathic pain in rats with chronic constriction injury by inhibiting the JNK/CXCL1/CXCR2 signaling pathway, which contributes to improved oxidative stress (137). A pharmaceutical co-crystal composed of pentoxifylline and PCA effectively reduced allodynia in rats with complex regional pain syndrome following chronic ischemia, through mechanisms involving reduced peripheral tissue ischemia/hypoxia and suppression of hypoxia-induced mitochondrial dysfunction (138).

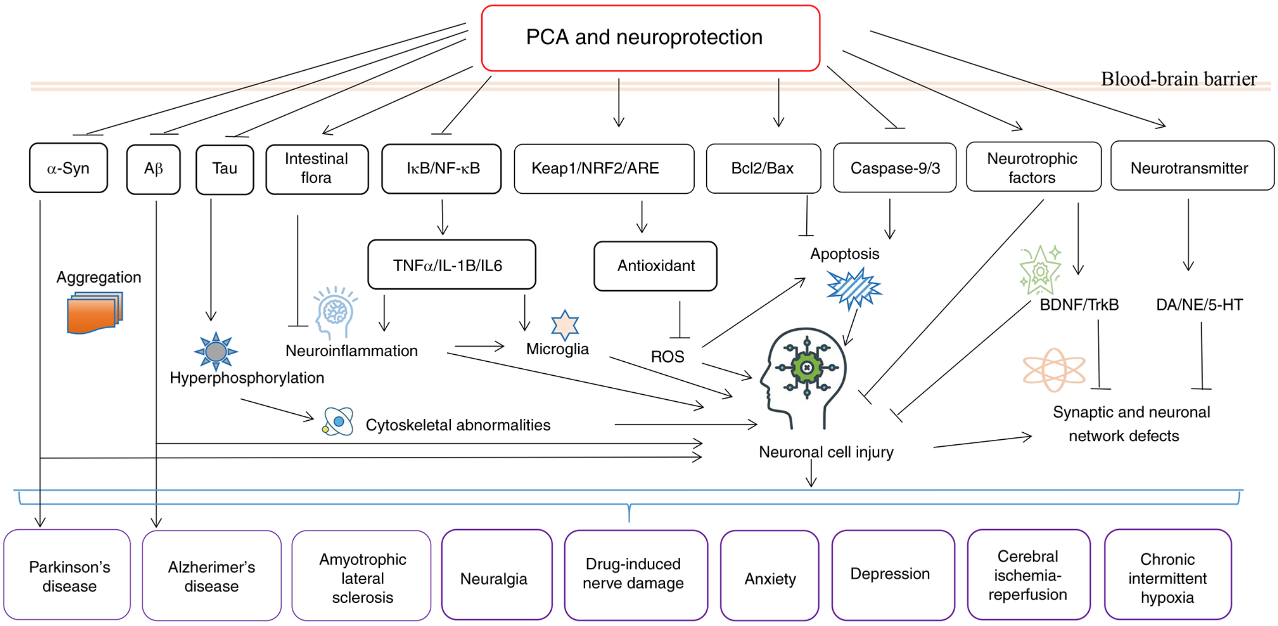

Figure 2. Roles and mechanisms of PCA in neuroprotection-related signaling pathways. Antioxidant activity, anti-inflammatory modulation, anti-apoptotic regulation, mitochondrial protection and homeostasis maintenance of PCA are summarized. PCA, protocatechuic acid; TNF-α, tumor necrosis factor-α; IL, interleukin-6; IκB, inhibitor of nuclear factor-κB; NF-κB, nuclear factor-κB; AKT, protein kinase B; MAPK, mitogen-activated protein kinases; ERK, extracellular regulated protein kinases; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; α-syn, α-synuclein; Aβ, amyloid-β; BDNF, brain-derived neurotrophic factor; TrkB, tropomyosin receptor kinase B; ROS, reactive oxygen species.

Roles of PCA in other neurological diseases. Additionally, various other neurological diseases are associated with neuroprotection and PCA. PCA prevents blood-spinal cord barrier disruption and hemorrhage by downregulating sulfonylurea receptor 1/transient receptor potential melastatin 4 and matrix metalloproteinases, thereby enhancing functional recovery following spinal cord injury (139). Administration of PCA reduced elevated levels of ROS, protein carbonyls, carboxymethyl lysine and methylglyoxal in the brains of D-galactose-treated mice, indicating its potential to delay or prevent age-related changes (140). PCA regulated blood glucose levels, alleviated cerebral mitochondrial dysfunction and prevented oxidative stress in the brains of streptozotocin-induced diabetic rats (141).

In a rat model of thiamine deficiency, PCA not only ameliorated systemic rigidity and improved motor coordination but also enhanced cognitive function, specifically memory consolidation and retrieval, while restoring normal alanine and glutamate concentrations in the medulla oblongata, which are dysregulated due to the deficiency (142). In a rat model of chronic intermittent hypoxia, which mimics the hallmark cognitive impairment of obstructive sleep apnea, PCA mitigated cognitive dysfunction by reducing cerebral IL-1β levels, upregulating BDNF and synapsin expression, attenuating oxidative stress, apoptosis and reactive gliosis, and ultimately improving learning and memory (143). Beyond neurological effects, PCA exhibited organoprotective properties, demonstrating cardioprotective and lipid-lowering activity in rats with high-fat/high-fructose-induced coronary artery disease (144).

Key mechanisms of PCA in neurological disorders. Neuronal death is a common feature of neurological diseases, and protecting neurons and rebuilding damaged neural networks are key to treating NDs such as HD (145). In fact, neuronal injury and death across various NDs converge on shared pathological mechanisms, including oxidative stress, neuroinflammation, ion dyshomeostasis and proteotoxicity (146,147). PCA has exerted broad protective effects across multiple ND models, not by targeting a specific disease but by modulating these fundamental, shared pathological pathways. The most prominent and conserved mechanisms of PCA in NDs include inhibiting abnormal protein aggregation (such as Aβ and α-syn), attenuating neuroinflammation (for example, suppressing the NF-κB pathway), enhancing antioxidant defenses, and modulating autophagy and cell survival signaling (for example, Akt/GSK-3β). These mechanisms often work in concert, ultimately promoting neuronal survival and function (Table II). The roles and mechanisms of PCA related to neuroprotection are summarized in Fig. 2, including antioxidant activity, anti-inflammatory modulation, anti-apoptotic regulation, mitochondrial protection and homeostasis maintenance.

5. Clinical studies and translational considerations of PCA

To establish the efficacy and safe dosage of PCA, conducting rigorous human clinical trials, including pharmacokinetic, dose-finding and efficacy studies as a single compound, is essential. In a mouse study, PCA appeared to be rapidly absorbed, achieving a peak plasma concentration of 73.6 μM at 5 min, with an initial elimination half-life of ~3 min and a terminal half-life of 16 min, and remaining detectable for up to 8 h (148). A pH-responsive, rapidly adjustable hydrogel based on PCA enabled sustained and controlled drug release, demonstrating excellent clinical potential for NDs (149). However, clinical observations indicate a higher incidence of stroke onset during the human active phase (daytime), whereas most rodent models are conducted during the animals' inactive phase, introducing a chronobiological discrepancy that may limit translational predictability (150). Currently, there are limited direct clinical studies on PCA; it is more frequently investigated as a metabolite, and since it derives from various natural sources often containing other compounds, detected doses across studies may vary substantially (151). As a phenolic acid metabolite from anthocyanin degradation, PCA is a key urinary bioactive compound whose increased excretion is associated with reduced serum oxidant status, indirectly supporting its role in boosting antioxidant defences (152).

While PCA exhibited neuroprotective properties in animal models by mitigating oxidative stress and neuronal apoptosis, a 9-week clinical trial using PCA-rich juices (such as cranberry or red grape) in elderly men (age ≥67 years, n=30) with memory deficits showed no notable improvement in choice memory scores, but led to a reduction in biomarkers of inflammation and tissue damage (153). This finding is significant, indicating successful engagement of the intended therapeutic targets, namely, the suppression of chronic inflammatory and oxidative stress pathways. The negative primary cognitive outcome may be attributed to the short intervention duration, insufficient dosage, limited sample size or heterogeneity within the study population. Therefore, the reduction in inflammatory markers should be regarded as a positive pharmacodynamic signal, suggesting potential for cognitive benefit with optimized or longer-term intervention strategies.

Based on evidence from *in vitro* studies and human skin tests, PCA demonstrated promising potential for anti-wrinkle and anti-skin ageing treatments (154,155). The core molecular mechanisms involved, such as its antioxidant and anti-inflammatory activities, may also be relevant to the field of neuronal ageing. This connection provides a compelling rationale and valuable insights for exploring the role of PCA in mitigating brain ageing and associated NDs. Despite the use of high PCA doses in animal studies, current clinical research primarily focuses on PCA-enriched mixtures and their topical skincare applications. The safe dosage and therapeutic efficacy of PCA in humans remain to be fully elucidated.

6. Conclusion

PCA, a natural compound with multiple biological activities, exhibits considerable neuroprotective potential in diverse neurological disorders, including AD, PD and cerebral ischemia, primarily through mechanisms such as antioxidation, anti-inflammation and the promotion of neuronal survival. Although preclinical studies have underscored its broad efficacy, clinical translation remains limited by a scarcity of large-scale human trials and inconsistent outcomes attributable to its multi-target nature, which complicates mechanistic clarity and reproducibility. Future clinical studies to elucidate the disease-specific mechanisms of PCA, optimize its dosing and delivery strategies, and evaluate long-term safety and efficacy for neurological disorders are anticipated.

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Availability of data and materials

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Authors' contributions

XYX, YCL, SSS, LPW and LFW contributed to the manuscript conception and design. The first draft of the manuscript was written by XYX and LFW. XYX, YCL and LFW contributed to reference investigations and figure visualization. YCL, SSS and LPW commented and critically revised previous versions of the manuscript. All authors have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethical approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, the DeepSeek session on NewIdea AI tools (https://chat.newidea.pro/chat) were used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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