Natural products and neurocognitive disorders: Mechanistic insights and research advances (Review)

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Abstract. Neurocognitive disorders (NCDs) are major conditions which impair the cognitive abilities of older adults and other populations worldwide, with incidence rising steadily every year. They constitute a group of acquired disorders characterized by progressive cognitive decline, encompassing delirium, mild and major NCD. These conditions exert wide-ranging and profound adverse effects, including diminished quality of life, increased risks of falls, malnutrition, infections, reduced treatment adherence, and greater family caregiving and societal burdens. The pathogenesis of NCDs involves multiple coexisting factors and complex pathway interactions. Such heterogeneity and interwoven mechanisms contribute to the limited efficacy of existing pharmacological therapies. Current drugs such as acetylcholinesterase inhibitors and N-methyl-D-aspartate receptor antagonists can provide partial symptom relief but cannot fundamentally halt disease progression. Moreover, current drugs are limited by notable side effects and, importantly, no effective standard treatment strategies exist for mild cognitive impairment, postoperative cognitive dysfunction or delirium. Against this background, natural compounds with multi-target mechanisms, diverse biological activities such as anti-inflammatory, antioxidant, neurotrophic and synaptic regulatory activities, and relatively low toxicity, for example flavonoids, alkaloids, terpenoids and polyphenols, are emerging as promising therapeutic candidates and major research foci. The aim of the present review was to summarize the pathogenic mechanisms of NCDs and highlight recent advances in the study of natural products for treatment, thereby providing a theoretical and research foundation for future translational applications in clinical prevention and therapy.

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Contents

1. Neurocognitive disorders (NCDs)

Definition. NCDs are a group of acquired conditions characterized by a decline in one or more cognitive domains, including memory, attention, language, learning ability, executive function and social cognition. Unlike neurodevelopmental disorders which are present from birth or early life, NCDs reflect a deterioration of previously attained cognitive levels (1).

According to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, the spectrum of NCDs comprises three syndromes: i) Delirium; ii) mild NCD (MCI); and iii) and major NCD. Within this framework, disorders such as Alzheimer's disease (AD), cerebrovascular disease, dementia with Lewy Bodies (DLB), Parkinson's disease (PD) dementia, Huntington's disease (HD) and traumatic brain injury are considered etiological conditions which may lead to MCI and/or major NCD, rather than categories separate from the NCD framework (2).

Elderly individuals are the most susceptible population for NCDs. According to estimates from the Global Burden of Disease study and the World Health Organization, the number of patients with dementia worldwide has already exceeded 55 million and is projected to surpass 150 million by 2050 (3). MCI, as a transitional state between normal aging and dementia, affects 15-25% of individuals >60 years old and >30% of those >80 years old (4).

In elderly hospitalized or surgical patients, perioperative NCDs (PNDs) represent a related clinical spectrum of cognitive impairment, including postoperative delirium (POD) and postoperative cognitive dysfunction (POCD). POD is

characterized by an acute onset of fluctuating disturbances in attention and awareness typically occurring within hours to days after surgery, whereas POCD presents as a more subtle and persistent decline in cognitive functions, often identified days to weeks after surgery. The incidence range of POD and POCD in elderly patients is 15-50 and 30-40%, respectively (5).

NCDs exert wide-ranging and profound negative effects. The continuous decline in cognitive function limits daily living activities and results in loss of independence, which severely impairs quality of life and increases the risk of falls, malnutrition, infections and other chronic complications (6). Moreover, these disorders impose a heavy burden on caregivers and healthcare systems, markedly elevating socioeconomic costs. Therefore, early identification and effective intervention are of great clinical importance in slowing disease progression and reducing the risk of adverse outcomes.

Major pathological mechanisms of NCDs. NCDs are clinically heterogeneous conditions with complex pathogenesis involving multiple interconnected pathological processes. The focus of the present review is on the major mechanisms shared across NCDs and representative disorders associated with cognitive impairment such as AD, DLB, PD dementia, HD, vascular cognitive impairment and PNDs. These mechanisms include neuroinflammation, oxidative stress and mitochondrial dysfunction, abnormal protein aggregation, neurotransmitter imbalance, reduced neurotrophic factor expression and disruption of the blood-brain barrier (BBB; Fig. 1).

Among these processes, neuroinflammation is widely recognized as a central driving factor (7). Studies in rodent models of AD have shown that Aβ deposition and tau hyperphosphorylation activate microglia and astrocytes, leading to the release of proinflammatory cytokines such as IL-1β, IL-6 and TNF-α, thereby inducing synaptic damage and neurodegeneration (8,9). Similarly, in POD and POCD, peripheral inflammatory mediators can cross the BBB, sustaining microglial activation and triggering the overproduction of nitric oxide (NO) and reactive oxygen species (ROS). This cascade results in neuronal and synaptic dysfunction (10-12), a mechanism confirmed in several animal models.

Oxidative stress and mitochondrial dysfunction constitute another key pathogenic pathway (13). In this context, non-enzymatic glycation and oxidation of proteins act in an interdependent manner to induce structural and functional alterations, with reactive dicarbonyls such as methylglyoxal driving excessive ROS generation, impairing antioxidant defenses, and thereby exacerbating oxidative stress and mitochondrial dysfunction (14). In AD brains, elevated levels of lipid peroxidation products and ROS, along with decreased activity of mitochondrial respiratory chain complexes are commonly observed (15). Likewise, in vascular dementia (VD) secondary to cerebral small vessel disease, ischemia and hypoxia directly induce mitochondrial injury, leading to neuronal energy deficits (16). In POCD models, reduced ROS clearance and mitochondrial membrane potential loss have been associated with impaired learning and memory (17,18).

Abnormal protein aggregation is a hallmark feature of several neurodegenerative disorders associated with cognitive impairment. In AD, Aβ plaques and hyperphosphorylated tau form neurofibrillary tangles, which induce synaptic toxicity and neuronal apoptosis (8). In POD and POCD, perioperative changes in Aβ, tau phosphorylation and synapse-associated proteins have been reported, although the available evidence remains limited and is largely based on preclinical studies and selected clinical observations (19,20). In DLB, α-synuclein (α-syn) aggregates to form Lewy Bodies (21), while in HD, mutant huntingtin protein disrupts intracellular homeostasis and provokes neuroinflammation, exacerbating neuronal loss (22). In some of these disorders, pathogenic proteins may propagate through 'seeding'-like mechanisms, further amplifying neurodegeneration.

Neurotransmitter system imbalance also substantially contributes to pathogenesis, particularly within cholinergic, glutamatergic and dopaminergic circuits (23). Cholinergic dysfunction, first identified in AD, is characterized by decreased choline acetyltransferase activity, reduced acetylcholine levels and neuronal loss (24). In patients with MCI, functional imaging reveals diminished cholinergic metabolism in the prefrontal cortex and striatum, suggesting a sensitive early biomarker (25). Glutamatergic dysregulation induces N-methyl-D-aspartate (NMDA) receptor-mediated excitotoxicity, leading to neuronal injury, a mechanism confirmed in AD, POD and post-stroke cognitive impairment (26-29). Dopaminergic dysfunction underlies PD dementia and DLB, manifesting as attentional fluctuations and psychiatric symptoms (30,31), whereas dopaminergic hyperactivity in POD and POCD may reflect postoperative inflammation-induced neural dysregulation (32,33). Additional imbalances in γ-aminobutyric acid (GABA) ergic, histaminergic and noradrenergic systems have been documented in POCD (34-37).

Other contributing mechanisms include reduced expression of neurotrophic factors and BBB dysfunction. Downregulation of brain-derived neurotrophic factor (BDNF) impairs synaptic plasticity, limiting synaptic remodeling and neurogenesis, and serves as a molecular basis for loss of cognitive reserve (38,39). BDNF reduction has been documented in AD, MCI and POD, negatively associated with memory impairment (38,40-42). BBB breakdown, particularly evident in VD and AD, allows inflammatory cells and toxic molecules to enter the brain parenchyma through endothelial injury and reduced tight junction protein expression, thereby exacerbating neuroinflammation and oxidative stress (43,44).

Although NCDs differ in etiology and clinical presentation, ranging from neurodegenerative diseases such as AD, PD dementia and HD to vascular and perioperative conditions such as POD and POCD, they share several common pathological features. Accumulating evidence suggests that processes such as neuroinflammation, oxidative stress, mitochondrial dysfunction, protein aggregation and synaptic impairment are consistently involved across these conditions, even though their relative contributions may vary. These overlapping mechanisms provide a useful framework for understanding NCDs as a group of disorders with shared biological underpinnings. Importantly, a number of natural products exert multi-target effects across these interconnected pathways rather than acting on a single disease-specific mechanism. Therefore, considering these shared pathological features may better highlight the therapeutic potential of natural compounds in targeting core processes underlying NCDs.

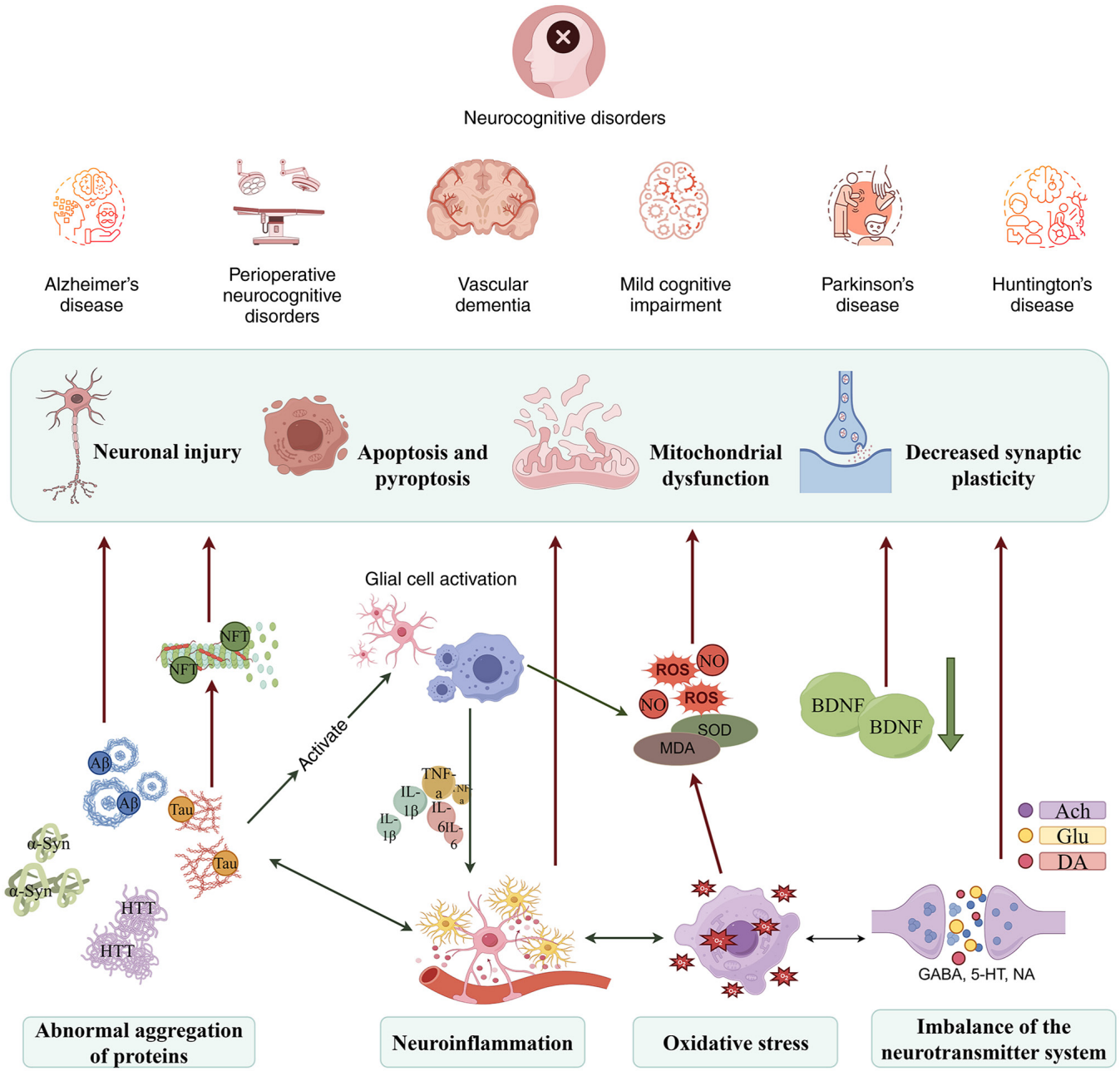

Figure 1. Major pathological mechanisms involved in neurocognitive disorders discussed in the present review. Schematic illustration of the key mechanisms including neuroinflammation, oxidative stress and mitochondrial dysfunction, abnormal protein aggregation, neurotransmitter imbalance, reduced neurotrophic factor expression and blood-brain barrier disruption. Created using Figdraw 2.0 (https://www.figdraw.com/; accessed on April 11, 2026). MDA, malondialdehyde; SOD, superoxide dismutase; ROS, reactive oxygen species; BDNF, brain-derived neurotrophic factor; NO, nitric oxide; Ach, acetylcholine; Glu, glutamate; DA, dopamine; GABA, gamma-aminobutyric acid; 5-HT, 5-hydroxytryptamine; NA, noradrenaline; NFT, neurofibrillary tangles; α-syn, α-synuclein; HTT, huntingtin.

Limitations of current pharmacological treatments. Given the coexistence of multiple factors and the interaction of diverse pathways in the pathogenesis of NCDs, the highly complex pathological background makes it challenging for single-target drugs to achieve optimal therapeutic outcomes. At present, pharmacological treatment mainly relies on cholinesterase inhibitors, NMDA receptor antagonists or dopaminergic agents; however, their efficacy is limited and patients frequently experience side effects. For example, donepezil and memantine, the primary drugs for AD, act only on the cholinergic or glutamatergic systems and cannot halt or reverse disease progression (45). Dopaminergic medications can improve symptoms in PD dementia, but drug tolerance often develops, diminishing therapeutic efficacy (46). Moreover, for acute cognitive impairments such as POCD and POD, effective preventive or neuroprotective strategies are still lacking, with management relying mainly on supportive and symptomatic care. Long-term use of these drugs further increases the risk of adverse effects such as gastrointestinal discomfort, bradycardia, or central nervous system (CNS) symptoms, which negatively impact patients' quality of life (47). In addition, interindividual variability in drug response complicates treatment planning as some patients may not benefit from standard therapies due to genetic factors or comorbid health conditions, thereby increasing therapeutic challenges (48).

Therefore, the development of novel therapeutic strategies to overcome these limitations has become a major focus of current research. Naturally derived bioactive compounds have gained increasing attention for their multi-target synergistic regulatory capacity, favorable safety profile and potential to modulate neuroinflammation, oxidative stress, synaptic plasticity and neurotrophic signaling. Systematic exploration of natural medicines holds promise for providing more comprehensive and effective interventions for the prevention and treatment of NCDs.

2. Major active compounds from natural products in improving NCDs

Overview of major natural compounds and their mechanisms. Accumulating evidence indicates that major bioactive compounds derived from natural products exert neuroprotective effects through multiple interconnected biological processes. These compounds regulate antioxidant defenses, neuroinflammatory cascades, apoptotic and autophagic pathways, mitochondrial homeostasis, as well as processes related to synaptic plasticity, neurogenesis and angiogenesis, thereby alleviating cognitive impairment across diverse NCDs (Fig. 2).

However, these findings should be interpreted with caution. Differences in experimental conditions, including animal age and sex, dosing regimens, routes of administration, and behavioral assessment methods, may influence study outcomes and make direct comparisons across studies challenging. In addition, results are not always consistent across different models, and the relative contribution of specific mechanisms remains incompletely defined.

Moreover, translational challenges, such as limited brain bioavailability, rapid metabolism, uncertainty in dose equivalence between experimental models and humans, and the lack of direct evidence for target engagement in clinical settings, may further limit the clinical applicability of these findings. Importantly, these bottlenecks may not affect all compounds to the same extent, as their impact is likely to depend on compound-specific properties such as BBB penetration, metabolic stability, formulation characteristics and the availability of human pharmacological data. These considerations suggest that further well-designed and standardized studies are needed to better support the clinical application of natural compounds in NCDs. To facilitate comparison across compounds, a summary of representative compounds and their major mechanisms is provided in Table I.

Flavonoids

Quercetin. Quercetin is a widely distributed dietary flavonoid found in fruits and vegetables, with pronounced antioxidant, anti-inflammatory and neuroprotective properties (49). Across NCD models, particularly those of AD and POCD, quercetin has shown therapeutic promise. Lasure *et al* (50) and Lu *et al* (51) reported that a quercetin-enriched diet improved cognition in amyloid precursor protein/presenilin-1 (APP/PS1) transgenic mice and in intranasal Aβ-challenged models, largely by enhancing Aβ clearance, reducing tau phosphorylation and dampening astrocyte activation; these benefits appeared to be most evident during the early to middle stages of AD. Its antioxidant and anti-inflammatory effects may also contribute substantially to these benefits. Cheng *et al* (52) observed increased serum superoxide dismutase (SOD) and glutathione (GSH), reduced malondialdehyde (MDA) and amelioration of AD-like pathology in APP/PS1 mice, which were associated with activation of antioxidant signaling pathways, including Keap1/Nrf2/HO-1, as well as reduced neuronal apoptosis. In parallel, Du *et al* (53) showed that quercetin targets heat shock protein 90 to restrain microglial NLRP3 inflammasome activation, thereby improving depression-related cognitive deficits. In POCD, quercetin was found to modulate the miR-138-5p/LCN2 axis to curb hippocampal inflammation and improve behavioral outcomes, while Khan *et al* (54) linked its effects to preserved mitochondrial function through normalization of the Bax/Bcl-2 ratio and suppression of cleaved PARP-1. Taken together, quercetin acts on multiple molecular targets and shows promise for further development against cognitive decline. However, the current evidence is still derived predominantly from preclinical studies using heterogeneous animal models and exposure paradigms, including APP/PS1 mice, intranasal Aβ challenge and LPS-related models. Variability in dosing strategies, treatment timing and behavioral assessment methods may limit direct comparison across studies and should be considered when interpreting its overall efficacy. In addition, the translational relevance of quercetin may also be influenced by its pharmacokinetic profile and the limited availability of direct evidence for target engagement in humans.

Baicalein. Baicalein, a major flavonoid derived from *Scutellaria baicalensis* (Huangqin), can cross the BBB and has drawn interest for CNS-related indications. In an AD-related study, baicalein was shown to engage several signaling pathways that alleviate cognitive deficits (55). Zhang *et al* (56) showed that baicalein activates $GABA_A$ receptors, shifts APP processing toward the non-amyloidogenic pathway, and reduces Aβ accumulation, thereby improving learning and memory. Electrophysiological work by Gu *et al* (57) demonstrated increased AKT phosphorylation, rescue of Aβ-impaired hippocampal long-term potentiation (LTP) and restoration of synaptic function. Baicalein also appears to reprogram microglial states through CX3CR1-related inflammatory signaling pathways, thereby mitigating neuroinflammation and improving cognitive performance (58). Beyond the brain, a 14-day course reshaped gut microbial composition and regulated amino-acid, GSH and histidine metabolism, changes that were accompanied by cognitive improvement (59). In VD models, baicalein reduced proinflammatory microbiota ratios, suppressed hippocampal gliosis and limited cytokine release through TLR4/MyD88/NF-κB (60). In anesthesia-related injury, it attenuated sevoflurane-induced neuronal apoptosis and degeneration via the PI3K/AKT/GSK-3β and JNK/ERK pathways (61). Converging evidence from network pharmacology, docking and cell studies points towards AKT1 and GSK-3β as key effectors (62). Overall, baicalein exhibits multi-target neuroprotective effects across AD, VD, POCD and MCI models. However, the reported benefits are based on heterogeneous experimental settings, ranging from transgenic AD models to VD and anesthesia-related injury models, and the relative contribution of individual mechanisms may vary across these settings. In addition, differences in treatment duration, routes of administration, and outcome measures

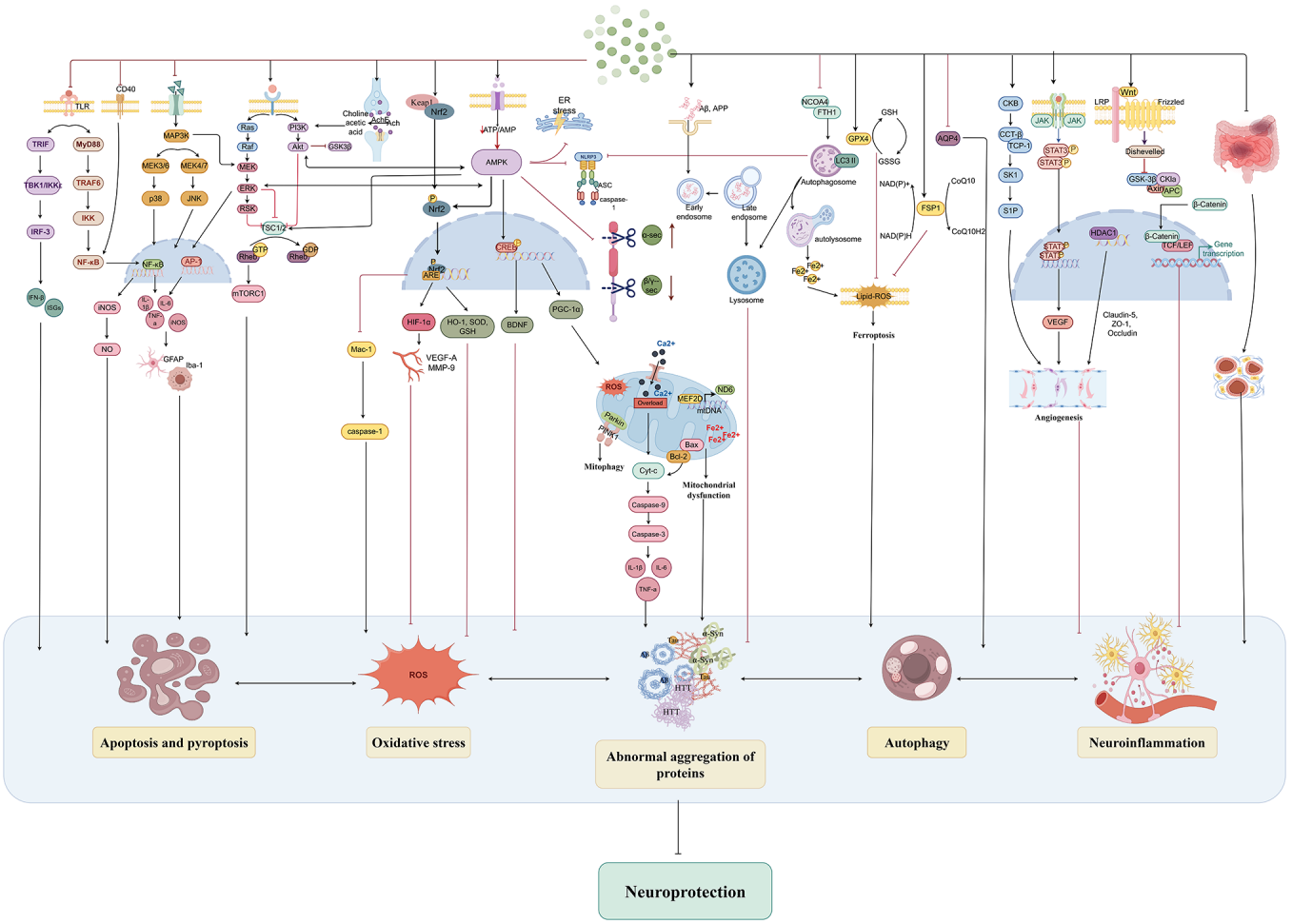

Figure 2. Representative signaling pathways underlying the neuroprotective effects of natural compounds. Schematic illustration of the major signaling cascades modulated by natural compounds relevant to neurocognitive disorders. Key mechanisms include antioxidant defense such as Keap1/Nrf2/HO-1 and AMPK/Nrf2, anti-inflammatory signaling such as TLR4/NF-κB, CX3CR1/NF-κB and NLRP3/caspase-1, regulation of apoptosis and autophagy such as PI3K/AKT/GSK-3β and MAPK, and mitochondrial homeostasis such as PINK1/Parkin. Additional pathways involve synaptic plasticity, neurogenesis and angiogenesis. Collectively, these interconnected mechanisms converge to attenuate oxidative stress, neuroinflammation, mitochondrial dysfunction and protein aggregation, thereby supporting cognitive function. Created using Figdraw 2.0 (https://www.figdraw.com/; accessed on April 11, 2026). BDNF, brain-derived neurotrophic factor; NO, nitric oxide; iNOS, inducible nitric oxide synthase; NCOA4, nuclear receptor coactivator 4; ER, endoplasmic reticulum; GPX4, glutathione peroxidase 4; ROS, reactive oxygen species; NLRP3, NLR family pyrin domain containing 3; HDAC1, histone deacetylase 1; SOD, superoxide dismutase; HO-1, heme oxygenase-1; GSH, reduced glutathione; GSSG, glutathione disulfide; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; mtDNA, mitochondrial DNA; FTH1, ferritin heavy chain 1; CoQ10, coenzyme Q10; AQP4, aquaporin-4; FSP1, ferroptosis suppressor protein 1; Nrf2, nuclear factor erythroid 2-related factor 2; HIF-1α, hypoxia-inducible factor 1α; GSK-3β, glycogen synthase kinase-3β; APP, amyloid precursor protein; ARE, antioxidant response element; GFAP, glial fibrillary acidic protein; Iba-1, ionized calcium-binding adaptor molecule 1; TCP-1, T-complex protein 1.

limit direct comparison among studies. Although baicalein can cross the BBB, its translational interpretation is still limited by the predominance of preclinical evidence, uncertainty regarding clinically relevant exposure levels, and the lack of direct evidence for target engagement in human studies.

Rutin. Rutin, also known as vitamin P, is a natural flavonoid glycoside composed of quercetin and rutinose and is widely distributed in buckwheat, citrus fruits, pagoda tree flowers and onions (63). It exerts antioxidant, anti-inflammatory, anti-apoptotic, antidepressant, anticonvulsant and vasoprotective effects, and has shown benefits in AD, HD and POCD models (64). In AD, rutin attenuates tau hyperphosphorylation, limits neuroinflammation and boosts microglial Aβ clearance (65); the derivative sodium rutin further increases clearance and lowers cerebral Aβ burden (66). In PD dementia paradigms, rutin and its analogues protect dopaminergic neurons and blunt 6-hydroxydopamine (6-OHDA)-evoked apoptosis, astrogliosis and oxidative stress (67). In HD, Cordeiro *et al* (68) showed that chronic dosing reduces polyglutamine (polyQ) aggregation and neuronal loss via insulin/insulin-like growth factor 1 signaling and autophagy. For POCD, Ji *et al* (69) identified regulation of microglial polarization and pyroptosis through the Nrf2/Mac-1/caspase-1 axis. Rutin also protects against anesthesia-related neurotoxicity in neonates and confers benefit in ischemia-reperfusion and scopolamine models by modulating NO, suppressing ROS and improving cerebral microcirculation (64,70). Sun *et al* (71) further reported enhanced brain microvascular endothelial cell proliferation, migration and angiogenesis, and activation of the endothelial HDAC1/claudin-5 pathway, restoring BBB integrity and reducing neuroinflammation and cognitive decline. Taken together, rutin exhibits a broad range of mechanisms, including antioxidation, anti-inflammation, regulation of protein aggregation, autophagy, and BBB

Table I. Representative natural compounds and their associated mechanisms.

Compound	Class	Nrf2 (antioxidant)	NF-κB/NLRP 3 (inflammation)	PI3K/AKT (survival)	Autophagy	Mitochondria	BDNF/synaptic	BBB/ vascular
Quercetin	Flavonoid	Yes (Keapl/Nrf2/HO-1)	Yes (NLRP3)	No	-	Yes	Yes (Aβ/tau)	-
Baicalein	Flavonoid	Limited (ERK-related) antioxidant	Yes (NF-κB)	Yes	-	-	Yes (LTP)	Yes
Rutin	Flavonoid	Yes	Yes	-	Yes	Yes	Yes (Aβ/tau)	Yes
Huperzine A	Alkaloid	Limited	Yes (NF-κB)	Yes	No	Yes	Yes (BDNF/TrkB)	Limited
Berberine	Alkaloid	Yes (AMPK/Nrf2)	Yes (NLRP3)	Yes	Yes	Yes	Yes (Aβ/tau)	Yes
Ginsenosides (Rg1)	Terpenoid	Yes (AMPK/Nrf2)	Yes (NF-κB)	Yes	Yes	Yes	Yes (BDNF/NGF)	Yes
Ginkgolides	Terpenoid	Yes	Yes (NLRP3)	Yes	Yes	Yes	Yes (Aβ/α-syn)	Yes
Resveratrol	Polyphenol	Yes (Nrf2/SIRT1)	Yes (NF-κB)	Yes	Yes	Yes	Yes (BDNF)	Yes
Curcumin	Polyphenol	Yes (Nrf2)	Yes (NF-κB/NLRP3)	Yes	Yes	Yes	Yes (BDNF)	Yes
Salidroside	Polyphenol	Yes (Nrf2/GPX4)	Yes (NLRP3)	Yes	Yes	Yes	Yes (BDNF)	Yes

'Yes' indicates that involvement of the pathway has been reported in at least one study as described in this review; 'Limite' indicates that evidence is relatively limited or indirectly discussed; '-' indicates that this pathway was not specifically addressed for the given compound in this review and does not exclude its potential involvement. Nrf2, nuclear factor erythroid 2-related factor 2; BDNF, brain-derived neurotrophic factor; NLRP3, NLR family pyrin domain containing 3; BBB, blood-brain barrier.

support, highlighting its therapeutic potential. However, the available evidence spans diverse disease models, including AD, HD, POCD and ischemia-reperfusion injury, which makes mechanistic interpretation more complex. Moreover, variability in acute vs. chronic dosing regimens and in the experimental endpoints assessed may contribute to differences in the reported magnitude of benefit. The clinical translation of rutin may be further complicated by its glycoside nature, which may affect absorption, metabolism and effective brain exposure, as well as by the limited evidence linking experimental mechanisms to target engagement in humans.

Overall, flavonoids show relatively broad and generally consistent neuroprotective potential across different NCD models, with evidence mainly supporting antioxidant, anti-inflammatory and synaptic regulatory effects. Their modulation of pathways such as Nrf2, NF-κB and inflammasome-related signaling has been observed in multiple studies. However, differences in experimental models, dosing strategies, and outcome measures make direct comparisons challenging. In addition, most current evidence remains preclinical, and compound-specific issues such as variable pharmacokinetics, brain exposure, and limited human target-engagement data should also be considered when evaluating their clinical relevance and therapeutic potential.

Alkaloids

Huperzine A (HupA). HupA is a natural alkaloid extracted from *Huperzia serrata*, acting as a highly selective and reversible acetylcholinesterase inhibitor (AChEI). With BBB permeability, it has become one of the most studied and clinically applied natural drugs for cognitive disorders (72). Owing to potent AChEI activity, HupA is used for AD and has been approved in China as a first-line therapy (72). Beyond augmenting cholinergic tone, HupA promotes α-secretase-biased APP processing while suppressing β- and γ-secretases, thereby reducing Aβ production and deposition. It also activates BDNF/TrkB, PI3K/AKT and PI3K/TrkB/mTOR to support synaptic plasticity and neuronal survival, and downregulates IL-1β, IL-6, TNF-α and NF-κB to temper neuroinflammation (72,73). Non-cholinergic mechanisms include preservation of mitochondrial structure and function, regulation of brain Fe^{2+} homeostasis and mitigation of oxidative stress; Wnt pathway activation has been proposed to underpin plasticity and structural integrity (72). Beyond AD, HupA improves motor and cognitive outcomes, and limits dopaminergic degeneration in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced PD dementia models, likely via anti-inflammatory effects and normalization of oxidative phosphorylation (74). In VD, it benefits chronically hypo-perfused rats through cholinergic support, free-radical scavenging and improved energy metabolism (75); in transient ischemia-reperfusion, MAPK/ERK and cholinergic anti-inflammatory signaling may mediate neurotrophic effects (76). Although evidence remains preliminary, BDNF-linked protection suggests a role in POCD (77,78). Taken together, HupA is a multi-mechanistic small molecule with potential for use as either a first-line or adjunctive therapy across NCDs. However, despite its relatively clear pharmacological targets and some existing clinical application, much of the mechanistic evidence discussed in the present review

still originates from experimental models with distinct pathological backgrounds. In particular, while cholinergic target engagement is pharmacologically plausible, direct clinical confirmation of several proposed non-cholinergic mechanisms remains limited. This heterogeneity, together with differences in treatment duration and outcome assessment, may contribute to variability in the reported findings across AD, VD and perioperative settings.

Berberine (BBR). BBR is a natural isoquinoline alkaloid widely found in *Coptis chinensis* and *Phellodendron amurense*, with favorable oral bioavailability and CNS penetration (79). In recent years, increasing evidence has demonstrated notable neuroprotection in AD, VD and PD dementia models (80). In AD, BBR restores mitophagy via the PINK1/Parkin axis to alleviate D-ribose-induced mitochondrial injury and cognitive deficits (81), inhibits GSK-3β to reduce tau hyperphosphorylation and downregulates BACE1 through AMPK signaling to lower Aβ production (82,83). It increases hippocampal LC3-II and Beclin-1, facilitating Aβ/APP clearance and improving histopathology and memory (84). A recent study added a microbiome dimension; BBR reshapes gut communities, strengthens barrier function and stabilizes the brain-gut axis (85). In VD, it enhances neuronal plasticity, suppresses microglial activation and promotes a shift from M1 to M2 (86); ERK-related antioxidant pathways, together with reductions in VEGF-A/MMP-9 and improved BBB integrity, have been implicated in these effects (87). In perioperative settings, BBR limits anesthesia/surgery-related decline by tuning CREB1 and preventing PI3K/AKT overactivation (88,89); in neonatal sevoflurane exposure, it lowers neuronal apoptosis and improves cognition (90). PD dementia studies indicated improved dopamine biology via microbiota modulation, AMPK-dependent autophagy enhancement, NLRP3 suppression and dopaminergic neuroprotection (91-94). Notably, BBR also reduces mutant huntingtin by boosting autophagy, improving motor function and survival in HD models (95). Taken together, BBR demonstrates broad therapeutic potential across NCDs by integrating anti-inflammatory, antioxidant, mitochondrial, autophagic and microbiome-modulating effects. Nevertheless, most of the available evidence remains preclinical and comes from heterogeneous disease models with different mechanistic readouts, including mitophagy, autophagy, microbiota-related changes and inflammatory signaling pathways. In addition, variation in dosing regimens, formulation properties, and routes of administration may contribute to the inconsistency of findings across studies. Its translational interpretation is also influenced by pharmacokinetic complexity, including formulation-dependent exposure and metabolism-related variability, while direct evidence linking these mechanisms to target engagement in humans remains limited.

Taken together, alkaloids appear to have relatively well-defined pharmacological mechanisms, particularly in the case of HupA, which also has some degree of clinical application. However, the consistency of findings across different disease models remains variable, and for several compounds, the available evidence is still derived mainly from experimental studies. Therefore, questions regarding long-term efficacy, optimal dosing, broader clinical applicability, and compound-specific human target engagement remain to be clarified through more rigorous and standardized research.

Terpenoids

Ginsenosides. Ginsenosides are triterpenoid saponins extracted from the roots of *Panax ginseng*, with broad neuroprotective, physiological regulatory and anti-ageing effects (96). Among them, ginsenoside Rg1 is the most extensively studied and broadly active representative compound. Other ginsenosides, including Rk1, Rk3, Ro, Rb1, Rg3 and Rf, have also demonstrated unique advantages in different disease models (97). AD is the most widely investigated NCD. Studies have shown that Rg1 reduces p-tau levels, Aβ production and APP expression, increases BDNF levels and alleviates hippocampal pathology (97,98). Moreover, Rg1 may also improve AD-related pathology by modulating gut microbiota composition (99). She *et al* (100,101) reported that Rk1/Rk3 activate AMPK/Nrf2, restoring mitochondrial potential, reducing ROS and curbing Aβ generation, while Rk3 additionally promotes neurogenesis and synaptogenesis via CREB/BDNF. Ro has emerged as a candidate acting through IBA1/GFAP-MAPK pathways (102). In VD, Rg1 restores amino acid balance and neurotransmission via Adcy1/Kdr-mediated cholinergic synapses and PI3K/AKT, dampening oxidative stress and neuronal injury (103). Zhou *et al* (104) further showed BBB protection by downregulating aquaporin 4 (AQP4), reducing edema and suppressing microglial activation through TLR4/MyD88/NF-κB and TLR4/TRIF/IRF-3. In POCD, Rg1 counters isoflurane-induced deficits via PI3K/AKT/GSK-3β and enhances microglial Aβ clearance through endolysosomal pathways (105,106). Total ginsenosides raise hippocampal nerve growth factor (NGF) and BDNF, and improve fear, working and spatial memory after anesthesia (107). In HD models, Rg1 attenuates striatal inflammation via MAPK and NF-κB inhibition (108). Rg3 and Rf further suppress apoptotic signaling and improve lysosomal function (109). Taken together, ginsenosides exhibit multi-target neuroprotective effects across cognitive impairment models, with reported actions involving oxidative stress, inflammation, mitochondrial function and synaptic plasticity. Nevertheless, the available evidence is complicated by the wide range of ginsenoside subtypes investigated, such as Rg1, Rk1, Rk3, Ro, Rg3 and Rf, which may differ in their pharmacological profiles. As a result, heterogeneity in both compound subtype and experimental design makes it challenging to directly compare results and to clarify the contribution of individual ginsenosides. Furthermore, potential differences in absorption, metabolism, and effective brain exposure make it difficult to determine which individual ginsenoside species are most relevant for clinical translation.

Ginkgolides. Ginkgolides are characteristic diterpene lactones isolated from *Ginkgo biloba* leaves and constitute major active components of the ginkgo extract. They act through anti-inflammatory, antioxidant, anti-apoptotic, energy-regulatory and neuroprotective mechanisms (110). The major subtypes include ginkgolide A (GA), ginkgolide B (GB), ginkgolide C (GC) and ginkgolide K (GK). Among these, GB is the most extensively studied due to its strong antagonism of platelet-activating factor (111). In AD models, GB protects cognition in SAMP8 and APP/PS1 mice by reducing oxidative stress, inflammation and ferroptosis (112); autophagy-mediated inhibition of NLRP3/caspase-1 may contribute (113). At the cellular level, GB limits $A\beta_{1-42}$-induced

cytotoxicity via AMPK-dependent control of ER stress and energy metabolism and improves cognition by normalizing gut microbiota (114,115). In VD, GB blocks ferroptosis by disrupting NCOA4-FTH1 or engaging GPX4/FSP1, reduces oxidative stress and guards against ischemia-reperfusion injury (116,117); it also promotes angiogenesis and reperfusion, with candidate targets including creatine kinase B and the CCT/TRiC-SK1 axis (118). Fang *et al* (119) showed that intravenous GB within 2 h of reperfusion reduces infarct volume and cerebral edema, supporting a clinically relevant window. In POCD, GB improves perioperative cognition by suppressing iNOS/NO signaling, oxidative stress, apoptosis and postoperative microglial overactivation (120). In a PD dementia study, it mitigated α-syn-driven toxicity, likely by enhancing astrocytic autophagic clearance (121). Other subtypes contribute distinct effects. GA activates autophagy to reduce Aβ and strengthens synaptic plasticity via PI3K-AKT/mTOR (122); GC inhibits CD40/NF-κB and modulates the gut-brain axis to ease neuroinflammation and oxidative stress (123,124); GK promotes angiogenesis through JAK2/STAT3 (125), downregulates the mitochondrial calcium uniporter to limit apoptosis and facilitates autophagic clearance of mutant A53T α-syn (126,127). Overall, ginkgolides show therapeutic potential in NCDs and may provide tractable leads for further development. Nevertheless, the available studies encompass multiple ginkgolide subtypes and diverse experimental settings, ranging from AD and VD models to perioperative and PD-related injury paradigms, which introduces substantial heterogeneity. In addition, variation in subtype selection, route of administration, and treatment window may contribute to differences in reproducibility and limit the translational interpretation of these findings. Direct evidence for subtype-specific target engagement in humans also remains scarce.

Overall, terpenoids demonstrate activity across multiple pathological pathways, including oxidative stress, neuroinflammation, mitochondrial dysfunction and BBB regulation, indicating promising therapeutic potential. Nevertheless, the current evidence is heterogeneous, with some compounds supported by multiple models while others remain less extensively studied. Variability in compound subtypes, formulations and experimental conditions may also affect reproducibility. In addition, subtype-specific pharmacokinetic and translational differences remain insufficiently defined for numerous terpenoid compounds. Further studies are needed to better define their mechanisms and evaluate their translational relevance.

Polyphenols

Resveratrol (RES). RES, widely found in grape skins and *Polygonum cuspidatum*, combines antioxidant, anti-inflammatory, mitochondrial-protective and autophagy-enhancing activities via SIRT1, AMPK, Nrf2/HO-1, NF-κB and PI3K/AKT (128). In AD, it lowers Aβ and BACE1, improves learning and memory, and restores proteostasis through AMPK/SIRT1 and the ubiquitin-proteasome system; it also eases tau pathology and oxidative stress (129-131). In VD, RES reduces MDA, boosts SOD/GSH and preserves the BBB by rebalancing MMP-9/TIMP-1 (132); suppression of TLR4/NF-κB and microglial overactivation further limits neuroinflammation (133). Li *et al* (134) reported reduced infarct volume and apoptosis (increased Bcl-2 and decreased Bax). Under chronic hypoperfusion, it prevents cholinergic loss and maintains hippocampal plasticity (135). In POCD or POD, preoperative RES activates SIRT1 to alleviate ER stress and inflammation, it inhibits tau acetylation/hyperphosphorylation in a SIRT1-dependent manner (136), curbs aberrant microglial activity via SIRT1/NF-κB and modulates BDNF (137); Nrf2/HO-1 activation lowers IL-1β/IL-6 while raising IL-10 (138). In PD dementia, RES limits 6-OHDA toxicity, enhances autophagic α-syn clearance through SIRT1-dependent LC3 deacetylation and prevents VDAC1-mediated mitochondrial injury (139,140); protective effects extend to HD through mitochondrial and metabolic support (141). Collectively, the available data suggest that RES warrants further translational investigation in NCDs. At the same time, most of the supporting evidence remains preclinical and is characterized by substantial variability in model type, dosing schedule and formulation. This heterogeneity, together with recognized issues related to bioavailability, rapid metabolism, and uncertain target engagement at clinically achievable exposure levels, may contribute to the gap between promising mechanistic observations and the inconsistent cognitive benefits reported across studies.

Curcumin. Curcumin, the principal curcuminoid from *Curcuma longa*, shows potent free-radical-scavenging capacity and broad neuroprotection (142). It targets dual AD pathologies by blocking Aβ self-assembly, inhibiting tau hyperphosphorylation and suppressing inflammation/oxidative stress, potentially via HMGB1-RAGE/TLR4-NF-κB (143). Sha *et al* (144) reported cognitive gains after a 10-day regimen, with AMPK activation implicated. Additional mechanisms include PI3K/AKT, GSK-3β/Wnt/β-catenin and CREB/BDNF, which together promote adult neurogenesis and recovery (145). Curcumin improves mitochondrial performance, enhances cell viability and reduces synaptic toxicity. Reddy *et al* (146) suggested prophylaxis may confer greater benefit. Delivery innovations, nanocarriers and curcumin-primed exosomes, facilitate brain entry, activate AKT/GSK-3β to suppress tau phosphorylation and improve cognition (147). In PD dementia models, curcumin counters JNK-driven mitochondrial dysfunction; it reduces α-syn-triggered ROS, depolarization, cytochrome c release and caspase-9/-3 activation, thereby limiting mitochondrial apoptosis (148,149). Rathore *et al* (150) demonstrated upregulation of the p62-Keap1-Nrf2 axis, enhanced autophagy and improved motor coordination; curcumin also dampens NLRP3-mediated inflammation. Zhong *et al* (151) and Cai *et al* (152) pointed to gut-brain contributions via colonic SIRT1/Nrf2 and short-chain fatty acid metabolism. In VD, curcumin modulates inflammatory and oxidative stress-related pathways, including NF-κB and Nrf2 signaling, thereby reducing edema and neurological deficits (153). It also activates Wnt/β-catenin to promote dentate neurogenesis (154). Vascular benefits include restoration of endothelial vasodilation (AMPK/UCP2) and improved cholesterol transport through LXR-β/RXR-α/ABCA1/apoA-I (155,156); the derivative Cur20 adds HIF-1α/VEGF/TFEB-mediated angiogenesis (157). In POCD, curcumin limits microglial activation and oxidative stress and elevates BDNF and synaptic function (158,159). It reduces polyQ toxicity in

Drosophila HD, although bioavailability remains a constraint, nano-delivery and exosome strategies offer practical solutions (160,161). Nevertheless, interpretation of the current evidence on curcumin requires caution because studies differ considerably in formulation, delivery strategy, and treatment protocol, while curcumin itself is also limited by poor bioavailability and variable brain exposure. Moreover, differences in experimental models and assessed endpoints may partly explain the inconsistency in the magnitude of the reported neuroprotective effects, and direct evidence for target engagement in humans remains limited.

Salidroside. Salidroside, a principal *Rhodiola* constituent, has a long history of anti-fatigue and anti-hypoxia use and exhibits antioxidant, anti-inflammatory, anti-apoptotic and neuroprotective effects, with additional benefits to energy metabolism, angiogenesis and immune regulation (162). In AD models, it reduces Aβ and tau hyperphosphorylation, and rescues LTP and synaptic function. In SAMP8 mice, Yang *et al* (163) noted reduced $CD8^+$ T-cell infiltration, less iron deposition and improved mitochondrial/lipid metabolism, likely via Nrf2/GPX4. Cai *et al* (164) highlighted the role of NLRP3-mediated pyroptosis in AD and showed that salidroside suppresses TLR4/NF-κB/NLRP3/caspase-1, lowers IL-1β/IL-18 and mitigates Aβ/tau abnormalities. *In vitro*, it activates ERK1/2 and AKT to shield PC-12 cells from Aβ-induced apoptosis and engages NRF2/SIRT3 to promote mitophagy and mitochondrial homeostasis, attenuating neuritic injury (165). Modulation of the gut-microbiota-brain axis further suggests both therapeutic and preventive potential (166). Beyond AD, salidroside benefits VD by reducing brain edema, normalizing free-radical metabolism and improving cognition after global ischemia-reperfusion, with contributions from TLR4/NF-κB, PI3K/AKT/HIF and PI3K/PKB/Nrf2/NF-κB pathways (167-169). It also promotes neurogenesis, upregulating BDNF/NGF and activating Notch1/Hes1 to stimulate subventricular zone proliferation and $doublecortin^+$ neuroblast differentiation, and angiogenesis via Sonic hedgehog signaling to enhance microvascular density and cerebral perfusion, reducing infarct volume and restoring function (170,171). In PD dementia, salidroside protects dopaminergic neurons through multiple pathways in MPTP mice, inhibits pyroptosis, maintains autophagy and thereby limits the aggregation of α-syn/DJ-1/Parkin (172-174). Although perioperative evidence remains sparse, available data indicate AMPK-dependent suppression of microglial inflammation and protection against isoflurane-related memory deficits, with restoration of cholinergic markers and antioxidant enzymes (175,176). Overall, salidroside shows broad potential for NCD prevention and treatment owing to its apparent safety and multi-mechanistic actions. At the same time, the supporting evidence remains largely preclinical and spans diverse disease models, including AD, VD, PD-related injury, and perioperative cognitive dysfunction. Such heterogeneity, together with differences in experimental conditions, treatment duration, and mechanistic focus, may affect cross-study comparability. In addition, although salidroside shows a favorable safety profile in experimental settings, its clinical translation remains limited by the lack of direct data on human brain exposure and target engagement, indicating that further standardized validation is needed.

Polyphenols are among the most extensively investigated natural compounds in NCD research and exhibit broad activity in modulating oxidative stress, inflammation, mitochondrial function and autophagy. However, much of the current evidence is derived from preclinical studies, and differences in experimental models, formulations, bioavailability and metabolism may influence outcomes. Future research should place greater emphasis on pharmacokinetics, delivery strategies, human target engagement, and clinical validation to better support their therapeutic application.

Taken together, although different classes of natural products exhibit distinct pharmacological features, a wide range of compounds have demonstrated neuroprotective effects across diverse experimental models. Most of the available evidence is derived from preclinical studies, and differences in experimental design, including animal characteristics, dosing regimens, routes of administration and outcome measures, limit direct comparison across findings. In addition, reproducibility across models is not always consistent, and the relative contribution of specific mechanisms remains to be further clarified. Beyond these general methodological issues, individual compounds may also face distinct translational bottlenecks related to BBB penetration, metabolism, formulation dependence, subtype heterogeneity, and limited evidence for target engagement in humans. These limitations highlight the need for more standardized experimental approaches and well-designed clinical studies to better validate the therapeutic potential of natural compounds in NCDs.

3. Applications, challenges and future directions of natural products

Clinical applications. In recent years, clinical evidence for natural products in NCDs has gradually accumulated, with *Ginkgo biloba* extract showing the most robust support. Dong *et al* (177,178) reported that intravenous ginkgolides improved prognosis in acute ischemic stroke and reduced recurrence within 72 h in patients with intracranial arterial stenosis. A recent meta-analysis of 782 patients with mild dementia, confirmed benefits in cognition, daily living activities, global assessment and quality of life (179). Other natural products have also shown promise. Curcumin treatment has markedly improved behavioral symptoms in AD (180,181); however, a meta-analysis by Zhu *et al* (182) suggested greater efficacy for improving cognition in the elderly than for alleviating symptoms of AD or schizophrenia. Importantly, formulations designed to enhance curcumin bioavailability have shown encouraging outcomes. In a U.S. 18-month randomized, double-blind trial, oral theracurmin (commercial curcumin formulation; 90 mg twice daily) notably improved verbal and visual memory and attention, with PET imaging showing reduced amyloid and tau deposition (180). RES has been associated with improved cerebrovascular reactivity and inflammatory biomarkers. In trials of mild to moderate AD, long-term supplementation lowered cerebrospinal fluid MMP9, TREM2, Aβ40 and plasma Aβ40, suggesting anti-inflammatory and neuroprotective mechanisms (183,184). Beyond these examples, clinical evidence for other compounds remains limited. Salidroside has shown cognitive benefits under stress in small observational studies

but has not been validated in MCI or dementia. Research on ginsenosides, BBR and other agents is largely restricted to preclinical and mechanistic studies, with robust clinical validation still lacking.

Current major challenges. Despite growing evidence, the clinical translation of natural products faces major challenges. First, existing evidence remains weak and inconsistent. Most trials are limited to small sample sizes, short follow-up and inadequate randomization or blinding, leading to low statistical power. Even large-scale trials yield divergent findings: i) GuidAge (n>2,800; 5-year follow-up); and ii) GEMS (n>3,000; 6-year follow-up) found no effect of *Ginkgo biloba* extract on reducing progression from MCI or normal aging to dementia. Likewise (185,186), 6- to 12-month placebo-controlled trials failed to show cognitive improvement with curcumin in AD or older adults (187). Although RES increases cerebral blood flow in a dose-dependent manner, studies by Wightman *et al* (188) and Kennedy *et al* (189) observed no cognitive benefits. Collectively, current clinical evidence remains insufficient to support definitive conclusions regarding therapeutic efficacy.

Second, the complexity of active components obscures mechanisms. Natural products usually contain multiple active compounds which may act synergistically or antagonistically. Moreover, differences in origin, processing and extraction can further alter composition. This variability complicates the elucidation of mechanisms, targets and pharmacokinetics, and introduces uncertainties regarding safety and drug interactions. For example, *Ginkgo* may increase bleeding risk, high-dose RES can cause weight loss and gastrointestinal symptoms, and BBR may disrupt drug metabolism by altering hepatic enzymes and transporters.

Third, standardization and quality control remain inadequate. Growth conditions, harvest time, processing and extraction methods all affect content and stability of active compounds, undermining reproducibility. While modern methods such as ultrasonic and microwave extraction improve efficiency, ensuring both stability and efficacy of active compounds remains a challenge.

Taken together, these limitations not only restrict the reproducibility of findings, but also represent major barriers to the clinical translation and standardized application of natural products in NCDs.

Future directions. Future research on natural products for NCDs must advance on multiple fronts. Strengthening clinical evidence is top priority; large-sample, multicenter, long-term randomized clinical trials should be undertaken, incorporating both cognitive scales and biomarkers as endpoints to comprehensively assess efficacy and mechanisms. In parallel, modern technologies offer new opportunities. Network pharmacology and systems biology can illuminate multi-target, multi-pathway features at the systems level, facilitating the identification of key compounds and core networks. Nano-delivery systems provide solutions to poor solubility and bioavailability, enhancing stability and targeting to improve efficacy while minimizing off-target effects. Finally, the rise of precision medicine opens avenues for tailored applications in specific populations and disease stages. Integration of genomics and biomarker studies may enable individualized interventions, boosting efficacy while reducing adverse effects. In summary, the development of natural products for NCDs will rely on interdisciplinary collaboration and technological innovation, spanning evidence validation, mechanistic exploration, formulation optimization and personalized application, ultimately paving the way for standardized clinical implementation.

4. Conclusion

Natural products exhibit multi-target and multi-pathway advantages in the management of NCDs. Compounds such as ginkgolides, ginsenosides, curcumin, RES, salidroside and BBR have shown cognitive benefits in preclinical models and some clinical studies. However, current evidence remains limited and inconsistent, constrained by small sample sizes, short follow-up, compositional complexity and inadequate quality control, leaving clinical consensus elusive. Future efforts should focus on large, multicenter randomized trials, integrating cognitive endpoints with biomarkers to better establish efficacy and mechanisms. Advances in network pharmacology, systems biology and nano-delivery may clarify targets, optimize formulations and overcome bioavailability barriers. The rise of precision medicine further offers opportunities for individualized application across populations and disease stages. In summary, natural products for NCDs remain at a stage of 'high potential but insufficient evidence'. Advances in evidence-based validation and technological innovation will be essential to bridge this gap and establish their role in prevention and management.

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Authors' contributions

WL conceived the study and drafted the manuscript. WW, XH and YL contributed to literature analysis and interpretation, and participated in manuscript writing and revision; WW also prepared the figures. QH and GG revised the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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