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Polyphenols: Natural food grade biomolecules for treating neurodegenerative diseases from a multi-target perspective

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As natural functional bioactive ingredients found in foods and plants, polyphenols play various antioxidant and anti-inflammatory roles to prevent the development of disease and restore human health. The multi-target modulation of polyphenols provides a novel practical therapeutic strategy for neurodegenerative diseases that are difficult to treat with traditional drugs like glutathione and cholinesterase inhibitors. This review mainly focuses on the efficacy of polyphenols on ischemic stroke, Parkinson's disease and Alzheimer's disease, including *in vivo* and *in vitro* experimental studies. It is further emphasized that polyphenols exert neuroprotective effects primarily through inhibiting production of oxidative stress and inflammatory cytokines, which may be the underlying mechanism. However, polyphenols are still rarely used as medicines to treat neurodegenerative diseases. Due to the lack of clinical trials, the mechanism of polyphenols is still in the stage of insufficient exploration. Future large-scale multi-center randomized controlled trials and in-depth mechanism studies are still needed to fully assess the safety, efficacy and side effects of polyphenols.

KEYWORDS

polyphenols, antioxidant, anti-inflammation, neurodegenerative diseases, efficacy, mechanism

Introduction

Neurodegenerative diseases are a heterogeneous group of diseases characterized by irreversible, progressive degeneration and death of neuronal cells (1). At present, the cause of this kind of disease is still unclear and cannot completely cured yet, which poses a severe challenge to human health and a substantial economic burden. Neurons present in the body can maintain cellular homeostasis by dealing with different stressors (2). However, two conditions usually lead to neuronal death. The first one is when multiple stressors accumulate and exceed the cell's ability to recover, various damages to cells will eventually lead to neuronal death. The formation of higher-order aggregates is a significant cause of neuronal stressor, and eventually triggers consequent cytotoxic events and cell death (3–6). Another cause of neuronal death is the traumatic events, such as ischemic stroke, which usually leads to a massive decrease in neuronal function in the affected area and

subsequently induces acute neuronal cell death (7). In recent years, the improvement of neurodegenerative diseases through natural medicines such as polyphenols has increasingly become a research hotspot.

Polyphenols are secondary plant metabolites with highly diversified chemical structures (8). They are the largest class of plant chemicals. The basic structure of polyphenols is to connect at least one aromatic ring with one or more hydroxyl functional groups (i.e., several hydroxyl groups on the aromatic ring). Thousands of such polyphenol structures have been identified in plants and foods, mainly including flavonoids (60%), phenolic acids (30%), and other polyphenols, such as stilbene and lignans (8, 9). Flavonoids can be divided into anthocyanins, flavan-3-ol, flavonoids, flavanone, and other flavonoid subclasses. Phenolic acid exists in free form in fruits and vegetables, and they often exist in a conjugated state in bran and shell (10–12). Wine and red wine contain stilbene in other polyphenols, and lignans are found in many grains, such as sesame (13, 14). Polyphenols, as a powerful antioxidant, can play an essential role in the treatment of oxidative stress and neuroinflammation-related diseases. It has been found that supplementing antioxidant vitamins and enzymes, such as vitamins C, E, carotene, and other antioxidants, can protect the organism against external stimuli, reduce and eliminate the level of reactive oxygen species (ROS) (14, 15). Recently, the side effects of traditional drugs used to treat neurodegenerative diseases, such as cholinesterase inhibitors and NMDA antagonists, have become more widely recognized (16). Compared to other drugs, polyphenolic natural medicines are often found in our daily diet, and they have fewer side effects. Many plant foods that are common in our daily lives contain polyphenols, such as tea, cocoa, fruits, and vegetables. In addition to this, polyphenols have also been found in traditional Chinese medicine (17).

The preventive and therapeutic effects of polyphenols on neurodegenerative diseases have been investigated in previous studies (18–20). Although there are relatively many studies on polyphenols, the underlying core mechanism of polyphenols in neurodegenerative diseases is still unclear. This review will focus on the effects of polyphenols on neurodegenerative diseases, including cerebral ischemic stroke (CIS), Parkinson's disease (PD), and Alzheimer's disease (AD), which covers both *in vitro* and *in vivo* studies. Furthermore, the underlying mechanisms that polyphenols exert neuroprotective effects are also reviewed.

Effects and mechanisms of polyphenols in the treatment of neurodegenerative diseases

As shown in Figure 1, the pathogenesis of neurodegenerative diseases, as well as the core target and underlying mechanism of polyphenols in the treatment of neurodegenerative diseases are described, including cerebral ischemic stroke (CIS), Parkinson's disease (PD), and Alzheimer's disease (AD). Table 1 further illustrates the type of polyphenols, and the effects and mechanism *in vitro* and *in vivo* experiments.

Cerebral ischemic stroke

Cerebral ischemic stroke is one of the leading causes of disability in the world's population. CIS is caused by the sudden interruption of blood flow to the brain, leading to brain cell death and neuronal damage (35). Because of the poor regenerative capacity of the adult brain, neuronal damage is almost impossible to reverse (36). Therefore, it is essential to reduce the loss of neurons or tissues after CIS (37). Cerebral ischemia/reperfusion (I/R) injury is an important risk factor for stroke because the process of I/R may further aggravate the initial ischemic injury. For this reason, the pathogenesis of CIS has not been fully clarified, and there is a lack of effective treatments (38).

In vitro studies

Oxidative stress caused by excessive ROS production is closely related to the pathogenesis of CIS. At the same time, oxidative stress is one of the most important processes in brain I/R injury and the main risk factor for neural cell apoptosis (39). Excessive ROS production leads to neuronal dysfunction through a variety of mechanisms, including inflammation, cell apoptosis and necrosis (40), which is considered to be the main factor leading to brain damage (41, 42). Resveratrol is a natural plant antitoxin, which has neuroprotective, antioxidant, anti-cancer, and anti-inflammatory properties (43–45). A study has found that resveratrol exerts its protective effects against the damage of oxygen glucose deprivation and reperfusion (OGD/R), at least in part, by promoting mitophagy (23). Resveratrol attenuates OGD/R-induced oxidative stress and preserves mitochondrial function, exerting neuroprotective effects through PINK1/Parkin-mediated mitophagy. Grape seed proanthocyanidins (GSP) are one of the complex flavonoid polymers. Many studies show that GSP have anti-inflammatory, anti-apoptotic, antioxidant, and free radical scavenging properties (29, 46, 47). One study established an OGD/R model using primary brain cell cultures (48). They found that GSP could prevent the damages of OGD/R, inhibit OGD/R-induced cell death and improve cell viability. Pretreatment with GSP can efficiently prevent the cells from almost all inflammatory factors. Another experiment identified the main biological activity of TPE and TPB by high performance liquid chromatography (HPLC) as phenolic acids after grading and purification of crude extracts (21). It was found that TPE and TPB facilitated the translocation of nuclear factor erythroid-2 related factor 2 (Nrf2) to the nucleus and enhanced Nrf2 expression in the nucleus, restored OGD/R-induced oxidative damage in BV2 microglial cells. Pelargonium is a polyphenol extracted from *Phyllanthus amarus*, which has a wide range of biological and pharmaceutical activities, including antioxidant, anti-inflammatory, antithrombotic, and other biological activities. In addition, pelargonium has been found to activate the nuclear factor erythroid-2 related factor 2/heme oxygenase-1 (Nrf2/HO-1) signaling pathway and protect PC12 cells from cytotoxicity, as well as oxidative stress and apoptosis caused by OGD/R (22).

Polyphenols and Neurodegenerative Disease

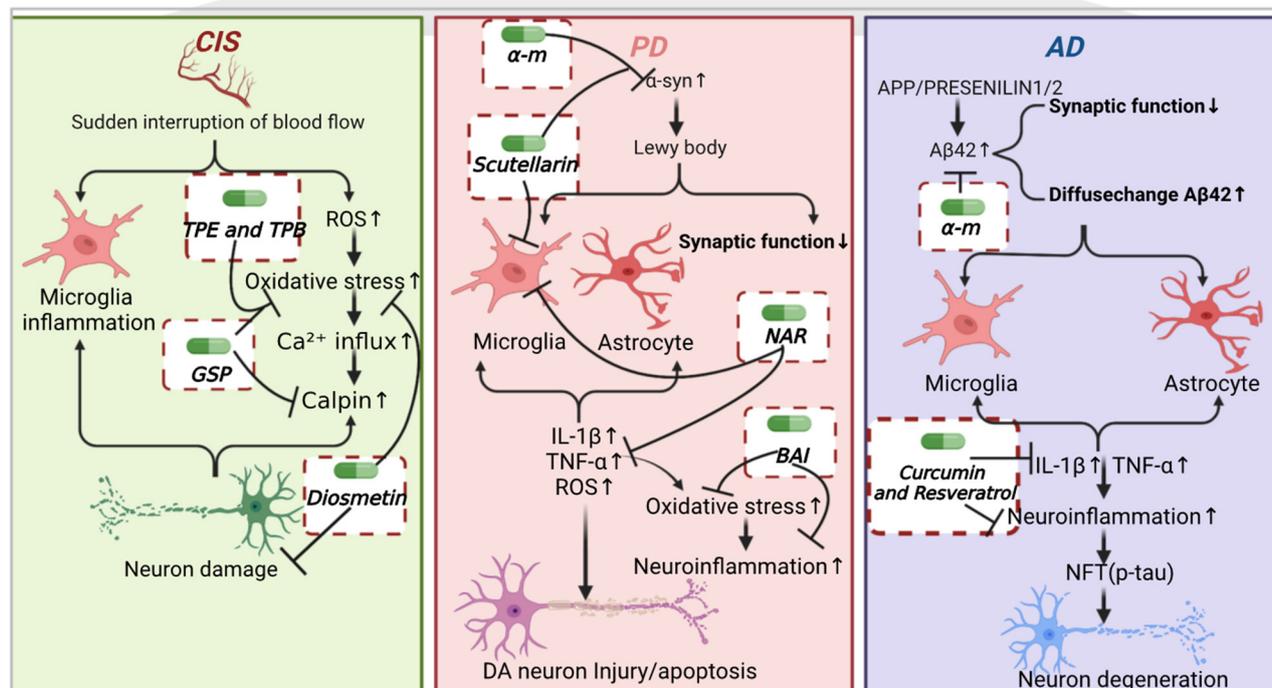


FIGURE 1

Polyphenols and neurodegenerative diseases. CIS is caused by the sudden interruption of blood flow to the brain, leading to brain cell death and nerve damage. Subsequently, it causes microglia activation, elevates ROS, inward calcium flow, and calmodulin release, leading to neuronal death. TPE, TPB, GSP, and diosmetin inhibited oxidative stress. GSP also inhibited calpain activation, and diosmetin exerted neuroprotective effects. PD is caused by the aggregation of α -syn proteins into Lewy bodies, leading to decreased synaptic function, and further activation of microglia and astrocytes. This leads to the release of inflammatory factors such as IL- β , TNF- α , and ROS, causing elevated levels of oxidative stress, neuroinflammation and damage or apoptosis of DA neurons. α -M and scutellarin inhibited the aggregation of α -syn oligomers. Scutellarin and NAR inhibited the activation of microglia. NAR inhibited the release of inflammatory factors. BAI inhibited the oxidative stress and neuroinflammation. AD is caused by the deposition of A β 42 aggregates, which activates microglia and astrocytes to release inflammatory factors and leads to neuroinflammation as well as NFT. α -M inhibited the aggregation of A β 42 oligomers. Curcumin and resveratrol inhibited the release of inflammatory factors and neuroinflammation, thereby attenuating neuronal degeneration.

In vivo studies

Two-month-old male SD rats were modeled by middle cerebral artery occlusion (MCAO) (24), and rehabilitation training plus resveratrol was used for treatment. It was found that resveratrol improved the recovery of neurological and motor function in MCAO rats through the silent mating type information regulation 2 homolog-1 (Sirt1) signaling pathway, and activated brain-derived neurotrophic factor/tyrosine kinase receptor b (BDNF/TrkB) signaling pathways. By modeling the I/R injury of male Wistar rats (48), it was found that the treatment of GSP reduced the size of cerebral infarct and clearly improved both behavioral and overall activities of rats as it allowed to restore rearing and crossing scores to near control level. Another study demonstrated that the TPE and TPB alleviated the reduction of antioxidant enzyme activity in cerebral ischemia-reperfusion injury, and exerted protective effects in MCAO

mice by inhibiting apoptosis and stimulating the Nrf2/HO-1 signaling pathway (21). Geraniin can reduce brain I/R damage by inhibiting oxidative stress (22). Geraniin can activate Nrf2/HO-1 signal pathway, reduce I/R damage of the middle cerebral artery occlusion-reperfusion (MCAO/R) in rats, significantly increase the number of surviving neurons, and inhibit oxidative stress induced by MCAO/R.

Therefore, polyphenols can inhibit oxidative stress to prevent neurons against the damage of ROS, exerting neuroprotective effects on CIS.

Parkinson's disease

Parkinson's disease (PD), a progressive motor dysfunction, is defined as a significant loss and misfolding of dopaminergic

TABLE 1 Effects and mechanisms of polyphenols in the treatment of neurodegenerative diseases.

Compounds	Disease	Model		Effects and mechanisms		References
		<i>In vitro</i>	<i>In vitro</i>	<i>In vitro</i>	<i>In vitro</i>	
TPE and TPB	CIS	BV2 microglial cells	Mice: MCAO	Facilitated the translocation of Nrf2 to the nucleus and enhanced Nrf2 expression in the nucleus and restored OGD/R-induced oxidative damage	Alleviate the reduction of antioxidant enzyme activity in cerebral ischemia-reperfusion injury, exerted protective effects in MCAO mice by inhibiting apoptosis, and stimulating the Nrf2/HO-1 signaling pathway	(21)
Geraniin		PC12 cells	SD rats: MCAO/R	Protect PC12 cells from OGD/R-induced cytotoxicity and oxidative stress, protect PC12 cells from OGD/R-induced cell apoptosis, activate of the Nrf2/HO-1 signaling pathway <i>in vivo</i> and <i>in vitro</i>	Protects against I/R injury, suppresses oxidative stress induced by MCAO/R, attenuates MCAO/R-induced neuronal apoptosis <i>in vivo</i>	(22)
GSP		Primary brain Neuron-astrocyte cell: OGD/R	Wistar rats: MCAO	GSP improved cell viability, exerted a powerful anti-inflammatory effect as it counteracted OGD-induced pro-inflammatory cytokines expression or anti-inflammatory cytokines expression	GSP-induced calpain activity inhibition or enhancement of neurotrophic factors such as BDNF	(22)
Resveratrol		Neurons: OGD/R	SD rats: MCAO	Inhibit the decrease of cell viability and apoptosis induced by OGD/R, and activate the mitochondrial phagocytosis induced by OGD/R, improve the recovery of motor function.	Improve the recovery of motor function	(23, 24)
Scutellarin	PD	α -Syn fibrillation: Fe ³⁺ - and Al ³⁺ induced		Inhibited the activation of microglia and inhibited the release of inflammatory factors		(25)
CGA		Enteroendocrine L Cells	Male C57BL/6J mice	Increased intracellular cAMP levels, increased the release of GLP-1 and GLP-1 release	Improves rotenone-induced behavioral and cognitive deficits in mice, recovers rotenone-induced oxidative damage to the striatum and cortex of Parkinson's disease	(26)
NAR		BV-2 cells	SD rats	Inhibited the Activation of Microglia and NLRP3 Inflammasome	It can reduce the loss of LPS-induced DA neurons	(27)
α -Mangostin (α -M)		PC12 cell: rotenone-induced	Male C57BL/6J mice: rotenone-induced	Promotes autophagy-directed clearance of α -Syn majorly through the activation of AMPK	It inhibits oxidative stress in the cortex, improves rotenone-induced behavioral defects in mice treated with rotenone, alleviates rotenone-induced striatal DA ergic neuron degeneration and rotenone-treated SNc in mice, and alleviates rotenone-induced α -Syn accumulation	(28)

(Continued)

TABLE 1 (Continued)

Compounds	Disease	Model		Effects and mechanisms		References
		<i>In vitro</i>	<i>In vitro</i>	<i>In vitro</i>	<i>In vitro</i>	
Procyanidin A2 (PCA2)	AD	RAW264.7: LPS stimulation	Mice: D-galactose-induced aging mice	Anti-inflammatory and antioxidant effects	Down-regulate NLRP3 inflammatory body signal pathway to inhibit inflammation in brain tissue	(10, 29)
Curcumin		PC12 cell: A β stimulation	Rats: damaged by H2O2	The neuroprotective effect, lower A β Oligomer induced neurotoxicity, reducing LPS-induced neuroinflammation	Anti-oxidative properties of AM, reduce senile plaque and repair neuron damage	(30, 31)
Baicalin		Neuroblast: Exposure to A β Oxidative stress model of neuroblastoma SH-SY5Y cell line	APP/PS-1 double transgenic mice	Reduce oxidative stress and neuroinflammation and protect nerves. Reduced ROS production, reduced oxidative stress, inhibited tau hyperphosphorylation, and protected SH-SY5Y cells from A β O Damage	Effectively improve memory impairment and restore cognitive function	(32)
Trehalose		HAW cells: overexpress the APP695 gene 20E2 cells: overexpress the APP695 gene	Mice: Bilateral intraventricular injection A β fragment.	It affects App Processing and Decreases A β	Blocked A β Deposition and microglial activation	(33)
Resveratrol		PC12 cells: Add A β ₁₋₄₂ to the culture medium induction.	Mice: SIRT1Dex4/Nestin-Cre mice Rats: Ovariectomized (OVX) + d-galactose (d-gal)	Prevent neuronal damage, inhibit A β ₁₋₄₂ , Induces apoptosis, reduces oxidative status, and alleviate mitochondrial damage	Improve the impaired learning and memory in neurodegenerative diseases, and protect the memory decline in AD through its antioxidant activity	(34)

(DA) neurons in the substantia nigra (SN), α -Synuclein (α -Syn) aggregation in lous corpuscles, as well as motor dysfunction (static tremor, rigidity, and motor retardation) and non-motor symptoms (autonomic nervous dysfunction, cognitive impairment, depression, REM sleep behavior, etc.) that appears several years before the onset of the motor phenotype (49–54). Studies have found that most PD patients are sporadic, and the rest are mostly related to gene mutations caused by mitochondrial dysfunction. About 50% of early-onset PD patients have mutations in Parkin (55–57).

In vitro studies

α -Syn is one of the first genes found to be associated with PD. Research proves that α -Syn and Nrf2 deficiency aggravates protein aggregation, neuroinflammation, and neuronal death (58). A study has found that scutellarin can effectively inhibit metal-induced and uninduced α -Syn's fibrosis (25), and stabilize partially folded α -Syn intermediate to form an SDS-resistant high-order oligomer. Baicalin (BAI) is an important flavonoid compound. Another study by human cell line pLVX-Tet3G- α -synuclein SH-SY5Y found that BAI could protect DA neurons against ROS and decrease C/EBP β and α -Syn expression in pLVX-Tet3G- α -synuclein SH-SY5Y cells (59). Alpha-mangostin (AM), a polyphenolic xanthone obtained from Garcinia Mangostana L, can activate the autophagy in PC12

cells, playing roles in clearance of α -Syn (28). Chlorogenic acid (CGA) is a polyphenolic compound with antioxidant and anti-inflammatory properties. CGA initiated the SIRT1/NF- κ B signaling pathway and inhibited OGD/R-induced inflammation, oxidative stress, and neuronal apoptosis by upregulating MIR497HG to suppress miR-29b-3p expression (60). Naringin (NAR) is a natural flavone contained in citrus fruits and grapefruit, which has a lot of pharmacological activities. A study has proved that NAR protects DA neurons from lipopolysaccharide (LPS)-induced neurotoxicity by inhibiting the activation of inflammatory corpuscle signals of microglial NOD-like receptor pyrin domain containing 3 (NLRP3) and the subsequent release of proinflammatory factors (27).

In vivo studies

A study of rotenone-induced male C57BL/6J mice proved that AM improved the behavioral deficiency induced by rotenone (28), and offset the oxidative stress in striatum and cortex, and decreased the degradation of DA neurons. DA can regulate innate immunity and inhibit systemic inflammation through different subtypes of dopamine receptor (DR) (61). DA also inhibits neuroinflammation in the brain through astrocyte DR2 and downstream signal transduction (62). Neuroinflammation is related to DA neurodegeneration and is a critical factor in the pathogenesis and progression of PD (63–66). A study

modeled adult male C57BL/6 mice using LPS (67), and found that BAI could inhibit the activation of hippocampal glial cells and cytokine release, inhibit SIRT1 and downregulate the expression of high mobility group protein 1 (HMGB1) in microglial cells, preventing LPS-induced cognitive dysfunction and neuroinflammation, and producing neuroprotective effects. Another study modeled the male C57BL/6 mice *via* 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (59), and found BAI protected dopaminergic neurons and rescued motor dysfunction. Chlorogenic acid (CGA) could downregulate rotenone-induced phosphorylated α -Syn levels by upregulating PI3K/AKT signaling pathway and inactivating GSK-3 β *via* GLP-1, which improved rotenone-induced dopaminergic neurodegeneration and α -Syn accumulation in the substantia nigra, and enhanced striatal dopaminergic mean density of nerve fibers and eventually prevented rotenone-induced motor and cognitive impairments (26). NAR regulates PQ-induced DRD2, DAT, LRRK2, SNCA, β -linked protein, cystathionine-3 and BDNF genes, alleviates the loss of dopaminergic neurons (68). By modeling adult male Sprague-Dawley rats through LPS (27), it has been shown that NAR ameliorates LPS-induced decrease in TH protein expression and inhibits the activation of microglia and NLRP3 inflammasome, thus protecting DA neurons.

Therefore, it has been evidenced that polyphenols can disintegrate upstream α -Syn aggregation and inhibit the further development of PD. Moreover, polyphenols can also inhibit inflammation, reduce oxidative stress, play a neuroprotective role in regulating downstream events to protect DA neurons, and hinder the progression of PD.

Alzheimer's disease

AD is a neurodegenerative disease, which is the most common type of dementia. AD can lead to progressive cognitive decline, irreversible loss of memory and cognitive function, and interfere with daily activities. Its main characteristics are A β deposition of aggregates in extracellular amyloid plaques (senile plaques), followed by degenerated neurons containing neurofibrillary tangles (NFT), which are mainly composed of hyperphosphorylated microtubule-associated protein Tau and synaptic loss (1, 2, 69–73).

In vitro studies

The occurrence of AD is closely related to neuroinflammation. Some studies have found that neuroinflammation and microglia activation exist in the early stage of AD (74). In the AD model, microglia and astrocytes have been proven to produce various proinflammatory cytokines (3–5, 75). Resveratrol is a polyphenol commonly found in grape skins (Vitaceae). More and more studies have shown that resveratrol has anti-inflammatory, antioxidant, and anti-diabetes effects and can improve cognitive decline. Resveratrol has been proven to exert inhibitory activity on neuroinflammation and can inhibit the release of proinflammatory factors from microglia and astrocytes (76–78). Microglia can eliminate A β sediment and activate phagocytosis to restore tissue homeostasis (79, 80). However, when

activation becomes chronic, microglia release excessive cytotoxic mediators, including proinflammatory cytokines, chemokines, complement components, ROS, and nitrogen species, which will cause neuronal cell degeneration (81, 82). Curcumin was first isolated from *Curcuma longa* L. in 1870 as a low molecular weight polyphenol compound. Studies have shown that curcumin has many beneficial pharmacological effects, including anti-cancer, anti-virus, anti-arthritis, anti-oxidative stress, anti-inflammatory, and neuroprotective properties (83). Inhibiting inflammation-promoting factors released by microglia are important targets of curcumin in treating AD. It has been shown that curcumin and its analogs cur 6 and cur 16 inhibit the secretion of pro-inflammatory mediators IL-1 β and TNF- α released by microglia after stimulation of HMW A β ₄₂O_s (32). The senile plaque can induce AD, and the “amyloid cascade hypothesis” is the most accepted hypothesis of AD etiology (2). A β ₄₂ oligomer is a soluble and diffusible A β species that play a key role in synaptic loss and synaptic damage in individuals with mild cognitive decline and can further trigger synaptotoxicity and neurotoxicity, glial cell proliferation, and activation, inflammation, or cell death (3–7, 84). A β also has the ability to bind to pattern recognition receptors on glial cells (including astrocytes and microglia), and it contributes to the progression and severity of AD (32, 85, 86). α -Mangostin (α -M) is a kind of polyphenol flavone from *Polygonatum odoratum*, which has been proven to be effective for clearance of A β . It was found that α -M favored A β fiber generation, decomposition, uptake, and degradation, which reduced A β neurotoxicity induced by oligomer and prevented LPS-induced neuroinflammation (30).

In vivo studies

A study has investigated 90 AD patients by using a randomized double-blind method (87). Compared with the donepezil hydrochloride group, the resveratrol (RES) group achieved a significantly higher efficacy rate, MMSE score and FIM score, and the clinical indicators and ADAS cog score were significantly lower. There was no significant difference in the total incidence of adverse reactions. It proves that polyphenols have obvious effects on the treatment of AD diseases, including improvement of the inflammatory factor, and promotion of the cognitive function and prognosis (87).

Thus, polyphenols inhibit the formation and degradation of senile plaques in AD, thereby protecting the function of synapses. In addition, polyphenols play a role in inhibiting the release of inflammatory factors and neuroinflammation in AD, preventing the formation of NFTs and neuronal death, thus inhibiting the progression of AD.

Perspectives and conclusion

Polyphenols show a significant neuroprotective effect, but the lack of understanding of the underlying mechanism limits its clinical application. This minireview makes a comprehensive investigation to reveal the role and mechanism of polyphenols in the treatment of neurodegenerative diseases, including *in vitro* and *in vivo* studies. It has been found that polyphenols,

as multi-target drugs, play a crucial role in inhibiting the formation of pathological products, such as oxidative stress and inflammatory factors. Polyphenols have two advantages as drugs for the treatment of neurodegenerative diseases. Firstly, polyphenols are derived from natural plants and can be obtained in daily diet. They have fewer side effects and are suitable for long-term use. Secondly, polyphenols can treat neurodegenerative diseases through multiple targets, which is undoubtedly crucial for the therapy of heterogeneous diseases. However, polyphenols are currently rarely used as drugs for the treatment of neurodegenerative diseases. Future large-scale multi-center randomized controlled trials and in-depth mechanism studies are still needed to fully evaluate the safety, effectiveness and possible side effects of polyphenols as therapeutic agents.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of interest

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