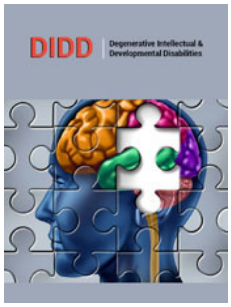
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Mini review

Plant-Derived Bioactive Compounds as Neuroprotective and Cognitive-Enhancing Agents: Sirtuin 1 As A Convergent Mechanism and the Gut-Microbiota-Brain Axis - A Mini Review



Qiancheng Mao[1], Suyun Li[1] and Haiyan Yang[2]

[1]Sun Yat-sen University, China

[2]Yunlin Clinic, China

***Corresponding author:** Qiancheng Mao, Sun Yat-sen University, China

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Abstract

Plant-derived bioactive compounds have long been recognized as a rich source of pharmacologically active molecules, and a growing body of evidence points to their potential to protect the brain and to preserve cognitive function. This mini review summarizes the principal classes of plant secondary metabolites -polyphenols and flavonoids, alkaloids, terpenoids and isothiocyanate derivatives - and their neuroprotective actions against oxidative stress, neuroinflammation, mitochondrial dysfunction and abnormal protein aggregation, which are shared pathogenic features of neurodegenerative and neurodevelopmental disorders. Representative compounds such as curcumin, resveratrol, quercetin, epigallocatechin gallate (EGCG), berberine, sulforaphane and ginsenosides, together with the botanical cognitive enhancers *Bacopa monnieri* and *Centella asiatica*, are discussed with respect to their mechanisms of action and preclinical evidence.

We then focus on sirtuin 1 (SIRT1), an NAD+-dependent deacetylase that has emerged as a convergent molecular node for these compounds: curcumin, resveratrol, quercetin, EGCG, berberine, sulforaphane and ginsenosides have each been reported to restore or enhance SIRT1 expression and activity, and SIRT1-mediated deacetylation of PGC-1α, FOXO3a, p53 and the p65 subunit of NF-κB provides a mechanistic link between energy metabolism, antioxidant defense, inflammatory control and synaptic function. Because SIRT1 also governs neural progenitor proliferation and differentiation, its modulation is of particular interest for intellectual and developmental disabilities. We further examine the gut-microbiota-brain axis, in which lipopolysaccharide (LPS) released by Gram-negative bacteria behaves as an endogenous SIRT1 inhibitor that is toxic to the brain and drives neuroinflammation when intestinal barrier integrity is lost, whereas microbial metabolites such as butyrate and polyphenol catabolites restore SIRT1 activity. Although the translational potential of these compounds remains limited by poor bioavailability and the scarcity of rigorous clinical trials, targeting SIRT1 - both directly and through the gut microbiota - offers a rational framework for the development of preventive and adjunctive strategies for cognitive impairment and neurodegeneration.

Keywords: Phytochemicals; Polyphenols; Neuroprotection; Cognitive function; Neurodegeneration; Sirtuin 1; Gut-microbiota-brain axis; Lipopolysaccharide; Neurodevelopment and Curcumin

Abbreviations: EGCG: Epigallocatechin Gallate; SIRT1: Sirtuin 1; AD: Alzheimer's Disease; PD: Parkinson's Disease; LPS: Lipopolysaccharide; IDD: Intellectual and Developmental Disabilities; CNS: Central Nervous System

Introduction

Plant secondary metabolites -also termed phytochemicals or specialized metabolites -constitute one of the most productive sources of pharmacologically active molecules known to medicine [1,2]. Historically, medicinal plants have furnished a substantial proportion of

approved drugs, and their diverse chemical scaffolds continue to inspire modern drug discovery [1,3]. Over the past two decades, attention has increasingly turned to the capacity of dietary and medicinal plant compounds to modulate the processes that underlie age-related cognitive decline and neurodegeneration, including oxidative stress, chronic neuroinflammation, mitochondrial dysfunction and abnormal protein aggregation [4,5].

Two conceptual developments now justify a reappraisal of this literature. The first is the recognition that many of the most frequently cited plant compounds - including curcumin, resveratrol, quercetin, EGCG, berberine, sulforaphane and the ginsenosides -converge on a single NAD+-dependent deacetylase, sirtuin 1 (SIRT1) [6,7]. Rather than acting through unrelated antioxidant chemistry, these chemically diverse molecules appear to recruit a common upstream regulator that couples cellular energy status to transcriptional programmes of mitochondrial biogenesis, antioxidant defense, inflammatory resolution and synaptic plasticity [7,8].

SIRT1 activity declines with age and with cellular NAD+ availability, and reduced SIRT1 signaling has been documented in the affected brain regions of patients with Alzheimer's disease (AD) and Parkinson's disease (PD), as well as in animal models of cognitive impairment [7,8]. The second development is the appreciation that the gut microbiota is a continuous source of neuroactive bacterial molecules, most notably the Lipopolysaccharide (LPS) of Gram-negative bacteria. LPS is toxic to the brain, sustains microglial activation and neuroinflammation, and acts as an endogenous inhibitor of SIRT1, so that diet- and microbiota-dependent changes in LPS burden may set the threshold at which SIRT1-dependent neuroprotection operates [9,10]. Together, these observations place SIRT1 at the interface between plant chemistry, host metabolism and the gut-microbiota-brain axis.

These mechanisms are particularly relevant to populations with intellectual and developmental disabilities (IDD), who are at elevated risk of developing neurodegenerative conditions such as dementia at an earlier age than the general population [4]. This excess risk is not fully explained by comorbidity, and converging evidence implicates shared substrates - impaired mitochondrial bioenergetics, chronically elevated oxidative and inflammatory tone, and altered NAD+ metabolism - in both neurodevelopmental and neurodegenerative conditions [7,11]. Because SIRT1 regulates neural stem and progenitor cell self-renewal, lineage commitment and dendritic and synaptic maturation, pharmacological or nutritional modulation of SIRT1 activity is a plausible route to interventions that act across the developmental-to-degenerative continuum rather than at a single disease stage [11]. Compounds that attenuate neuroinflammation and oxidative injury, or that support mitochondrial and synaptic function, therefore represent attractive candidates for preventive and adjunctive interventions in these vulnerable groups.

The aim of this mini review is to summarize the principal classes of plant-derived bioactive compounds and the preclinical evidence for their neuroprotective and cognitive-enhancing effects, to examine SIRT1 as a convergent mechanism of action for the most widely studied of these compounds, and to consider how bacterial LPS and the gut-microbiota-brain axis modify this mechanism. We conclude by outlining the translational challenges - bioavailability, target engagement, dose-response and clinical trial design - that will determine whether SIRT1-directed phytochemical strategies can be developed for clinical use.

Literature for this narrative mini review was identified by searching PubMed for publications between January 2000 and June 2025 using combinations of the terms 'phytochemical', 'polyphenol', 'curcumin', 'resveratrol', 'quercetin', 'epigallocatechin gallate', 'berberine', 'sulforaphane', 'ginsenoside', '*Bacopa monnieri*', *'Centella asiatica*', 'sirtuin 1', 'SIRT1', 'lipopolysaccharide', 'gut-microbiota-brain axis', 'neurodegeneration', 'cognitive impairment' and 'neurodevelopment'. Priority was given to mechanistic studies in neuronal and glial systems, in vivo studies with behavioral endpoints, systematic reviews and meta-analyses, and clinical trials. No language restriction was applied. The review is narrative rather than systematic, and no formal risk-of-bias assessment was performed.

Major Classes of Plant Bioactive Compounds

The bioactive constituents of plants are conventionally grouped by biosynthetic origin into several major classes. Phenolic compounds, including phenolic acids and the large family of flavonoids (flavonols, flavones, flavanones, flavan-3-ols and anthocyanidins), are the most widely distributed and are best known for their antioxidant and anti-inflammatory properties [4,5]. Alkaloids are nitrogen-containing molecules with potent activity against a range of molecular targets, including enzymes and neurotransmitter receptors [3].

Terpenoids - of which the triterpene saponins, such as the ginsenosides, form an important subfamily - display broad biological activities, while the glucosinolate-derived isothiocyanates, such as sulforaphane, are characteristic of cruciferous vegetables [3]. Within the central nervous system (CNS), these compounds act on multiple, often overlapping pathways, a pleiotropy that is characteristic of plant-derived agents and that distinguishes them from single-target synthetic drugs [3]. Importantly, this pleiotropy is not unstructured: several of the pathways engaged by polyphenols, alkaloids and terpenoids - mitochondrial biogenesis, antioxidant response element-driven gene expression, NF-κB-dependent cytokine transcription and AMPK-dependent energy sensing – are themselves deacetylase-dependent, which provides a mechanistic explanation for why compounds of unrelated structure nevertheless produce overlapping transcriptional signatures [6,7].

Polyphenols and Flavonoids in Neurodegeneration

Polyphenols are the most extensively studied class of neuroprotective phytochemicals. Preclinical and epidemiological evidence suggests that diets rich in polyphenols are associated with slower cognitive decline and a reduced risk of neurodegenerative disease [4]. Mechanistically, polyphenols counteract oxidative stress both by directly scavenging reactive oxygen and nitrogen

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species and by upregulating endogenous antioxidant defenses, while simultaneously suppressing neuroinflammatory signaling cascades such as nuclear factor kappaB (NF-κB) and the NLRP3 inflammasome [5]. Flavonoids also modulate energy-sensing and mitochondrial-biogenesis pathways, including AMPK and PGC-1α, which are increasingly recognized as central to neuronal resilience and cognitive function [12]. SIRT1 is now recognized as an integral component of these pathways rather than a parallel one: SIRT1 deacetylates and activates PGC-1α, and flavonoid-induced AMPK activation increases cellular NAD+ availability, thereby reinforcing SIRT1 activity in a feed-forward loop [12,13]. Quercetin, one of the most abundant dietary flavonols, has been shown to exert anti-inflammatory and neuroprotective effects that are relevant to brain health, supporting its consideration as a nutraceutical for cognitive protection [14]. Quercetin additionally increases SIRT1 expression and activity in several ageing-related disease models, and SIRT1 has been proposed as the principal mediator of its anti-ageing actions [13].

Curcumin

Curcumin, the principal curcuminoid of turmeric (*Curcuma longa*), is one of the most intensively investigated plant-derived neuroprotective agents. It interferes with multiple molecular targets, including the transcription factors NF-κB and STAT3, inflammatory cytokines and the amyloid-β and tau pathways that are central to AD. A recent narrative review of the neuroprotective role of curcumin, spanning molecular pathways to clinical translation, concluded that curcumin reduces oxidative and inflammatory injury, promotes neurogenesis and modulates synaptic function in preclinical models, although its clinical translation is constrained by poor bioavailability [15]. Approaches that enhance the delivery and systemic exposure of curcumin are therefore regarded as essential for its therapeutic development [15].

Curcumin is also one of the best-documented phytochemical activators of SIRT1. In cellular and animal models of AD, curcumin and its analogue bisdemethoxycurcumin increase SIRT1 expression and activity, and this increase is accompanied by deacetylation of the p65 subunit of NF-κB, reduced cytokine transcription and attenuated amyloid-β-induced injury [6]. In peripheral tissues, curcumin has similarly been reported to act through the SIRT1-FOXO1 and SIRT1/PGC-1α axes to suppress oxidative stress and apoptosis, indicating that the SIRT1-dependent arm of its activity is not confined to the CNS [6,7]. This has a practical consequence for formulation: because curcumin's oral bioavailability is very low, the SIRT1-dependent effects observed in vitro are unlikely to be reproduced by unformulated turmeric powder, and the development of phospholipid complexes, nanoparticles or piperine-containing preparations should be evaluated with SIRT1 target-engagement readouts rather than with plasma curcumin concentrations alone [15].

Resveratrol

Resveratrol, a stilbene present in grapes, red wine and several berries, has attracted attention for its ability to modulate sirtuins and other longevity-associated pathways. It is the prototypical phytochemical SIRT1 activator: resveratrol increases SIRT1-mediated deacetylation of PGC-1α, thereby enhancing mitochondrial biogenesis and oxidative phosphorylation in a SIRT1-dependent manner [16], and SIRT1 activation has been shown to be required for its beneficial effects on cognitive performance in rodent models [17]. A recent synthesis of the resveratrol-SIRT1 literature in neurodegenerative disease concluded that the interaction is bidirectional and cell-type dependent, with SIRT1 mediating both the anti-inflammatory and the adaptive-immune actions of resveratrol in AD models [18]. In the context of AD, resveratrol has been shown to regulate neuroinflammation and to induce adaptive immune responses, and it has been evaluated in clinical studies as a potential disease-modifying agent [19]. As with curcumin, however, the clinical utility of resveratrol is limited by its low oral bioavailability and rapid metabolism, so that continuous efforts have been directed towards improved formulations and dosing regimens [19]. A further caveat deserves emphasis: the direct activation of SIRT1 by resveratrol in cell-free assays has been questioned because some fluorogenic peptide substrates produce artefactual activation, and the concentrations required for direct enzymatic activation in vitro generally exceed those achieved in plasma after oral dosing [16,18]. Indirect mechanisms - AMPK activation, increased NAD+ availability and reduced inflammatory signaling - are therefore likely to account for a substantial part of the SIRT1-dependent effects observed in vivo, and this distinction should be made explicit when SIRT1 activation is claimed as a mechanism.

Green Tea Catechins (EGCG)

EGCG, the most abundant catechin in green tea (*Camellia sinensis*), exhibits antioxidant, anti-inflammatory and anti-amyloidogenic activities. It targets several processes implicated in brain ageing, including neuroinflammation, oxidative stress and the accumulation of misfolded proteins, and it has been proposed to have therapeutic potential for neuroprotection and for age-related neurodegenerative conditions [20]. EGCG also interacts with the gut microbiota, an emerging determinant of brain function, which may contribute to its systemic neuroprotective effects [21]. EGCG has been reported to upregulate SIRT1 and to require intact SIRT1/AMPK signaling for several of its antioxidant and anti-inflammatory actions [22], and SIRT1-dependent deacetylation has been proposed to contribute to its neuroprotective and anti-amyloidogenic effects [20]. As with resveratrol, however, the direction and magnitude of the EGCG-SIRT1 interaction depend on cell type, concentration and exposure time, and the low systemic bioavailability of catechins means that gut-level effects may be quantitatively more important than direct CNS effects [20,21].

Berberine

Berberine, an isoquinoline alkaloid obtained from Berberis and *Coptis species*, has been studied for its effects on cognition and has been shown to alleviate AD-like pathology by activating autophagy and inhibiting ferroptosis through the JNK-p38 MAPK signaling pathway [23]. Of direct relevance to the present review, berberine also ameliorates LPS-induced cognitive impairment in mice

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through the SIRT1/NRF2/NF-κB signaling axis: treatment restored hippocampal SIRT1 and NRF2 expression, suppressed NF-κB activation and microglial inflammatory signaling, and normalized behavioral performance in LPS-challenged animals [10]. This study is instructive because it demonstrates, within a single experimental system, the full logic proposed here - an exogenous bacterial endotoxin lowers SIRT1 activity, a plant alkaloid restores it, and the restoration is accompanied by recovery of cognitive function. Berberine is, however, a substrate of P-glycoprotein and has limited CNS penetration, which constrains the interpretation of systemic dosing studies and favours the development of delivery strategies that increase brain exposure [23].

Sulforaphane

Sulforaphane, an isothiocyanate derived from glucoraphanin in broccoli and other cruciferous vegetables, is best known as an activator of the Keap1-Nrf2-ARE pathway, which governs the expression of phase II detoxifying and antioxidant enzymes. Through this and other mechanisms, sulforaphane protects neurons against oxidative and inflammatory injury and has demonstrated neuroprotective effects in a range of experimental models [24]. Its favorable safety profile and well-characterized mechanism of action have made sulforaphane a leading candidate among dietary chemopreventive and neuroprotective phytochemicals [24]. SIRT1 has been incorporated into this mechanistic model: sulforaphane upregulates the SIRT1/PGC-1α/Nrf2 axis, and SIRT1 activity is required for part of its antioxidant and anti-apoptotic effects [25]. A recent mechanistic review of sulforaphane in neurodegenerative disease accordingly lists SIRT1 alongside Nrf2, NF-κB, TrkB, MAPK and JAK/STAT as the principal pathways through which this isothiocyanate acts [26]. Because sulforaphane bioavailability is strongly influenced by the co-consumed myrosinase activity of the food matrix and by individual gut microbial glucosinolate metabolism, inter-individual variability in the SIRT1-Nrf2 response is expected and should be addressed in trial design [24,27].

Ginsenosides

Ginsenosides are triterpenoid saponins from Panax ginseng and related species. Individual ginsenosides have been shown to improve cognitive impairments and pathological changes in models of AD; for example, ginsenoside RK1 ameliorates cognitive deficits through stimulation of the AMPK/Nrf2 signaling pathway [28]. These findings illustrate the ability of a single saponin to engage both metabolic and antioxidant-signaling nodes that are relevant to neuronal survival. Ginsenoside Rc has been characterized as a direct SIRT1 activator that promotes energy metabolism in both cardiomyocytes and neurons [29], and ginsenoside Rg1 improves mitochondrial function and AD-like pathology by suppressing miR-9-5p and thereby relieving SIRT1 repression [30]. The ginsenosides therefore illustrate two mechanistically distinct routes to the same node-direct allosteric activation and relief of microRNA-mediated repression-which may explain why different ginsenosides produce partially non-overlapping spectra of activity despite sharing a common aglycone scaffold [29,30].

Botanical Cognitive Enhancers: *Bacopa monnieri* and *Centella asiatica*

Two traditional botanical medicines deserve particular mention for their documented cognitive and neuroprotective effects. *Bacopa monnieri* has been used for centuries in Ayurvedic medicine to enhance memory. A systematic review of its neuroprotective and cognitive-enhancing effects concluded that its activity is mediated largely through the modulation of inflammation, oxidative stress, mitochondrial dysfunction and apoptosis [31]. *Centella asiatica*, another long-used botanical, has been the subject of detailed phytochemical characterization, and its constituents have demonstrated mechanisms of neuroprotection and cognitive enhancement in experimental studies [32]. Together, these botanicals exemplify how traditional knowledge can guide the identification of cognitively active plant preparations. Unlike the compounds discussed above, neither has been shown to act primarily through SIRT1: their activity is attributed to mixtures of saponins and other constituents acting on overlapping antioxidant and anti-inflammatory pathways, and SIRT1-dependent mechanisms remain to be established. They are included here as a contrast rather than as examples of the SIRT1-centred model, and they illustrate how difficult it is to attribute the effects of multi-constituent extracts to a single molecular target [3].

Sirtuin 1 as a Convergent Mechanism of Action

SIRT1 biology and downstream targets

SIRT1 is the most extensively studied of the seven mammalian sirtuins. It is an NAD+-dependent protein deacetylase that removes acetyl groups from histone H4 lysine 16 and histone H3 lysine 9 and, more relevant to short-term regulation, from transcription factors and co-regulators including PGC-1α, FOXO1/FOXO3a, p53, the p65 subunit of NF-κB, Nrf2, PPARγ and tau [7,8]. Through this repertoire it promotes mitochondrial biogenesis and oxidative phosphorylation, reinforces FOXO3a- and Nrf2-dependent antioxidant transcription, restrains NF-κB-driven cytokine expression by deacetylating p65, favors non-amyloidogenic processing of the amyloid precursor protein, promotes tau deacetylation and clearance, and modulates BDNF-dependent synaptic plasticity [7,8,17]. Because catalysis is strictly NAD+-dependent, SIRT1 functions as a metabolic sensor that converts changes in redox and energy state into durable transcriptional programmes, a property that distinguishes it from classical antioxidant enzymes [7]. Activity declines with age, with reduced NAD+ availability and under chronic inflammation, and lower SIRT1 has been reported in the affected brain regions in AD and PD and in the corresponding models [7,8] -precisely the condition in which dietary SIRT1-activating phytochemicals would be expected to be most effective, and a rationale for preventive rather than merely symptomatic use.

SIRT1 in neurodevelopment: relevance to intellectual and developmental disabilities

SIRT1 is expressed early in the developing nervous system, where it regulates neural stem and progenitor cell self-renewal,

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the balance between neuronal and glial lineage commitment, and the maturation of dendrites and synapses [11]. Genetic or pharmacological manipulation of SIRT1 in the developing cortex alters progenitor pool size and neuronal migration, and SIRT1-dependent deacetylation of transcription factors such as FOXO3a and p53 influences the survival of newly generated neurons [11]. In addition, SIRT1 couples developmental redox and metabolic status to epigenetic programmes, so that insults that deplete NAD+ - hypoxia, inflammation, oxidative stress - are translated into lasting changes in chromatin acetylation and gene expression [7,11]. Several conditions associated with intellectual disability, including Down syndrome, Rett syndrome and fragile X syndrome, display mitochondrial dysfunction, elevated oxidative stress and altered NAD+ metabolism, and preclinical studies in corresponding models have reported that NAD+ repletion or SIRT1 activation improves mitochondrial function, synaptic plasticity and behavioral outcomes [11,33]. These observations remain preliminary and have not been tested in clinical populations, but they identify SIRT1 as a mechanistically plausible target for interventions that span neurodevelopment and neurodegeneration.

A shared node across chemically unrelated compounds

Figure 1 integrates these observations into a single model of the direct and gut-mediated routes to SIRT1 activation, and Table 1 summarizes the SIRT1-related evidence for each compound. Three features are noteworthy. First, the evidence is not uniform: for resveratrol, quercetin, berberine and the ginsenosides, SIRT1 dependence has been demonstrated with genetic or pharmacological loss-of-function approaches, whereas for curcumin, EGCG and sulforaphane the evidence is largely correlative, based on parallel changes in SIRT1 expression and downstream deacetylation events. Second, the direction of the effect is context dependent: in inflammatory or metabolic stress models SIRT1 activation is protective, whereas constitutive SIRT1 overexpression can favour tumor cell survival and impair some forms of immune responses, which argues for transient, moderate and inflammation-targeted activation rather than maximal chronic activation [6,7]. Third, the effective concentrations in vitro frequently exceed those achievable in plasma, which is the single most important obstacle to translating SIRT1-based mechanisms into clinical benefit [6,15].

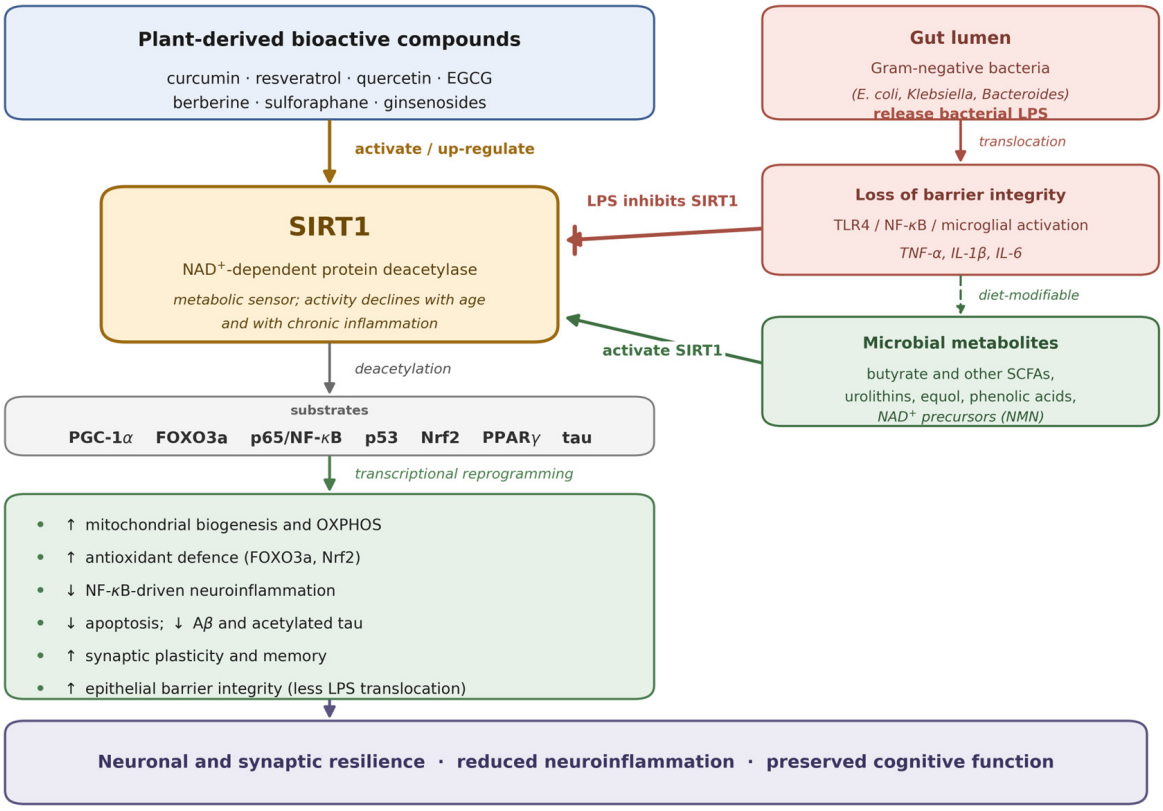


Figure 1: Sirtuin 1 (SIRT1) as a convergent node linking plant-derived bioactive compounds, bacterial lipopolysaccharide and the gut-microbiota-brain axis. Plant-derived compounds (blue) activate SIRT1 directly; SIRT1 deacetylates PGC-1α, FOXO3a, p65/NF-κB, p53, Nrf2, PPARγ and tau, thereby coordinating mitochondrial biogenesis, antioxidant defence, inflammatory resolution, reduced apoptosis and Aβ/tau pathology, synaptic plasticity and intestinal barrier integrity. LPS released by Gram-negative commensals after loss of barrier integrity inhibits SIRT1 (red), whereas microbiota-derived butyrate, polyphenol catabolites and NAD+ precursors activate it (green).

EGCG: Epigallocatechin-3-Gallate; LPS: Lipopolysaccharide; NMN: Nicotinamide Mononucleotide; OXPHOS: Oxidative Phosphorylation; SCFA: Short-Chain Fatty Acid

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Table 1: Representative plant-derived bioactive compounds: sources, principal neuroprotective mechanisms and SIRT1-related evidence. Supporting references are given in Sections 3-11.

Compound	Dietary source / chemical class	Principal neuroprotective mechanisms	SIRT1-related evidence	Evidence level
Curcumin	Turmeric (*Curcuma longa*) / curcuminoid polyphenol	NF-κB and STAT3 inhibition; Aβ and tau pathways; neurogenesis	Increases SIRT1 expression and activity; p65 deacetylation (largely correlative)	Preclinical; small trials
Resveratrol	Grapes, red wine, berries / stilbene	SIRT1-PGC-1α; anti-inflammatory; adaptive immunity	Prototypical activator; SIRT1 required for cognitive benefit	Preclinical; phase II trials
Quercetin	Onions, apples, tea / flavonol	NF-κB and NLRP3 suppression; AMPK activation	Increases SIRT1; SIRT1 proposed as principal mediator	Preclinical
EGCG	Green tea / flavan-3-ol	Anti-amyloidogenic; antioxidant; microbiota modulation	Upregulates SIRT1; SIRT1/AMPK-dependent effects	Preclinical
Berberine	Berberis, Coptis / isoquinoline alkaloid	Autophagy activation; anti-ferroptotic; JNK-p38 inhibition	Restores hippocampal SIRT1 in LPS-challenged mice	Preclinical
Sulforaphane	Broccoli, cruciferous vegetables / isothiocyanate	Keap1-Nrf2-ARE activation; NF-κB suppression	Upregulates SIRT1/PGC-1α/Nrf2 axis	Preclinical; early clinical
Ginsenosides	Panax ginseng / triterpenoid saponin	AMPK/Nrf2; mitochondrial function; neurogenesis	Rc is a direct SIRT1 activator; Rg1 relieves miR-9-5p repression of SIRT1	Preclinical
Bacopa monnieri	*Bacopa monnieri* / saponins (bacosides)	Anti-inflammatory; mitochondrial; anti-apoptotic	Not established (indirect)	Systematic review; small trials
Centella asiatica	*Centella asiatica* / triterpenoid saponins	Antioxidant; mitochondrial; cognitive enhancement	Not established (indirect)	Preclinical; small trials

SIRT1: Sirtuin 1; LPS: Lipopolysaccharide; AD: Alzheimer's Disease; NF-kappaB: Nuclear Factor KappaB; PGC-1alpha: Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-alpha

The Gut-Microbiota-Brain Axis: Bacterial LPS as an Endogenous SIRT1 Inhibitor

The distal intestine harbours a dense microbial community whose composition is strongly influenced by diet. Gram-negative members, including *Escherichia coli*, *Klebsiella spp.* and several Bacteroidetes, constitutively shed LPS, one of the most potent activators of innate immunity known [9,27]. Under conditions of homeostasis only trace amounts reach the portal circulation; when epithelial barrier integrity is compromised by ageing, dysbiosis, high-fat feeding, psychological stress or chronic inflammation, translocation increases and LPS, bound by LPS-binding protein, is transferred to CD14 and Toll-like receptor 4 (TLR4), triggering MyD88-dependent NF-κB activation and release of TNF-α, interleukin-1β and interleukin-6 [27]. Within the CNS, LPS activates microglia and disrupts blood-brain barrier tight junctions, producing a neuroinflammatory milieu associated with sickness behavior, depressive-like phenotypes and impaired learning and memory [9,10]. This diet- and microbiota-dependent endotoxin burden is now regarded as one of the mechanisms linking the gut to age-related cognitive decline (Figure 1).

Critically for the present argument, LPS is an endogenous inhibitor of SIRT1. In the postnatal rat brain, systemic LPS reduced SIRT1 and Nrf2 expression and increased oxidative injury, whereas stimulation of the SIRT1/Nrf2 axis restored antioxidant defenses and attenuated neuronal damage [9]. In mice, LPS-induced cognitive impairment was accompanied by hippocampal suppression of SIRT1 and NRF2 and by NF-κB activation, and restoring SIRT1 signaling reversed both the inflammatory and the behavioral phenotype [10]. The relationship is reciprocal: p65 is a direct SIRT1 substrate, so NF-κB activation both results from and reinforces the loss of SIRT1, creating a self-amplifying loop that is not interrupted by antioxidant scavengers alone but is amenable to deacetylase-based intervention [7,10]. SIRT1 also protects the barrier itself, since NAD+-SIRT1 signaling preserves epithelial tight junction integrity and enterocyte mitochondrial homeostasis; loss of SIRT1 therefore increases permeability and endotoxin translocation, closing a vicious circle [34].

The loop is, however, diet-modifiable in both directions. Butyrate and other short-chain fatty acids increase SIRT1 activity and NAD+ availability, and soybean genistin ameliorates metabolic pathology by driving butyrate production and activating SIRT1 signaling [35]. Nicotinamide mononucleotide reverses D-galactose-induced neurodegeneration while simultaneously improving intestinal barrier function in a SIRT1-dependent manner [33], and polyphenols are converted by colonic bacteria into better-absorbed catabolites - urolithins, equol and phenolic acids - that modulate neuroinflammation and neuromodulation [21]. Hormetic plant-derived stressors acting through Nrf2 and SIRT1 have been proposed to reinforce redox resilience specifically in gut-brain axis disorders [27]. These compounds therefore act on SIRT1 at two levels: directly, within neurons and glia, and indirectly, by restoring barrier integrity and shifting microbial metabolism towards SIRT1-activating catabolites, which helps to explain why whole-plant preparations and fibre-rich diets often outperform isolated compounds at equivalent nominal doses [3,21].

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These considerations are testable. Plasma LPS and LPS-binding protein, soluble CD14, intestinal fatty-acid-binding protein and zonulin are accessible markers of endotoxin burden and barrier integrity, and faecal short-chain fatty acid profiles and microbiome composition may serve as stratification variables; because baseline endotoxin burden probably modifies the magnitude of response, trials that ignore it may underestimate effect sizes in high-LPS individuals [27,33].

Mechanisms of Neuroprotection

Despite their structural diversity, plant bioactive compounds converge on a limited set of neuroprotective mechanisms. The most consistently reported are the attenuation of oxidative stress and neuroinflammation, the preservation of mitochondrial function and energy homeostasis, and the inhibition of apoptotic and ferroptotic cell death [5,12]. Flavonoids in particular modulate the AMPK/PGC-1α axis and interconnected pathways that regulate cellular energy metabolism and neuronal survival [12]. As summarized above, SIRT1 provides a molecular explanation for the convergence of these mechanisms, since PGC-1α, FOXO3a, p53 and p65 are shared substrates through which a single deacetylase can simultaneously influence mitochondrial biogenesis, antioxidant gene expression, apoptosis and cytokine transcription [7,8]. In addition, many phytochemicals exert indirect effects on the brain through the gut-microbiota-brain axis: polyphenols are metabolized by intestinal bacteria into bioactive catabolites that can influence neuroinflammation and neuromodulation, establishing a bidirectional interaction between these compounds, the microbiome and the CNS [21]. Conversely, bacterial LPS suppresses SIRT1 and disrupts barrier integrity, so that the net effect of a given compound on central SIRT1 activity reflects both its direct pharmacological action and its ability to reduce endotoxin burden [10,34]. The pleiotropic and often synergistic nature of these mechanisms helps to explain why whole-plant preparations frequently produce effects that cannot be attributed to a single constituent or target [3].

Limitations and Future Directions

Several limitations qualify these conclusions. Bioavailability remains the principal constraint: curcumin undergoes extensive phase II metabolism and has negligible systemic exposure without formulation, EGCG is unstable at intestinal pH, resveratrol is rapidly sulfated and glucuronidated, and the ginsenosides and berberine are actively effluxed. Plasma concentrations after oral dosing are typically one to three orders of magnitude below those used in the cell-culture experiments that established SIRT1 activation, a discrepancy rarely addressed when SIRT1 is invoked as a mechanism [6,15]. Second, SIRT1 activation is generally inferred from protein abundance or downstream acetylation rather than measured enzymatically, and the available pharmacological tools are imperfect; genetic models, NAD+ measurement and acetylome profiling are needed to establish causality [7]. Third, dose-response is likely to be hormetic and non-monotonic, and the optimal neuroprotective dose may differ from that for metabolic or anti-inflammatory effects [27]. Fourth, SIRT1 activation is not unconditionally desirable: SIRT1 is overexpressed in several malignancies and can promote chemoresistance, so chronic high-level activation requires formal safety evaluation, particularly in pediatric and IDD populations in whom exposure may begin early and continue for decades [7]. Fifth, most human studies are small, short and heterogeneous with respect to preparation, dose and cognitive endpoint, and few have measured target engagement [15,19].

Priorities for future work follow from these limitations. Formulation work should be paired with pharmacodynamic read-outs - acetylation of p65 or PGC-1α in peripheral blood mononuclear cells, NAD+ metabolites and, where feasible, CNS-derived markers - so that target engagement is demonstrated before efficacy is claimed. Trials should be stratified by baseline inflammatory and endotoxin burden and by microbiome composition, and should use outcome measures validated for the population studied rather than generic cognitive screening instruments [11,27]. Mechanistic work should move from single compounds to defined combinations that exploit complementary routes to SIRT1 activation, including NAD+ precursors, gut-derived butyrate and direct activators, and should test whether these act additively at lower individual doses. Finally, because the same pathways operate in development and in ageing, longitudinal designs beginning in childhood in IDD cohorts would provide information that studies in older adults cannot [11].

Conclusion

Plant-derived bioactive compounds represent a promising and chemically diverse source of neuroprotective and cognitive-enhancing agents. Polyphenols, alkaloids, terpenoids and isothiocyanate derivatives -exemplified by curcumin, resveratrol, quercetin, EGCG, berberine, sulforaphane and ginsenosides, as well as the botanical cognitive enhancers *Bacopa monnieri* and *Centella asiatica* - attenuate oxidative stress and neuroinflammation, support mitochondrial function and engage the gut-microbiota-brain axis. Beyond this descriptive catalogue, the evidence assembled here supports a more specific proposition: SIRT1 is a convergent mechanism through which these chemically unrelated compounds act, and the gut microbiota -through the balance between LPS-driven inhibition and butyrate- and polyphenol-derived activation of SIRT1 - sets the inflammatory and metabolic context in which this mechanism operates.

Framing the pharmacology of these compounds in terms of SIRT1 has three consequences: it identifies a measurable pharmacodynamic endpoint, it explains why combinations and whole-plant preparations may outperform isolated molecules, and it directs attention to the gut as a therapeutic target that is accessible through diet. For populations affected by intellectual, developmental and neurodegenerative disabilities, such compounds offer plausible routes to preventive and adjunctive interventions. Realizing this potential will require improved formulations to overcome poor bioavailability, mechanistic studies in disease-relevant models that establish SIRT1 dependence rather than mere association, stratification by inflammatory and microbial status, and rigorous, well-controlled clinical trials. Further interdisciplinary research is

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warranted to translate the remarkable chemical diversity of plants into safe and effective strategies for protecting the ageing and vulnerable brain.

Author Contributions

S.L. and Q.M. conceived the review; S.L. and H.Y. performed the literature search; S.L. drafted the manuscript; Q.M. revised it critically for intellectual content. All authors read and approved the final manuscript. (To be confirmed by the authors).

Conflict of Interest

The author declares that there is no conflict of interest (Please confirm that this statement applies to all authors).

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