Research Progress on Flavonoids Regulating Microglial Function to Ameliorate Cognitive Impairment

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Abstract

Alzheimer's disease represents the most prevalent form of dementia. Neuroinflammation triggered by homeostatic imbalance and excessive activation of microglia serves as the core pathological mechanism underlying cognitive decline. As naturally occurring polyphenols with high biosafety, flavonoids are capable of crossing the blood–brain barrier and exert multi-target regulatory effects on central nervous inflammation, rendering them promising natural bioactive agents for intervening cognitive impairment. Focusing on four subclasses including flavones, flavonols, flavanones and isoflavones, this paper systematically summarizes the molecular mechanisms by which various flavonoid monomers confer neuroprotective effects and alleviate cognitive damage. Such mechanisms comprise modulating M1/M2 polarization of microglia, blocking inflammatory signaling cascades such as NF-κB, MAPK and NLRP3 inflammasome, inhibiting amyloid-β (Aβ) deposition, ameliorating oxidative stress and correcting gut microbiota dysbiosis. Meanwhile, this review highlights that insufficient bioavailability restricts the clinical translation of flavonoids, while delivery technologies including nanoformulations and targeted sustained-release hydrogels can effectively overcome this limitation, providing theoretical evidence for the research and development of natural medicines against Alzheimer's disease.

Key words

Flavonoids; Cognitive impairment; Alzheimer's disease; Microglia;

1. Introduction

Cognitive impairment is characterized by single or multiple impairments in various cognitive domains including learning, memory, language and executive function, frequently accompanied by psychiatric, behavioral and personality abnormalities throughout the disease course. It is mainly divided into two stages: mild cognitive impairment and dementia. Patients with severe cognitive impairment require long-term professional care, and the global annual care cost exceeds one trillion US dollars. Delaying cognitive decline by one year can reduce the burden of family care by 40%[1]. Accordingly, exploring effective intervention strategies for cognitive impairment is of great significance for preserving cognitive function, alleviating medical and social burdens, and improving the health status of aging populations. Microglia are tissue-resident immune cells unique to the central nervous system. The neuroinflammatory cascade triggered by their homeostatic imbalance, aberrant polarization and excessive activation constitutes the core pathological mechanism underlying the initiation and progression of cognitive impairment[2]. As natural bioactive polyphenols with abundant sources, favorable safety profiles and multi-target regulatory properties, flavonoids possess anti-inflammatory, antioxidant and neuroprotective pharmacological activities, making them a research hotspot in the field of cognitive impairment intervention[3,4].This paper systematically reviews the core mechanisms by which flavonoids alleviate cognitive damage via regulating microglial function, and prospects optimized research directions, so as to provide theoretical evidence for basic research on cognitive impairment and the development of natural medicines.

2. Pathological Mechanisms Underlying Cognitive Impairment Mediated by Dysfunctional Microglia

Alzheimer's disease represents the predominant subtype of cognitive impairment, with its onset occurring at increasingly younger ages. Aberrant microglial activation acts as a central driving factor for AD progression. The following section elaborates the pathological mechanisms through which microglial dysfunction induces cognitive decline from three perspectives: physiological functions of microglia, toxic vicious cycle induced by M1/M2 polarization imbalance, and signaling pathways associated with Aβ and Tau-mediated microglial activation.

2.1 Characteristics and Functions of Microglia under Physiological Conditions

As resident immune cells of the central nervous system, microglia account for 5–10% of all brain cells in adults and were identified as brain phagocytes in 1919[5]. Under physiological conditions, microglia exhibit a resting phenotype without synthesizing pro-inflammatory cytokines or reactive oxygen/nitrogen species[6]. They secrete protective factors such as nerve growth factor and brain-derived neurotrophic factor, participate in neuronal development, synaptic remodeling, neuroinflammation regulation and toxic substance clearance, maintain central nervous system homeostasis, and engage in learning and memory processes[7].

2.2 Vicious Cycle of Neurotoxicity Mediated by Imbalanced Microglial Phenotypes

Imbalanced microglial phenotypes serve as a core driving factor for AD progression. The M1 phenotype is pro-inflammatory; upon activation, it secretes abundant pro-inflammatory cytokines as an initial defensive response against pathological stimuli. The M2 phenotype exerts anti-inflammatory effects and participates in angiogenesis, neurogenesis, anti-inflammatory repair and β-amyloid protein (Aβ) degradation[8]. Persistent excessive pathological stimulation drives microglia toward M1 polarization, and the released inflammatory cytokines damage neurons. Injured neurons further release toxic substances including Aβ, thereby forming a vicious cycle[9]. Meanwhile, Aβ-triggered microglial activation facilitates the production of reactive oxygen and nitrogen species via reduced nicotinamide adenine dinucleotide phosphate (NADPH) and inducible nitric oxide synthase (iNOS), which

further accelerates Aβ accumulation and amplifies neurotoxicity[10].

2.3 Regulatory Mechanisms of Key Signaling Pathways and Overall Pathological Damaging Effects

Resveratrol (Res) Beyond their direct effects, Aβ and Tau proteins can modulate microglial activation and inflammatory responses through multiple signaling pathways, including transient receptor potential melastatin 2 (TRPM2) channels, cyclic GMP-AMP synthase (cGAS)-stimulator of interferon gene (STING) pathway, NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome, and nuclear factor-κB (NF-κB)[11-14].

In summary, microglial dysfunction impairs the clearance of Aβ and Tau proteins and activates pro-inflammatory signaling pathways, which triggers a vicious cycle of "pathological protein deposition-excessive microglial activation-neuroinflammation-neurotoxicity", ultimately exacerbating neurodegenerative lesions and cognitive decline.

3. Neuroprotective Properties of Flavonoids and Their Mechanisms of Regulating Microglia to Alleviate Cognitive Impairment

Flavonoids are widely distributed in fruits, vegetables, traditional Chinese medicines, red wine and soybeans[15]. Their unique chemical structures endow them with multiple biological activities such as anti-inflammation and anti-oxidation, and they are capable of crossing the blood–brain barrier to exert effects in the central nervous system[16]. Epidemiological evidence indicates that long-term flavonoid intake ameliorates cognitive function and mental status[17]. With low toxicity and multi-target regulatory effects against AD pathological lesions, flavonoids exhibit favorable anti-AD efficacy when administered alone or in combination, possessing prominent development potential[18]. Flavones, flavonols, flavanones and isoflavones can regulate microglial polarization and suppress inflammatory signaling pathways to achieve neuroprotection. This review systematically sorts out the functional mechanisms by which these four subclasses alleviate cognitive impairment.

3.1 Flavones

Flavone monomers including baicalein, apigenin, luteolin and acacetin target inflammatory signaling pathways in microglia, block pro-inflammatory M1 polarization and attenuate neuronal damage, thereby improving cognitive function. Distinct monomers act through divergent pathways: acacetin inhibits the secretion of NO and PGE2 in LPS-stimulated BV-2 cells, downregulates iNOS and pro-inflammatory cytokines, and blocks the NF-κB and p38 MAPK pathways, which suppresses microglial activation both in vitro and in vivo[19]; luteolin regulates microglial polarization via the IL-17/TNF pathway, downregulates p-IκB-α, p-NFκB p65, MMP9 and pro-inflammatory cytokines, while upregulating Arg-1 and IL-10 to facilitate M2 phenotypic transformation and relieve central neuroinflammation[20]. In addition, baicalein also represses LPS-induced microglial activation[21]. In conclusion, flavones modulate microglial activation and polarization via multiple inflammatory pathways to hinder the progression of neuroinflammation..

3.2 Flavonols

Flavonols feature a 3-hydroxyflavone skeleton and mostly exist in glycoside forms with potent antioxidant activity. Their representative compounds include quercetin, kaempferol, myricetin and fisetin, among which the first three have been extensively investigated[22-25]. These compounds bind to Aβ to block the formation of toxic oligomers and fibrils, inhibit BACE1, alleviate oxidative stress, protect mitochondria, and activate autophagy to clear Aβ, thereby intervening in AD pathological progress through multiple targets[26,27]. Quercetin maintains neuronal homeostasis by activating the Nrf2/HO-1 and BDNF-TrkB pathways. Administration in AD mouse models has verified that quercetin balances M1/M2 microglial polarization, suppresses glial activation, reduces pro-inflammatory cytokines in brain tissue, and reverses cognitive impairment[26,28-30]. Triliin inhibits hippocampal glial activation in APP/PS1 mice in a dose-dependent manner, downregulates HMGB1, TLR4 and NF-κB, and blocks

inflammatory cascades, which validates the pharmacological efficacy of flavonols in regulating microglia and improving cognition[31].

3.3 Flavanones

Flavanones are abundant in citrus fruits with high lipophilicity, enabling them to readily cross the blood–brain barrier. Naringenin and hesperetin are their typical bioactive ingredients[21,32-34]. Naringenin reduces cerebral Aβ deposition in APP/PS1 mice and inhibits aberrant glial activation and the release of pro-inflammatory cytokines. In vitro, it alleviates inflammation in LPS/Aβ-stimulated BV-2 cells via suppressing phosphorylation of the MAPK pathway and decreasing secretion of TNF-α and IL-1β[35]. Hesperetin exerts neuroprotective effects through Nrf2-mediated anti-oxidation, NF-κB-dependent anti-inflammation and anti-apoptosis, and also inhibits the NLRP3 inflammasome and pyroptosis[36,37]. Experiments on BV-2 cells demonstrate that hesperetin upregulates antioxidant enzymes, activates the Keap1/Nrf2 pathway, downregulates PD-L1 and NF-κB -related genes, relieves chronic oxidative stress and neuroinflammation, and possesses potential for AD intervention[38].

3.4 Isoflavones

Isoflavones possess a 3-phenylbenzopyran skeleton and are classified into three subtypes: oxygen-substituted, isopentenyl-substituted and glycosidic forms. Aglycones such as daidzein and genistein in legumes serve as the major active components. Their structures resemble estrogen, endowing them with antioxidant, anti-inflammatory and neuroprotective properties[39,40]. Genistein downregulates TLR4/MyD88 and the phosphorylation of downstream MAPK and NF-κB, promotes microglial polarization toward the M2 phenotype, and alleviates isoflurane-induced hippocampal inflammation and apoptosis[41]. Puerarin suppresses the AKT1 pathway to reduce pro-inflammatory cytokines and relieve hippocampal neuronal injury; formononetin balances M1/M2 polarization and inhibits the NLRP3 inflammasome, both of which exhibit mild anti-inflammatory activity and favorable biosafety[42,43]. Daidzein, isoformononetin and other compounds restrain the secretion of inflammatory mediators through the Akt, ERK and NF-κB pathways[44]. Free isoflavone aglycones from fermented soybean yoghurt can suppress microglial inflammation, regulate gut microbiota in mice fed a high-fat diet, and preserve synaptic function simultaneously[45].

In summary, relying on their unique chemical structures, isoflavones exert neuroprotective effects via multiple approaches including modulating inflammatory signaling pathways, balancing microglial polarization and regulating gut microbiota, which makes them promising candidate natural ingredients for the treatment of neurodegenerative diseases.

4. Conclusion

At present, there is no curative clinical therapy for Alzheimer's disease. Acetylcholinesterase inhibitors including donepezil, galantamine and rivastigmine, as well as memantine (an N-methyl-D-aspartate receptor antagonist), only provide symptomatic intervention to delay cognitive and memory decline, yet fail to reverse core pathological processes such as Aβ deposition and neuroinflammation[46]. Oral administration represents the preferred administration route for chronic neurodegenerative diseases. Approximately one-third of drugs approved by the U.S. Food and Drug Administration over the past two decades are derived from natural products and their derivatives[47]. Flavonoids have become a research hotspot for AD treatment owing to their multi-target effects and low toxicity; nevertheless, their clinical translation is restricted by poor bioavailability. Dietary flavonoids predominantly exist as flavone/flavonol O-glycosides or flavone C-glycosides, which possess higher molecular weights and weaker lipophilicity compared with aglycones, leading to low intestinal absorption efficiency. Furthermore, their non-planar molecular structures, enterohepatic circulation, as well as the effects of metabolic enzymes and gut microbiota further aggravate absorption defects[48,49]. To address this limitation, formulation optimization and novel administration strategies have become major research focuses. Targeted delivery and local synergistic delivery systems also broaden the application scope of flavonoids. In conclusion,

breaking through the bottleneck of low bioavailability via targeted delivery technology is a critical direction to facilitate the clinical translation of flavonoids and advance the prevention and treatment of AD.

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