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Flavonoids: Mechanisms and Therapeutic Potential in Multitarget Intervention for Chronic Neuroinflammation

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ABSTRACT: Inflammation is a defensive response of the body to external stimuli. However, excessive or dysregulated inflammatory responses contribute to various chronic diseases, with neurodegenerative disorders accounting for approximately 30% of the global disease burden. Flavonoids are natural polyphenolic compounds widely distributed in plants. Unlike conventional anti-inflammatory drugs, which tend to induce drug resistance and cause severe side effects, these natural dietary components exhibit low toxicity, offering a safer alternative for the intervention of chronic inflammatory diseases, with particularly notable advantages in long-term therapeutic applications. Accumulating evidence indicates that they exert synergistic anti-inflammatory effects through multiple targets and pathways. In neuroinflammatory diseases, the interventional effects of these natural compounds are particularly prominent: nobiletin inhibits β -Amyloid (A β) aggregation via the Toll-like receptor 4/nuclear factor- κ B (TLR4/NF- κ B) pathway to ameliorate Alzheimer's disease (AD) pathology; baicalin alleviates neuroinflammation through the Nuclear factor erythroid 2-related factor 2-NOD-like receptor thermal protein domain associated protein 3 (Nrf2-NLRP3) axis to protect dopaminergic neurons in Parkinson's disease (PD); luteolin reduces mutant huntingtin protein aggregation to mitigate the progression of Huntington's disease (HD); quercetin activates the Sestrin2/adenosine monophosphate-activated protein kinase/sirtuin 1 (Sestrin2/AMPK/SIRT1) pathway to delay motor neuron degeneration in amyotrophic lateral sclerosis (ALS). Additionally, this review further analyzes the key challenges in the clinical translation of flavonoids, including insufficient blood-brain barrier penetration, limited bioavailability in vivo, and limitations of experimental models. To address these challenges, this review focuses on food science-oriented strategies, emphasizing two core directions: the construction of nanodelivery systems and molecular structural modification, while integrating advanced approaches such as humanized models, aiming to provide a theoretical basis and translational pathway for the clinical application of flavonoids in neuroinflammatory intervention.

Keywords: Flavonoids; NF- κ B pathway; MAPK pathway; Oxidative stress; Neural cells; Neuroinflammatory

1. Introduction

1.1. Complexity and Hazards of Neuroinflammation

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Inflammation is a complex series of physiological responses to foreign organisms (including human pathogens, dust particles, and viruses), serving as a primary immune defense mechanism against infections, trauma, toxin accumulation, and other pathological injuries. Under normal conditions, inflammation is a beneficial spontaneous defensive response of the body; however, under certain pathological states, the inflammatory response can also produce damaging effects. In the central nervous system (CNS), neuroinflammation is a tissue-specific inflammatory response, and its pathophysiological process exhibits high complexity and multi-dimensional characteristics. Neuroinflammation is closely associated with neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS). The inflammatory microenvironment accelerates neuronal damage and death, leading to cognitive impairment and motor dysfunction. Currently, neuroinflammation has become a significant topic in human disease research. Chronic neuroinflammation may have negative effects on aging, disease susceptibility, and people's healthy life expectancy. The global incidence of such chronic diseases has also increased. The World Health Organization (WHO) collectively refers to lifestyle-related diseases, allergies, and cancer as non-communicable diseases (NCDs), and emphasizes that they are key issues in future medicine, healthcare, and public health (Suzuki 2019). Therefore, exploring safe and effective anti-inflammatory strategies has become a major research topic urgently requiring solutions in the medical field.

1.2. Introduction to Flavonoids

Flavonoids are a class of structurally diverse natural polyphenolic substances widely present in vegetables, fruits, cereals, Chinese herbal medicines, and tea, exhibiting broad-spectrum pharmacological and multiple biological activities (Zheng, Zhang, and Zeng 2025). As plant secondary metabolites, flavonoids play critical roles in plant life activities and environmental responses, and related research has become an important direction in the field of human nutrition (Shen et al. 2022). Flavonoids are widely present in the human diet and possess various biological activities such as antioxidant and anti-inflammatory effects, which can reduce the risk of disease development (Shen et al. 2022). Their structures are highly diverse, and more than 10,000 flavonoid compounds have been isolated and identified. The basic structure of flavonoids consists of two aromatic rings, designated as Ring A and Ring B, which are linked by a central heterocyclic pyran Ring C (Ullah et al. 2020). Based on the oxidation state and saturation of Ring C, as well as the position and number of hydroxyl groups and other functional groups on Rings A and B, flavonoids are mainly classified into six major categories: flavones, flavonols, flavanones, isoflavones, chalcones, and anthocyanins (Ullah et al. 2020; Parmenter et al. 2025).

1.3. Functions of Flavonoids

Flavonoids are polyphenolic compounds abundant in the human diet, with a wide range of sources (Parmenter et al. 2025). Differences in their chemical structures, bioavailability, and metabolic characteristics enable different flavonoids to produce diverse biological effects. These effects include inhibiting platelet aggregation, reducing low-density lipoprotein oxidation, activating antioxidant defense systems, and alleviating neuroinflammatory responses (Qiu et al. 2018; Williamson, Kay, and Crozier 2018). Among these,

the anti-inflammatory and antioxidant properties are key to regulating the onset and progression of chronic neurological diseases (Ma et al. 2024). Several studies have shown that natural compounds, including flavonoids, can direct microglia to switch from a pro-inflammatory phenotype to an anti-inflammatory phenotype. This shift may help resolve pre-established inflammatory processes (Zhang, Gu, et al. 2024). The anti-inflammatory activity of flavonoids is attributed to multiple mechanisms. These include inactivation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B), regulation of mitogen-activated protein kinase (MAPK) and arachidonic acid pathways, and downregulation of phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt). Flavonoids also downregulate pro-inflammatory gene expression, reduce cytokine synthesis, and inhibit reactive oxygen species (ROS) and nitric oxide (NO) production (Yahfoufi et al. 2018). Additionally, they can activate antioxidant pathways and inhibit the secretion of inflammation-related enzymes such as lysozyme. Indirect anti-inflammatory effects occur through modulation of the gut microbiota and enhancement of intestinal barrier function. Together, these pathways form the core mechanism of the anti-inflammatory action of flavonoids.

Polyphenols and their metabolites exert multiple beneficial effects in the gastrointestinal tract by modulating the gut microbiota, enhancing intestinal barrier function, repairing the mucosa, alleviating oxidative stress, inhibiting the secretion of inflammatory factors, and regulating immune function (Lan, Wang, Chen, et al. 2024). However, the clinical application of these molecules is limited due to their low solubility, poor chemical stability, low bioavailability, and extensive intestinal metabolism in vivo. Studies have shown that the methylation and glycosylation pathways of natural plants can be utilized to prepare modified flavonoids with improved biophysical and pharmacokinetic properties for clinical application (Sajid et al. 2021).

1.4. Relationship between Flavonoids and Neuroinflammation

It is well-known that flavonoids possess excellent anti-inflammatory properties. The structure of flavonoids plays a crucial role in their anti-inflammatory activity (Al-Khayri et al. 2022). They have a planar ring structure with unsaturation at the C2-C3 position, and the position of hydroxyl groups is essential for endowing this property. The hydroxyl groups at the 3' and 4' positions of Ring B are particularly important; without these hydroxyl groups, the anti-inflammatory activity of the compound is lost (Choy et al. 2019). Studies have shown that flavonoids exert anti-inflammatory effects by activating antioxidant pathways. Inflammatory responses are regulated by multiple receptor-mediated pathways, including Toll-like receptors, the MAPK pathway, and the NF- κ B pathway (Fattori, Amaral, and Verri 2016).

Currently, the anti-inflammatory drugs commonly used in clinical practice include non-steroidal anti-inflammatory drugs (NSAIDs, such as ibuprofen and indomethacin) and steroidal anti-inflammatory drugs (SAIDs, such as prednisolone and dexamethasone). Although they have clear pharmacological effects, long-term use is associated with severe side effects. However, as potential therapeutic agents for chronic neuroinflammation, flavonoids can act on various chronic neuroinflammatory conditions and exhibit no serious side effects with long-term use. Therefore, in light of the limitations of existing anti-inflammatory

agents, flavonoids offer distinct advantages as novel anti-inflammatory agents for chronic diseases (Lim, Heo, and Kim 2019). This review focuses on elucidating the value of flavonoids as natural products in the intervention of chronic neuroinflammatory diseases, aiming to provide new insights for overcoming the limitations of conventional anti-inflammatory therapies that merely focus on cytokines and immune modulation (Figure 1). Herein, we summarize the research findings on anti-inflammatory flavonoids for the treatment of chronic neuroinflammatory diseases.

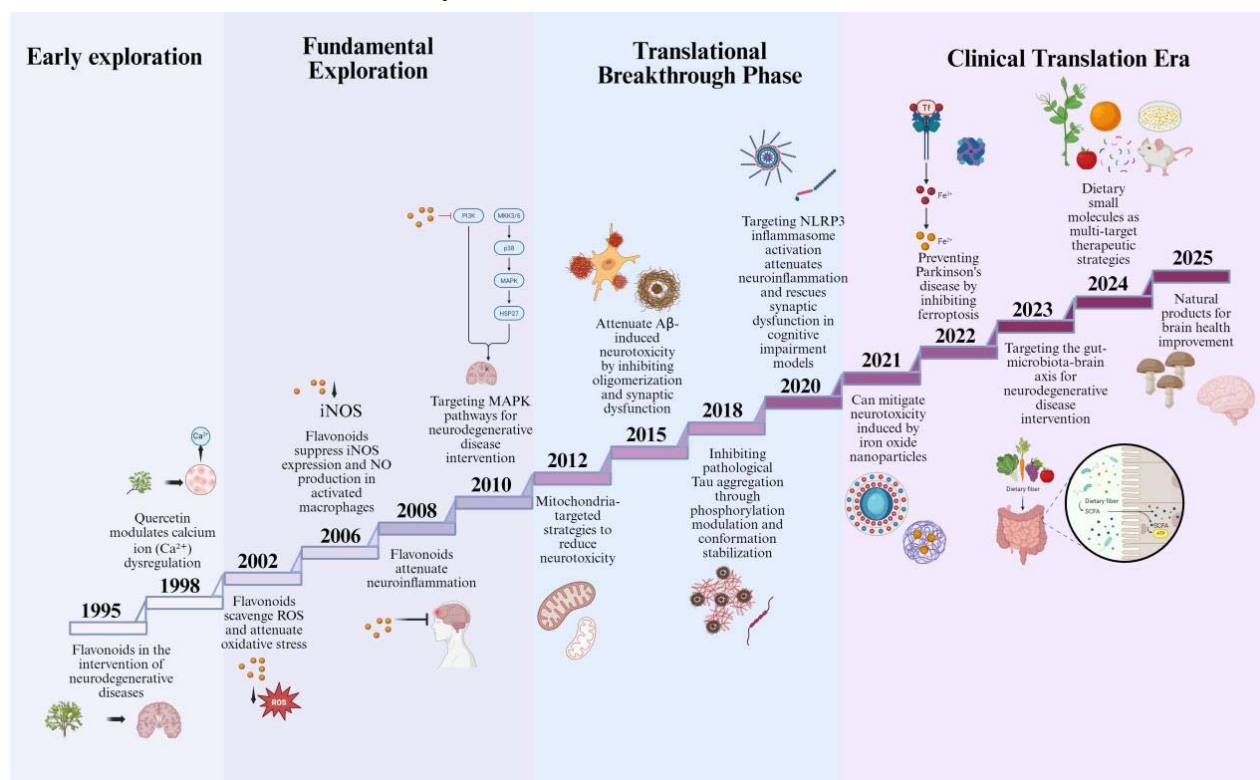


Figure 1: Event Axis Diagram of Flavonoid Intervention in Neurodegenerative Diseases

Created with BioRender. com. This diagram systematically outlines the structural evolution of research paradigms in this field since 1995, integrating historical progression with logical coherence. The initial exploratory phase focused on fundamental cellular processes such as calcium homeostasis (Matsuoka et al. 1995; Wang and Joseph 1999). Subsequently, the basic mechanism expansion phase progressively unveiled the regulatory roles of flavonoids within multi-target networks involving oxidative stress, neuroinflammation, protein aggregation, and mitochondrial dysfunction (Ross and Kasum 2002; Wang et al. 2006; Rezai-Zadeh et al. 2008; Munoz and Ammit 2010). In the systemic integration and translational phase, research emphasis shifted toward multi-target synergistic strategies and systemic regulatory mechanisms such as the gut-brain axis (Cheng et al. 2012; Kim et al. 2015; Chukwu et al. 2018; Lonnemann et al. 2020). Finally, the clinical translation and application phase is committed to advancing precision brain health intervention strategies based on natural flavonoids (Bardestani et al. 2021; Wang et al. 2022; Khatoon et al. 2023; Zhao et al. 2025; Rajchman et al. 2025). ROS: Reactive Oxygen Species; iNOS: Inducible Nitric Oxide Synthase; NO: Nitric Oxide; MAPK: Mitogen-Activated Protein Kinase; A β : Amyloid-Beta; Tau: Tubulin Associated Unit; NLRP3: NOD-, LRR- and Pyrin Domain-Containing Protein 3

1.5. Research Objectives

This review aims to comprehensively elucidate the mechanisms by which flavonoids intervene in neuroinflammation within a holistic “structure-mechanism-application” framework. It focuses on the latest advances, including structure-driven activity variations, shared and subclass-specific anti-inflammatory pathways, and novel modification strategies. By integrating the relationship between structural characteristics, mechanistic regulation, and clinical needs, it seeks to provide new strategies and theoretical insights for the intervention of chronic neuroinflammation with natural products, thereby transcending the limitations of

conventional anti-inflammatory therapies that primarily target cytokine modulation.

2. Search Strategy

2.1. Literature Retrieval Strategy

To obtain the latest international research progress on flavonoids and neuroinflammation, the following English literature retrieval strategy was adopted:

Database selection: Web of Science, PubMed, Google Scholar, and Scopus databases.

Search terms: Flavonoids; MAPK pathway; NF- κ B; Neural cells; Neuroinflammatory system diseases

Search time range: 2016-2026.

Search method: Precise search was conducted using keyword combinations, as well as subject terms and abstracts, to facilitate effective screening.

2.2. Literature Inclusion and Exclusion Criteria

Inclusion criteria: High-quality journal articles published in the past five years were selected, with articles with higher citation counts prioritized for inclusion. In addition, we also focused on selecting articles from top academic journals and those with high impact factors.

Exclusion criteria: Articles must focus on flavonoid intervention in neuroinflammation, be published in high-impact journals (such as Nature and Science) within the past five years, and be in English. Eligible articles may include reviews, basic research, case reports, or clinical studies.

3. Structure and Function of Flavonoids

Flavonoids usually exist in glycosylated or esterified forms and are mainly synthesized through the phenylpropanoid metabolic pathway. They contain 15 carbon atoms arranged into three rings (C6–C3–C6), namely Ring A and Ring B connected by a three-carbon Ring C (Wang, Li, and Bi 2018; Chen et al. 2023). Therefore, based on variations in substitution patterns, flavonoids can be divided into different subclasses, thereby providing an extremely diverse range of derivatives. Flavonoids are classified into various types based on their chemical structure, degree of unsaturation, and oxidation state of the carbon rings, including flavones, flavanones, isoflavones, flavonols, chalcones, flavanols, and anthocyanins (Figure 2, Table 1)(Chen et al. 2023). Vegetables and fruits are indispensable natural sources of flavonoids; however, recent studies have shown that microorganisms such as fungi and bacteria can also produce flavonoids from plant biomass (Liga, Paul, and Péter 2023)

Table1: Summary of Information on Natural Flavonoids

Subclass	Compound	Experimental Model	Intervention Condition	Action Mechanism	Observed Effect	Reference
Flavones	Apigenin	Adult male Wistar rats	Administered by oral gavage at a dose of 50 mg/kg per day for 14	Antioxidant	NO↓, AChE↓, GSH↑, SOD↑	(Oyagbemi et al. 2025)

			consecutive days			
Flavones	Luteolin	Male C57BL/6J mice	Intracerebroventricular injection of 1×10^8 TU/mL per day for 7 consecutive days	Potent anti-inflammatory	Suppresses NF- κ B, STAT1, and IRF-1 signaling	(Bi et al. 2023)
Flavonols	Quercetin	LPS-induced male C57BL/6J mice	Intraperitoneal injection at doses of 30/60 mg/kg per day	Neuroprotection	Increased TH expression	(Han et al. 2021)
Flavonols	Kaempferol	Experimental autoimmune neuritis (EAN) rats	Gastric gavage, 50 mg/kg and 100 mg/kg	Neuroprotection	TNF- α ↓、IL-1 β ↓、IL-6↓	(Wang, Gu, et al. 2025)
Flavanones	Naringenin	APP/PS1 mice	Oral gavage, 50 mg/kg/day, for 3 months	Reducing oxidative stress damage	Inhibit the MAPK signaling pathway	(Zhu et al. 2024)
Flavanones	Hesperetin	Human neuroblastoma SH-SY5Y cells	Pretreatment with 1/10 μ M for 3 h	Neuroinflammation alleviation	Downregulation of pro-inflammatory cytokine mRNA	(Shafiee et al. 2025)
Isoflavones	Genistein	Postnatal day 7 Sprague-Dawley rats	Intraperitoneal injection, 20/40/80 mg/kg/day	Potential neuroprotection	Reduced TLR4, MyD88, p-p38, p-I κ B α and p-NF- κ B	(Jiang et al. 2021)
Isoflavones	Daidzein	SH-SY5Y, C6 cells	0. 25/0. 5/1 μ M+2. 25 μ M A β	Anti-inflammatory	Inhibits the MAPK pathway, ROS↓	(Özdemir et al. 2025)
Chalcone	Licochalcone A	LPS-induced C57BL/6J male mice	Intraperitoneal injection, 15 mg/kg/day	Antioxidant	Enhances p-CREB, BDNF, PSD-95, DBN1	(Carrasco et al. 2025)
Chalcone	Isoliquiritigenin	MPTP-induced male C57BL/6 mice	Oral gavage, 20 mg/kg and 40 mg/kg, 10 consecutive days	Anti-inflammatory	Inhibition of the JNK/AKT/NF κ B signaling pathway, NO↓	(Bai et al. 2023)
Anthocyanidins	Cyanidin	Female APP ^{swe} /PS1 Δ E9 mice	Oral gavage, 30 mg/kg/d, 16 weeks	Potent antioxidant	Decreased phosphorylated-Akt/Akt、ERK/ERK	(Baek et al. 2023)
Anthocyanidins	Delphinidin	Male APP/PS1 mice	Oral gavage, 15 mg/kg/d, 8 weeks	Neuroprotection	Enhanced the AMPK/SIRT1 signaling pathway	(Liu et al. 2025)

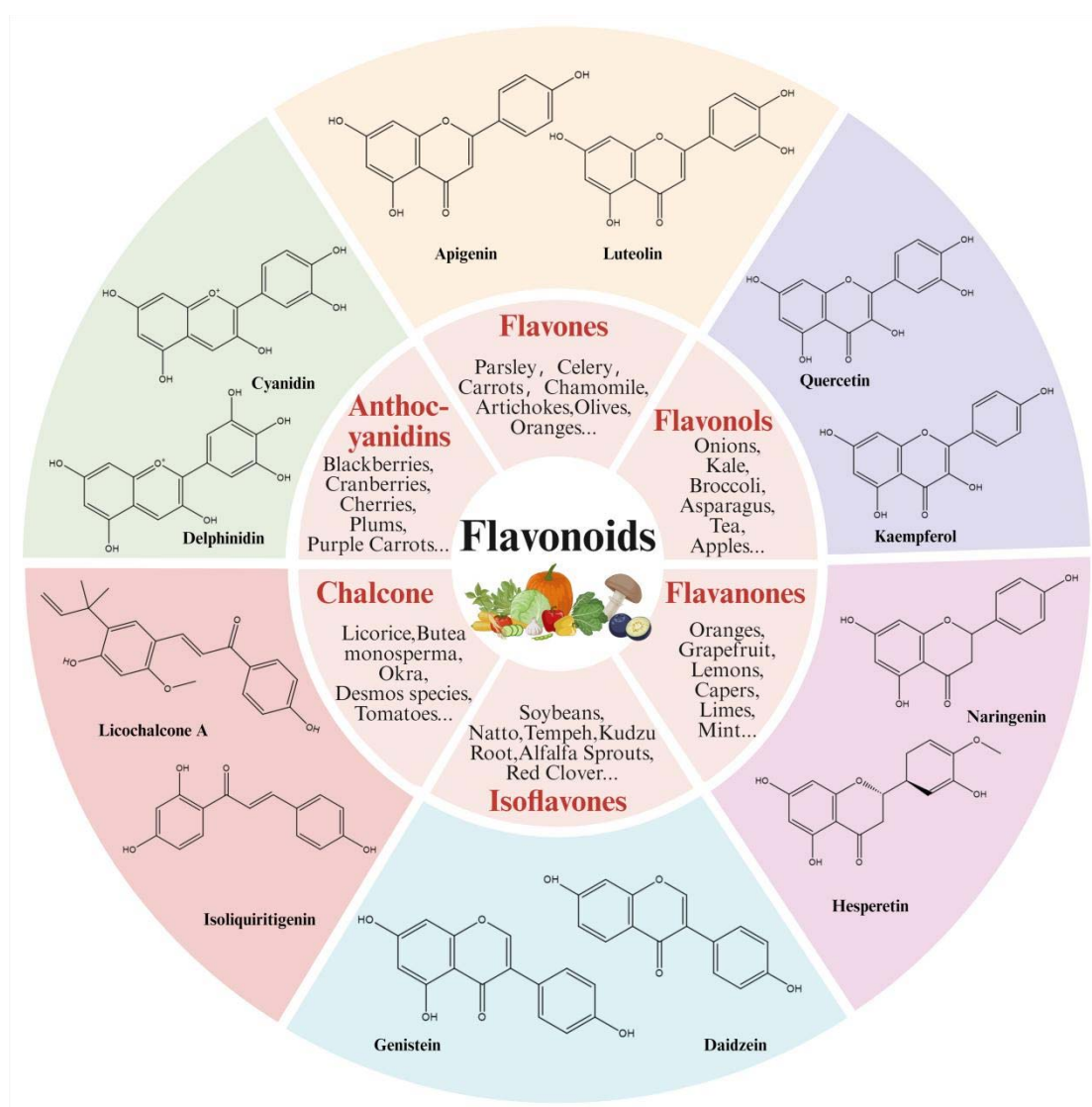


Figure 2: Structure of Flavonoid Compounds

Created with BioRender. com. This figure illustrates the chemical structures of representative compounds from different flavonoid subclasses, including flavones (apigenin, luteolin), isoflavones (genistein, daidzein), flavonols (quercetin, kaempferol), chalcone (licochalcone A, isoliquiritigenin), flavanones (naringenin, hesperetin), and anthocyanidins (cyanidin, delphinidin). Flavonoids, widely distributed in plants, exhibit diverse biological activities such as anti-inflammatory, antioxidant, and neuroprotective effects, playing crucial roles in the intervention of various diseases, including neurodegenerative disorders.

3.1. Flavones

The characteristic absence of a 3-hydroxyl group on the C-ring defines the distinct biological activity profile of flavone subclasses. Despite their highly similar structural backbones, the single difference in the number of hydroxylations on the B-ring leads to divergent targeting: luteolin primarily modulates oxidative stress and kinase signaling pathways, whereas apigenin preferentially acts on epigenetic regulators and nuclear receptor targets.

3.1.1. Apigenin

Apigenin (API), with the chemical name 4',5,7-trihydroxyflavone ($C_{15}H_{10}O_5$), belongs to the flavonoid subfamily and is one of the most widely distributed and well-studied flavonoids in plants (Salehi et al. 2019). In nature, API mainly exists in glycosylated forms, with primary sources including vegetables such as parsley,

celery, and onion; fruits such as oranges; medicinal and edible plants such as chamomile, thyme, oregano, and basil; as well as plant-based beverages such as tea, beer, and wine (Liu et al. 2024). As a natural metabolite of the phenylpropanoid pathway, API exhibits a variety of important physiological activities and possesses multiple core functions, including anti-inflammatory, antioxidant, and anticancer effects (Zhang, Xu, et al. 2025).

3.1.2. Luteolin

Luteolin (3,4',5,7-tetrahydroxyflavone) is a typical flavonoid compound widely present in various medicinal plants, fruits, and vegetables. In traditional Chinese medicine applications, plants rich in luteolin have often been used as adjunctive therapy for hypertension, inflammatory conditions, and tumor-related disorders. In the traditional Chinese medicine system, plant resources rich in luteolin have long been used for the management and intervention of hypertension, inflammatory diseases, and tumor-related disorders. Modern pharmacological studies have demonstrated that luteolin possesses broad and significant biological activities, with its core functions prominently manifested as multiple pharmacological properties, including anti-inflammatory, antioxidant, antitumor, antibacterial, and antiviral effects (Wang, Zhao, et al. 2024). This compound exhibits dual biochemical effects, acting either as an antioxidant or a pro-oxidant *in vivo*, and there are potential functional interconnections among its various biological effects, thereby providing an important theoretical basis for its application in the intervention of chronic diseases (Imran et al. 2019).

3.2. Flavonols

Within the flavonoid family, flavonols serve as a model subclass for studying neuroprotective mechanisms, owing to their characteristic chemical structure featuring a C2-C3 double bond and a 3-hydroxyl group. This section will focus on quercetin and kaempferol as primary exemplars. Quercetin, by virtue of its catechol structure and 3-OH group, primarily functions as a broad-spectrum kinase inhibitor and cellular defense activator. In contrast, kaempferol shifts the target spectrum towards nuclear receptor regulation, particularly exhibiting significant agonistic activity towards ER α .

3.2.1. Quercetin

Quercetin is a common class of natural flavonoid compounds, with its basic skeleton being the typical C6-C3-C6 structure of the flavonoid nucleus, on which five hydroxyl substituents are present, among which the 3-hydroxy group on the pyrone ring is an important structural feature (Nguyen and Bhattacharya 2022). Quercetin is widely present in various fruits, red onions, and the roots and leaves of many vegetables, and has gained extensive attention as a dietary component and nutritional supplement (Yi et al. 2024). Studies have shown that quercetin possesses a wide range of biological activities, primarily including antioxidant stress, anti-inflammatory, antimicrobial, immunomodulatory, and vasodilatory effects, making it a class of natural polyphenolic compounds with great potential for research and application (Agrawal et al. 2023).

3.2.2. Kaempferol

Kaempferol, also known as kaempferol III, is a natural flavonoid compound with the molecular formula $C_{15}H_{10}O_6$, and is a flavonol component widely present in various plant species (Jin, Zhang, and Wang 2023). Its primary sources include the rhizomes of the Zingiberaceae plant *Kaempferia galanga* L, and it is also widely distributed in various fruits, vegetables, and medicinal plants, being particularly common in traditional Chinese medicine (Chen et al. 2024). Modern studies have shown that kaempferol possesses significant core biological activities, primarily including neuroprotective, antioxidant, anticancer, and anti-inflammatory effects, making it one of the most active and important natural anti-inflammatory compounds known to date (Dong, Zhou, and Nao 2023; Nezhad Salari et al. 2024).

3.3. Flavanones

Flavanones are a distinct subclass within flavonoids characterized by a fully saturated C-ring (lacking the C2-C3 double bond), a structural feature that directly dictates their unique physicochemical properties and biological activities. In the context of neuroprotection, the absence of conjugated double bonds in flavanones confines their primary mode of action to two closely linked processes: combating oxidative stress and counteracting neuroinflammation.

3.3.1. Naringenin

Naringenin is a natural flavonoid organic compound with the molecular formula $C_{15}H_{12}O_5$ and the chemical name 4',5,7-trihydroxyflavanone. Its structure features a typical simple flavonoid skeleton, consisting of 15 carbon atoms, including two benzene rings and a three-carbon chain connecting them, forming a total of three ring structures. The primary source of naringenin is the seed coat of the Anacardiaceae plant cashew (*Anacardium occidentale*), and it is also widely present in various other natural plants (Cai et al. 2023). In addition to its antioxidant, anti-inflammatory, antiviral, antitumor, and cardioprotective properties, naringenin also exhibits neuroprotective effects (Ahmad et al. 2021). Furthermore, naringenin is capable of crossing the blood-brain barrier, where it demonstrates the ability to improve neuronal survival and cognitive function in neurodegenerative diseases such as Alzheimer's and Parkinson's, primarily through its anti-inflammatory and antioxidant mechanisms (Zhu et al. 2024).

3.3.2. Hesperetin

Hesperetin (Hst) is a natural citrus flavonoid with the chemical name 4-methoxy-3,5',7'-trihydroxyflavanone and the molecular formula $C_{16}H_{14}O_6$. Its primary sources are citrus fruits such as oranges and grapefruits, where it is distributed in the peel, albedo (white spongy layer), and pulp, with significantly higher content in the peel and albedo than in the juice (Akhter et al. 2024). As an important class of bioactive flavonoid components, hesperetin exhibits significant core biological activities, primarily including neuroprotective, anti-inflammatory, and anti-oxidative stress effects, along with certain hepatoprotective potential, rendering it considerable value for research and application (Li et al. 2024; Khan et al. 2020).

3.4. Isoflavones

Isoflavones constitute a distinct subclass both structurally and functionally, characterized by the unique

attachment of the B-ring at the C3 position—in contrast to the C2 linkage typical of other flavonoid subclasses. This structural hallmark underpins their role as phytoestrogens, through which they exert broad physiological regulatory effects.

3.4.1. Genistein

Genistein, with the chemical name 4',5,7-trihydroxyisoflavone and molecular formula $C_{15}H_{10}O_5$, belongs to the isoflavone class of compounds. It possesses a typical tricyclic skeleton (A ring, B ring, and a central pyran ring), with hydroxyl groups attached at the 4', 5, and 7 positions, a structural feature that confers strong hydrophilicity and antioxidant potential (Sharma et al. 2025). Genistein is one of the most common dietary isoflavones, with primary natural sources being leguminous plants such as soybean and kudzu. As the main active component of soy isoflavones, it is abundant in soy products, including tofu and soy milk, as well as in fermented foods such as natto (Li, Robinson, et al. 2022). Studies have shown that genistein possesses significant core biological activities: it alleviates mitochondrial dysfunction under various pathological conditions, downregulates cytokine-induced signaling cascades in cells, and reduces $A\beta$ aggregation, making it a class of natural isoflavone components with considerable research and application value (Mas-Bargues, Borrás, and Viña 2022).

3.4.2. Daidzein

Daidzein, with the chemical name 7,4'-dihydroxyisoflavone and molecular formula $C_{15}H_{10}O_4$, belongs to the isoflavone class of compounds and possesses high nutritional value. The core structural feature is the presence of one hydroxyl group at each of the 7 and 4' positions, which is key to its antioxidant activity (Alshehri et al. 2021). Daidzein is one of the core components of soy isoflavones, often existing in the form of aglycones or glycosides. Its primary natural sources include soybeans, kudzu, clover, alfalfa, and other leguminous forages and cereals, and it exerts biological effects after metabolism by the intestinal microbiota (Goleij et al. 2024). Studies have shown that daidzein possesses significant core biological activities, primarily including antioxidant, anti-inflammatory, anti-apoptotic, and neuroprotective effects. As a non-steroidal phytoestrogen compound, it holds unique research and application value distinct from other flavonoid components (Laddha and Kulkarni 2023).

3.5. Chalcones

Chalcones, serving as the precursor compounds in flavonoid biosynthesis, possess a distinctive open-chain α,β -unsaturated ketone structure. This unique feature renders them a special subclass with significant biological activities and notable potential for drug development. Within the realm of neuroprotection, the core function of chalcones precisely targets key regulatory nodes of redox homeostasis and neuroinflammation. Licochalcone A and isoliquiritigenin, often termed the “chalcone twin stars,” derived from licorice, exhibit structural similarity yet possess distinct key substituents. This differentiation allows them to excel in complementary biological activities, making both compounds valuable resources in drug development.

3.5.1. Licochalcone A

Licochalcone A is a natural flavonoid compound extracted from plants of the *Glycyrrhiza* genus, with the molecular formula $C_{21}H_{22}O_4$, belonging to the chalcone derivatives (Olloquequi et al. 2023). Its molecular structure exhibits typical features, including two benzene rings connected via an α,β -unsaturated ketone (Li, Xie, et al. 2022). As an important active component in *Glycyrrhiza* plants, licochalcone A possesses a broad range of core pharmacological bioactivities, ameliorating systemic inflammation-related cognitive decline and depressive symptoms through the regulation of oxidative stress, neuroinflammation, and metabolism (Carrasco et al. 2025).

3.5.2. Isoliquiritigenin

Isoliquiritigenin (ISL) has the chemical structure (E)-1-(2,4-dihydroxyphenyl)-3-(4-hydroxyphenyl)-2-propen-1-one, with the molecular formula $C_{15}H_{12}O_4$, and belongs to the chalcone class of flavonoid compounds (Shi et al. 2020). Isoliquiritigenin is a bioactive chalcone compound isolated from licorice, primarily derived from the roots and rhizomes of *Glycyrrhiza* plants, and is also distributed in plants such as *Astragalus*, *Hedysarum*, and *Dianthus*. Modern studies have confirmed that isoliquiritigenin possesses a wide range of pharmacological activities (Lan, Wang, Liu, et al. 2024). It inhibits oxidative stress damage, regulates mitochondrial biogenesis, fusion-fission balance, and mitophagy, and suppresses neuronal apoptosis. Therefore, isoliquiritigenin is a natural active ingredient of great research value (Shi et al. 2020; Lan, Wang, Liu, et al. 2024).

3.6. Anthocyanidins

Anthocyanins are a subclass of water-soluble flavonoids responsible for the vibrant colors in plants, with their potent antioxidant capacity rooted in the unique oxonium ion structure. In the field of neuroprotection, anthocyanins extend beyond direct free radical scavenging to engage in complex mechanisms, including modulating cellular autophagy, regulating NLRP3 inflammasome activity, promoting microglial polarization toward the neuroprotective M2 phenotype, and intervening in cellular senescence processes.

3.6.1. Cyanidin

Cyanidin belongs to the anthocyanidin class of compounds and predominantly exists in glycosylated forms in nature, among which the most common is cyanidin-3-O-glucoside (C3G) with the molecular formula $C_{21}H_{21}O_{11}$. Glycosylation modification is an important structural feature that significantly enhances the stability and water solubility of cyanidin (Li, Yao, et al. 2021). The primary sources of cyanidin include natural plants such as black rice, black beans, and purple sweet potato. They possess potent antioxidant activity, along with multiple core pharmacological potentials including anti-aging, anticancer, anti-inflammatory, neuroprotective, and cardioprotective effects, making them a class of natural anthocyanin active ingredients with great research and application value (Sanjay et al. 2022b).

3.6.2. Delphinidin

Delphinidin (DP) has the molecular formula $C_{15}H_{11}O_7$, belongs to the anthocyanidin class of compounds, and is one of the 20 naturally occurring anthocyanidins identified in nature. In its natural state, it

predominantly exists in various glycosylated forms, ranging from glucosides to arabinosides, and glycosylation modification effectively enhances its water solubility and stability (Chen et al. 2019). As a health-promoting candidate component with great development potential, DP can be used in the research and development of pharmaceuticals and nutraceuticals, and it inhibits tau protein hyperphosphorylation (Heysieattalab and Sadeghi 2020). It possesses multiple core potential activities, including anti-aging, antioxidant, anti-inflammatory, antibacterial, neuroprotective, and anticancer effects (Dong et al. 2022).

4. Molecular Mechanisms of Flavonoid Intervention in Inflammation

The core of flavonoid-mediated intervention in neuroinflammation is achieved through the multidimensional interaction of four key elements: the NF- κ B pathway, the MAPK pathway, ROS, and neural cell regulation, rather than the independent action of a single mechanism. These four elements form a closed-loop regulatory network characterized by “signal pathway crosstalk-oxidative stress mediation-neural cell feedback” (Figure 3), which achieves synergistic effects through bidirectional crosstalk, cascade amplification and, negative regulation, collectively enhancing the neuroprotective effect and providing critical theoretical support for flavonoid-based intervention in neurodegenerative diseases such as AD. ROS accumulation is the initial trigger of pathological cascade reactions. As redox-sensitive signaling molecules, excessive ROS production can directly activate the NF- κ B and MAPK pathways, induce IKK kinase activation to promote the nuclear translocation of NF- κ B p65 (Guo et al. 2024b), and upregulate the transcription of pro-inflammatory factors such as TNF- α . It also activates the phosphorylation of the MAPK family to enhance NF- κ B activity (Sies and Jones 2020) and simultaneously activates the NLRP3 inflammasome to amplify inflammatory signals (Paik et al. 2025). Sustained activation of these pathways, in turn, exacerbates ROS accumulation by inducing the expression and activity of ROS-generating enzymes such as NOX, thus forming a vicious cycle of “ROS initiation-pathway activation-ROS amplification” (Vermot et al. 2021). These cascade signals are further transmitted to neural cells. Excessive ROS and pro-inflammatory factors synergistically drive the polarization of microglia toward the M1 phenotype, and the pro-inflammatory factors secreted by M1 microglia can reactivate the above pathways and induce ROS production, while triggering the abnormal activation of astrocytes. Abnormally activated astrocytes further amplify ROS production and pathway activation by exacerbating A β aggregation and inhibiting autophagy, ultimately leading to neuronal damage and forming a secondary glia-mediated cascade amplification (Simpson and Oliver 2020). Flavonoids can target multiple nodes to interrupt the above cascade reactions: they not only inhibit IKK activity and MAPK phosphorylation to block pathway activation and the synthesis of downstream molecules, but also chelate ROS-related metal ions via phenolic hydroxyl groups and activate the Nrf2 pathway to enhance the activity of antioxidant enzymes for scavenging excessive ROS. Meanwhile, flavonoids induce the M2 polarization of microglia and regulate astrocyte function, achieving synchronous intervention at the origin and transmission links of the pathological cascade and thus converting the vicious cycle into a benign one (Lv et al. 2021; Falcicchia et al. 2020; Manavi et al. 2025).

4.1. Inhibition of the Synthesis and Release of Inflammatory Mediators

Flavonoids play a core role in intervening in neurodegenerative diseases by regulating the NF- κ B and MAPK pathways (Figure 3).

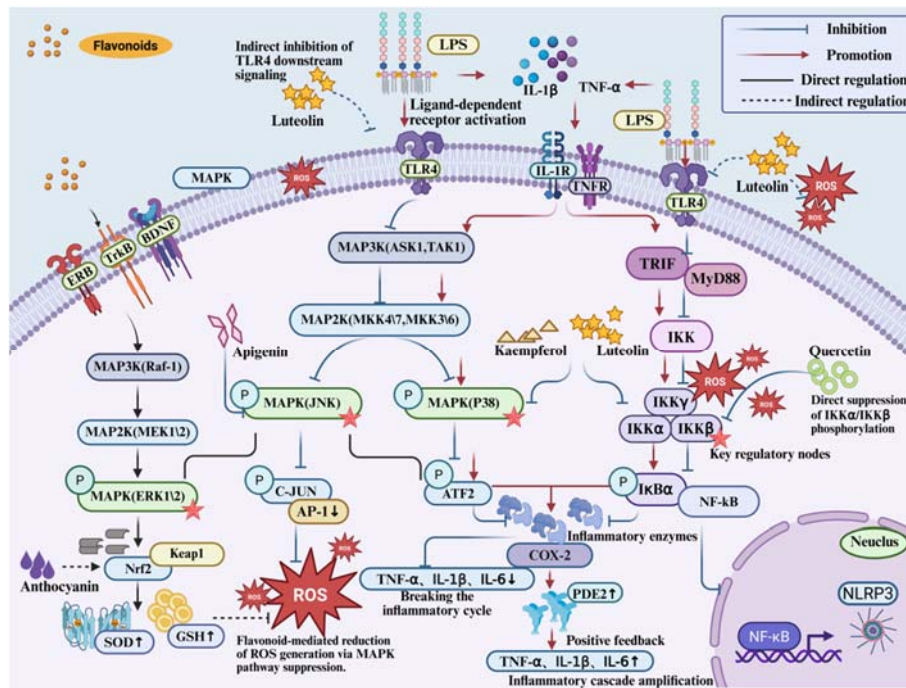


Figure 3: Molecular Mechanism Schematic of Flavonoids Intervening in Neuroinflammation via Multi-Target Regulation of the NF- κ B/MAPK Pathways

Created with BioRender. com. Flavonoids, as natural bioactive compounds, target key nodes in inflammatory pathways to alleviate neuroinflammation in neurodegenerative diseases, making them promising intervention candidates. Therefore, their regulatory mechanisms are highlighted in pathway diagrams. ERB: Erythroblastic Leukemia Viral oncogene homolog; TrkB: Tropomyosin receptor kinase B; BDNF: Brain-Derived Neurotrophic Factor; MAP3K (Raf-1): Mitogen-Activated Protein Kinase Kinase Kinase (Raf-1); MAP2K (MEK1/2): Mitogen-Activated Protein Kinase Kinase (MEK1/2); MAPK (ERK1/2): Mitogen-Activated rotein Kinase (Extracellular signal-Regulated Kinase 1/2); Nrf2: Nuclear factor erythroid 2-related factor 2; Keap1: Kelch-like ECH-associated protein 1; SOD: Superoxide Dismutase; GSH: Glutathione; ROS: Reactive Oxygen Species; RNS: Reactive Nitrogen Species; TLR4: Toll-Like Receptor 4; ASK1: Apoptosis signal-regulating kinase 1; TAK1: TGF- β -activated kinase 1; JNK: Jun N-terminal Kinase; MAPK (P38): p38 Mitogen-Activated Protein Kinase; AP-1: Activator Protein-1; ATF2: Activating Transcription Factor 2; IL-6: Interleukin-6; IL-1 β : Interleukin-1 beta; TNF- α : Tumor Necrosis Factor-alpha; COX-2: Cyclooxygenase-2; TRIF: TIR-domain-containing adapter inducing interferon- β ; MyD88: Myeloid differentiation primary response 88; IKK: I κ B Kinase; IKK γ (NEMO): NF- κ B Essential Modulator; IKK α : IKK alpha; IKK β : IKK beta; NF- κ B: Nuclear Factor kappa-light-chain-enhancer of activated B cells; NLRP3: NOD-, LRR- and pyrin domain-containing protein 3

4.1.1. Inhibition of the Nuclear Factor- κ B (NF- κ B) Pathway

NF- κ B is a major regulator of inflammatory responses and a key regulatory node in the complex inflammatory signaling network. As an inducible and redox-sensitive transcription factor, it can form specific signaling complexes (Guo et al. 2024a). It regulates the cell cycle and selectively modulates the expression of relevant genes in acute inflammation by regulating the expression of target genes such as BCLXL, BCL2, and BCLXS (Rius-Pérez et al. 2020). IL-1 β and TNF- α are involved in the initiation and progression of acute inflammation, and NF- κ B plays a key role in the maintenance and regulation of acute inflammation (El-Shitany and Eid 2019). Pure flavonoids or enriched extracts can reduce the expression of pro-inflammatory cytokines IL-6, TNF- α , IL-1 β , and COX-2, downregulate inflammatory markers, and prevent nerve damage. This anti-inflammatory effect is primarily mediated by modulating microglia and via the MAPK and NF- κ B signaling pathways (Spagnuolo, Moccia, and Russo 2018).

Studies have shown that Api exerts anti-inflammatory effects by inhibiting NF- κ B activation and reducing ROS production (Pratas et al. 2024); Luteolin can downregulate pro-inflammatory cytokines such as IL-1 β , IL-6, and IL-8, and modulate the NF- κ B, JAK-STAT, and TLR signaling pathways. It can inhibit the protein expression of nuclear p65, ASC, NLRP3, and cleaved caspase-1, while increasing the protein expression of Nrf2 in oxyhemoglobin-induced primary cortical neurons and glial cells (Gendrisch et al. 2021; Kou et al. 2022). Wang et al. demonstrated that naringenin inhibits NLRP3 expression by suppressing the activation of the NLRP3/NF- κ B pathway stimulated by OA and LPS (Wang et al. 2020); Genistein can also alleviate TNF- α -mediated inflammatory responses via the CB1 receptor, reduce the phosphorylation level of NF- κ B in mouse serum, and increase SOD expression (Wei et al. 2022).

Flavonoids offer a novel intervention strategy distinct from traditional transcription inhibitors for the treatment of inflammatory diseases, holding promise as potential molecular templates for developing proteolysis-targeting anti-inflammatory agents.

4.1.2. Inhibition of the MAPK Pathway

MAPK is a heterotrimeric Ser/Thr protein kinase. Its activation can promote the hyperphosphorylation of neuronal Tau protein and is involved in regulating A β metabolism, cell proliferation, apoptosis, and inflammatory responses. As a family of serine/threonine protein kinases that mediate fundamental biological processes and cellular responses to external stress signals, the MAPK family includes three main subfamilies: ERK, JNK, and p38. This pathway regulates the synthesis of the NLRP3 inflammasome and apoptosis-related factors, serves as a key route for the transduction of inflammatory signals from the cell membrane to the nucleus, and can synergize with the NF- κ B pathway to upregulate the expression of pro-inflammatory genes (Ren et al. 2020).

Flavones can reduce the levels of inflammatory mediators, including NO, TNF- α , IL-6, IL-1 β , MCP-1, CXCL10, iNOS, COX-2, and lipocalin-2. They act on the MAPK signaling pathway to regulate the phosphorylation of ERK1/2, JNK, and p38, thereby blocking the transmission of downstream inflammatory signals (Gong et al. 2020; Song et al. 2021; Chen et al. 2022). API induces apoptosis by activating the extrinsic caspase-dependent pathway through upregulating the mRNA expression of caspase-3, caspase-8, and TNF- α (Imran et al. 2020). Jo et al. demonstrated that hesperetin reduces the overexpression levels of inducible NO synthase, pro-inflammatory cytokines, and the MAPK extracellular signal-regulated kinases ERK1/2 and p38 in LPS-stimulated BV-2 mouse cell lines (Jo et al. 2019). It also inhibits the MAPK pathway by decreasing the phosphorylation levels of JNK and p38, thereby blocking the inflammatory cascade (Wang, Yao, et al. 2024; Shen et al. 2024). Quercetin reduces phagocytic capacity, decreases the levels of inflammatory mediators and lipocalin-2, and increases the secretion of IL-10 by activating the MAPK and Nrf2 signaling pathways and inhibiting the NF- κ B signaling pathway (Tsai et al. 2021; Han et al. 2021). Yao et al. demonstrated that ISL can regulate the TLR4/NF- κ B signaling pathway, inhibit the expression of TLR4 and phosphorylated NF- κ B p65 protein, and exert its anti-inflammatory activity by mediating various cellular processes (Yao et al. 2024).

Through molecular dynamics simulation studies based on molecular docking results, Zu et al., identified MAPK as a core target of quercetin. Jiang et al., demonstrated the anti-apoptotic effect of quercetin through the MAPK and PI3K/Akt/GSK3 β signaling pathways by pre-incubating HT22 cells with 5 μ mol/L of the drug for 12 hours (Zu et al. 2021; Jiang et al. 2016).

4.2. *Flavonoids Scavenge Reactive Oxygen Species and Inhibit Oxidative Stress*

Under normal and healthy physiological conditions, there is a balance between the formation of ROS and the endogenous antioxidant defense mechanism. However, if this balance is disrupted, it can lead to oxidative stress and associated damage. This state of oxidative stress can cause damage to DNA, proteins, and membrane lipids, and may lead to cell death. Antioxidants play an important role in neuroinflammation; the accumulation of ROS can activate neuroinflammatory signaling pathways and damage cells (Arulselvan et al. 2016). ROS are free radical derivatives, such as singlet oxygen and hydrogen peroxide (Madreiter-Sokolowski, Thomas, and Ristow 2020). Numerous studies have shown that flavonoids and phenols contribute to the antioxidant activity of natural compounds. Due to the presence of multiple phenolic hydroxyl groups in their molecular structure, flavonoids possess strong antioxidant capacity: they can reduce the accumulation of ROS, enhance the activities of superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH), improve the body's antioxidant capacity, and indirectly inhibit neuroinflammatory responses (Ye et al. 2021).

Quercetin's ability to reduce ROS formation is achieved by chelating metals involved in ROS production, inhibiting various ROS-generating enzymes, or downregulating the expression of related enzymes (Atala et al. 2017). Naringenin 6-PN inhibits the production of pro-inflammatory cytokines and ROS by downregulating the protein levels of the receptor for advanced glycation end products (RAGE) and NADPH oxidase. Osteoarthritis inhibits intracellular ROS levels through the Nrf2-mediated antioxidant response (Xian et al. 2021). Yuan et al. demonstrated that kaempferol activates nuclear factor erythroid 2-related factor 2 (Nrf2)/SLC7A11/GPX4 signaling, enhances antioxidant capacity, and inhibits the accumulation of lipid peroxidation in neurons treated with oxygen-glucose deprivation/reperfusion (OGD/R) (Yuan et al. 2021). Data show that cyanidin-3-O-glucoside inhibits NLRP3 inflammasome activation in vivo and in vitro, eliminates damaged mitochondria, so as to maintain mitochondrial homeostasis and alleviate oxidative stress (Li et al. 2020). Chen et al. demonstrated that delphinidin reduces the accumulation of ROS after angiotensin II (Ang II) stimulation by directly activating AMP-activated protein kinase (AMPK) and subsequently inhibiting the activity of Rac1 and the expression of p47, thereby eliminating the excessive levels of ERK1/2, P38, and JNK1/2 phosphorylation induced by oxidative stress (Chen et al. 2020). DP exhibits hypoxic-resistant neuroprotective activity; it can attenuate the oxidative stress of H₂O₂ in SK-N-SH cells by inactivating the ASK-JNK/p38 signal transduction pathway. Additionally, Dp shows an effective response to A β _{25–35}-induced cytotoxicity by eliminating intracellular calcium influx and tau phosphorylation (Husain et al. 2022).

Flavonoids exert multi-faceted inhibition of oxidative stress by directly scavenging ROS through their unique phenolic hydroxyl structures and by activating the cellular intrinsic antioxidant defense system.

4.3. *Regulation of Neural Cells by Flavonoids*

The mechanism of action of flavonoids is not a single target; they can delay disease progression by regulating the functional states of microglia and astrocytes (Figure 4).

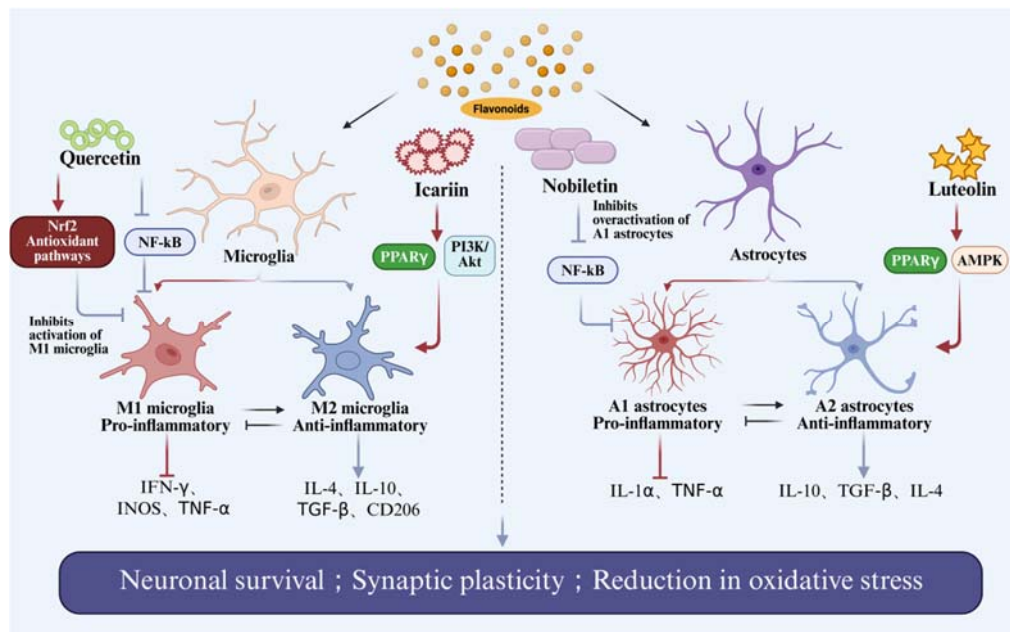


Figure 4: Regulation of Neural Cells by Flavonoids

Created with BioRender. com. IFN- γ : Interferon gamma; iNOS: inducible Nitric Oxide Synthase; TNF- α : Tumor Necrosis Factor-alpha; IL-1 α : Interleukin-1 alpha; IL-4: Interleukin-4; IL-10: Interleukin-10; TGF- β : Transforming Growth Factor-beta; CD206: Cluster of Differentiation 206

4.3.1. Regulation of Microglia by Flavonoids

As the inherent population of mononuclear phagocytes in the CNS, microglia serve as the first line of immune defense and play an irreplaceable role in maintaining intracerebral immune homeostasis. However, in the pathological microenvironment of neurodegenerative diseases, the abnormal activation of microglia disrupts the aforementioned balance. It amplifies the pathological cascade by excessive release of pro-inflammatory factors and exacerbation of oxidative stress, ultimately leading to progressive neuronal damage and the aggravation of neurodegeneration (Sadeghdoust, Das, and Kaushik 2024). M1 microglia primarily mediate inflammatory responses by releasing pro-inflammatory cytokines such as IL-1 β , IL-6, and TNF- α ; in contrast, M2 microglia secrete anti-inflammatory and neurotrophic factors, including IL-4, IL-10, TGF- β , IGF-1, and BDNF, thereby exerting neuroprotective effects. Therefore, targeted regulation of microglial polarization from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype has become an important strategy for blocking the neuroinflammatory cascade.

Quercetin regulates the M1/M2 phenotypic transition of microglia, leading to increased production of IL-4 and IL-10, while inhibiting the release of TNF- α and IL-1 β (Li et al. 2023). Dihydroquercetin (DHQ) can exert neuroprotective effects by regulating the activation of triggering receptor expressed on myeloid cells 2 (TREM2) in microglia, thereby alleviating lipopolysaccharide (LPS) and/or 6-hydroxydopamine (6-OHDA)-induced toxic damage to dopaminergic (DA) neurons (Yang et al. 2024). Olloquequi et al. demonstrated that LCA, as a protein tyrosine phosphatase 1B (PTP1B) inhibitor, exhibits an inhibitory effect on microglial activation, thereby alleviating neuroinflammation (Olloquequi et al. 2023). Huang et al. found that LCA significantly inhibits LPS-stimulated production of pro-inflammatory mediators and microglial activation by blocking the phosphorylation of extracellular signal-regulated kinase (ERK1/2) and NF- κ B p65

in BV2 cells(Huang et al. 2017). Studies have shown that ISL exerts an immunomodulatory effect by effectively inhibiting the activation of BV2 microglia and the expression of pro-inflammatory cytokines through suppressing the secretion of pro-inflammatory cytokines (Zhang, Qu, et al. 2024). Sanjay et al. demonstrated that C3G can shift the M1 phenotype of microglia to M2 by decreasing the expression of M1-specific markers (CD86 and CD80), inflammatory cytokines (IL-1 β , IL-6, TNF- α), and ROS, while increasing the expression of M2-specific markers (CD206 and CD163) (Sanjay et al. 2022a). Liu et al. demonstrated that delphinidin can ameliorate cognitive deficits, synaptic loss, and A β peptide plaque deposition in APP/PS1 mice by downregulating the gene signature of senescent microglia and preventing cellular and microglial senescence, thereby attenuating AD pathology (Liu et al. 2025)

Through multi-target mechanisms, flavonoids finely regulate the activation state of microglia, inhibit senescence-associated β -galactosidase activity and the senescence-associated secretory phenotype (SASP), thereby exerting anti-neuroinflammatory and neuroprotective effects.

4.3.2. Regulation of Astrocytes by Flavonoids

As multifunctional glial cells in the CNS, astrocytes play a core role in neural support and maintenance of internal environment homeostasis, providing crucial support for the survival and functional maintenance of neurons (Patani, Hardingham, and Liddelow 2023). In neurodegenerative diseases represented by AD, astrocytes are both active inducers of neuroinflammation and dynamic responders to the inflammatory microenvironment, and participate in the pathological process of the disease through this “bidirectional interaction” (Kim, Lim, and Oh 2024). Astrocytes can phagocytose and degrade nearby A β . Research results have shown that AST (presumably referring to a specific astrocyte regulator or flavonoid; context-dependent) activates autophagy in AD mice, inhibits the apoptosis of hippocampal astrocytes, and improves the cognitive deficits of animals by downregulating the Fas/FasL-VDAC1 signaling pathway (Wang, Yang, et al. 2025).

Quercetin can reduce astrocyte biomarkers in the brain and effectively inhibit the abnormal accumulation of oligomeric pyroglutamylated β -amyloid (A β 3 (pE)-42) in astrocytes (Arndt et al. 2025). Pretreatment with Icariside II (ICS II) provides potent neuroprotective effects through the Nrf2-mediated OXPHOS/NF- κ B/ferroptosis axis in astrocytes (Gao et al. 2023). The dasatinib-quercetin combination drug reversed cellular senescence in primary cultured astrocytes induced by LPS stimulation and reduced the levels of pro-inflammatory factors (Du et al. 2023). Flavonoids have been demonstrated to ameliorate neurological deficits, reduce astrocyte activation, and suppress pro-inflammatory cytokines (Li et al. 2025). Nobiletin ameliorates A β 42-induced astrocytic pathological injury through its multi-dimensional actions, including anti-inflammatory, antioxidant, calcium homeostasis regulation, and pathway remodeling. This provides a potential natural active compound and therapeutic target for AD treatment(Sanjay et al. 2024).

Flavonoids modulate astrocytic function through multiple targets and pathways, primarily centered on suppressing inflammation and regulating cellular phenotypes, thereby improving the neuropathological microenvironment and exerting neuroprotective effects.

5. Intervention of Flavonoids in Neurological Inflammatory Diseases

Neuroinflammation is a fundamental immune response of the CNS to various stimulating factors, characterized by the production of inflammatory mediators, activation of microglia and astrocytes, and recruitment of innate and adaptive immune cells to the inflammatory site. This process can be involved in the pathological progression of related brain diseases such as AD, PD, HD, and ALS (Figure 5). As an important class of natural compounds, flavonoids have been widely shown to alleviate neuroinflammation by inhibiting the production of pro-inflammatory mediators, increasing the secretion of anti-inflammatory factors, and regulating the polarization of microglia and astrocytes. Specifically, they reduce the synthesis of inflammatory mediators mainly by inhibiting signaling pathways such as NF- κ B and MAPK, scavenge ROS to alleviate oxidative stress, and simultaneously regulate neural cell function, ultimately achieving anti-inflammatory effects (Chen et al. 2022).

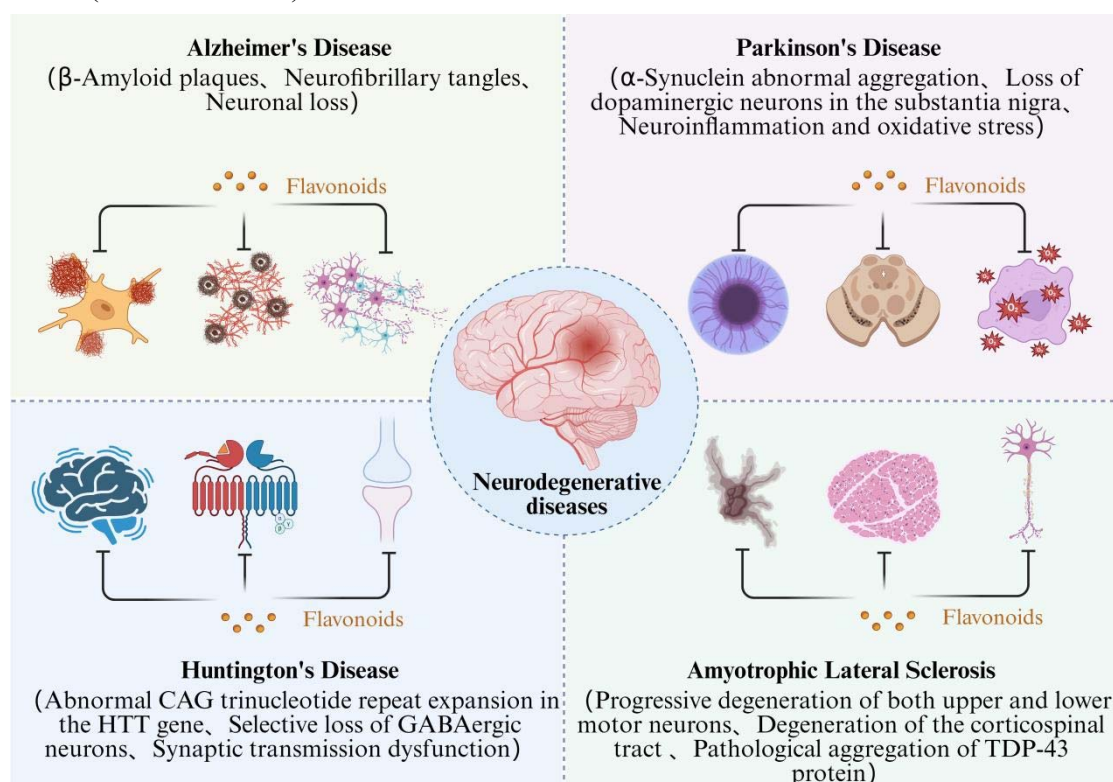


Figure 5: Intervention of Flavonoids in AD, PD, HD, and ALS

Created with BioRender. com. CAG: Cytosine-Adenine-Guanine; HTT: Huntingtin; GABA: Gamma-Aminobutyric Acid; TDP-43: TAR DNA-binding Protein 43 kDa

5.1. Alzheimer's Disease

Alzheimer's Disease (AD) is the primary cause of dementia and has rapidly become one of the most economically burdensome, highly fatal, and socially impactful diseases of the 21st century. According to 2018 data from AD International, the global prevalence of dementia is estimated to be approximately 50 million people; this number is projected to triple by 2050, with two-thirds of patients residing in low and middle-income countries (Scheltens et al. 2021). Currently, the pharmacological treatment of AD is limited to symptom relief, including donepezil, rivastigmine, galantamine, and the NMDA receptor antagonist memantine. These drugs can improve cognitive function and activities of daily living, but they cannot halt disease progression (Zheng and Wang 2025). Flavonoids can intervene in the pathological mechanisms of AD through multiple dimensions, featuring the advantages of natural low toxicity and synergistic efficacy. Therefore, the role of flavonoids in ameliorating neuroinflammation has received extensive

attention (Borowiec and Michalak 2022).

The mechanism of action of flavonoids in AD involves inhibiting acetylcholinesterase, butyrylcholinesterase, Tau protein aggregation, β -secretase, oxidative stress, inflammation, and apoptosis by regulating signaling pathways associated with cognitive and neuroprotective functions (Calderaro et al. 2022). Sang et al. found that the citrus flavonoid nobiletin (NOB) exerts multi-pathway synergistic neuroprotective effects in A β 42-induced primary astrocytes by inhibiting the TLR4/NF- κ B and Keap1-Nrf2 pathways to alleviate inflammation and oxidative stress, respectively, and by regulating IP3R-mediated Ca²⁺ homeostasis (Sanjay et al. 2024). Pan et al. demonstrated that sodium rutin (NaR) alleviates A β deposition, neuroinflammation, and synaptic damage, thereby improving learning and memory deficits in AD model mice, by upregulating the TREM2 receptor and promoting mitochondrial oxidative phosphorylation (Pan et al. 2019). Kou et al. found that luteolin ameliorates spatial learning and memory deficits in 3 $\times$ Tg-AD mice by inhibiting the expression of endoplasmic reticulum stress markers GRP78 and IRE1 α , thereby reducing excessive astrocyte activation and the release of downstream pro-inflammatory factors, including COX-2 and iNOS proteins (Kou et al. 2022). Wu et al. demonstrated that icariin alleviates ceramide-induced neuronal senescence by directly targeting and inhibiting the P53 signaling pathway (Wu et al. 2024). Meanwhile, Zheng et al. demonstrated that icariin (ICA) reduces abnormal A β accumulation and alleviates neuroinflammation in AD models by modulating pathways such as the NF- κ B and JNK/p38 MAPK pathways (Zheng et al. 2023).

AD, as a complex neurodegenerative disorder, involves multiple pathological processes including A β deposition, tau protein aggregation, neuroinflammation, and oxidative stress. Current clinical treatments primarily focus on symptom alleviation and are largely ineffective in halting disease progression. In contrast, flavonoids leverage their natural low toxicity and multi-target intervention properties to act synergistically on the core pathological mechanisms of AD. This characteristic not only provides critical clues for elucidating their pharmacodynamic basis but also lays a solid theoretical foundation for developing diversified therapeutic strategies capable of effectively slowing disease progression.

5.2. Parkinson's Disease

Parkinson's disease (PD) is the second most common neurodegenerative disease after AD. Its occurrence is attributed to the loss of dopaminergic neurons in the substantia nigra, leading to reduced dopamine production in the striatum, which in turn causes motor dysfunction accompanied by PD-like motor symptoms such as bradykinesia with resting tremor, rigidity, or both. PD is a well-recognized clinical syndrome with diverse etiologies and clinical manifestations. The primary neuropathological hallmark of PD is the loss of dopaminergic neurons in the substantia nigra pars compacta (SNc) (Poewe et al. 2017; Talebi et al. 2022), and over 6 million people worldwide suffer from PD (Bloem, Okun, and Klein 2021; Armstrong and Okun 2020). Levodopa is the most commonly used first-line therapeutic drug, but it cannot reverse the disease or halt its progression. Moreover, over time, patients require increased doses of L-DOPA, which leads to severe side effects such as dyskinesia. Therefore, the development of interventions to slow or stop the progression of PD remains a top priority for patients and researchers. A growing body of research has shown that flavonoids can intervene in PD by scavenging oxidative stress, inhibiting neuroinflammation, regulating the dopaminergic system, and suppressing α -synuclein aggregation (Varshney and Siddique 2024).

Various neurotoxins are used to induce Parkinsonism, including 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), 6-hydroxydopamine (6-OHDA), and rotenone (ROT). Flavonoids can exert effects through multiple pathways: they can upregulate the levels of neurotransmitters such as dopamine (DA), 3,4-dihydroxyphenylacetic acid (DOPAC), and homovanillic acid (HVA), reduce the accumulation of α -synuclein (SNCA), and possess potential dopamine-increasing, anti-inflammatory, and antioxidant properties. Furthermore, in addition to anti-inflammatory and antioxidant effects, flavonoids exert multiple impacts on PD, such as increasing dopamine levels, reducing oxidative stress, improving motor dysfunction, and alleviating dopaminergic neuron loss and α -synuclein aggregation (Açar et al. 2023). Huang et al. demonstrated that API activates chaperone-mediated autophagy (CMA) by upregulating the Nrf2 signaling pathway, promotes the degradation of pathological α -synuclein (SNCA), and ameliorates SNCA aggregation-induced neuronal apoptosis and neuroinflammation in PD models (Huang et al. 2025). Meng et al. demonstrated that a novel flavonoid 1,3,4-oxadiazole derivative (Compound F12) reduces oxidative stress by promoting Nrf2 nuclear translocation, alleviates inflammatory responses by inhibiting NF- κ B nuclear translocation, thereby reducing dopaminergic neuron loss and improving motor dysfunction in MPTP-induced mouse models of PD (Meng et al. 2023). Lin et al. confirmed that quercetin (QCT) significantly inhibits ferroptosis by activating the Nrf2 pathway, reduces lipid peroxidation and oxidative stress damage, thereby protecting dopaminergic neurons from death in MPP⁺/MPTP-induced PD models (Lin et al. 2022). Huang et al. demonstrated that baicalin exerts neuroprotective effects in the treatment of PD by upregulating the expression of Nrf2 and its downstream antioxidant enzymes, inhibiting the activation of the NLRP3 inflammasome, and alleviating oxidative stress (Huang et al. 2024). Isoliquiritigenin (ISL) exerts neuroprotective effects by alleviating neuroinflammation through the inhibition of the JNK/AKT/NF- κ B signaling pathway, which suppresses microglial activation and the release of pro-inflammatory factors in PD models (Bai et al. 2023).

Therefore, flavonoids show broad application prospects in the intervention of PD. They enhance antioxidant defense by activating the Nrf2/ARE pathway, attenuate neuroinflammation by inhibiting the NF- κ B/NLRP3 and other pathways, and promote the clearance of pathogenic α -synuclein through chaperone-mediated autophagy. These multi-target and synergistic mechanisms not only improve dopaminergic neurotransmitter levels and alleviate motor dysfunction, but also directly protect neurons by targeting core pathological processes such as oxidative stress, inflammatory responses, and proteostasis.

5.3. Huntington's Disease

Huntington's Disease (HD) is an autosomal dominant neurodegenerative disease caused by the abnormal expansion of CAG trinucleotide repeats in the first exon of the HTT gene, which encodes the toxic mutant huntingtin protein (mHTT). Its clinical phenotypes include chorea-like involuntary movements, progressive cognitive decline, depression, and impulsivity. It mostly onsets in middle age with a chronic progressive course, and patients experience slow and continuous decline in neurological function and quality of life over approximately 20 years (Tabrizi et al. 2022). Currently, there are no approved disease-modifying treatments for HD, which highlights the urgency of in-depth research on its pathogenesis and the development of therapeutic strategies. Tetrabenazine, a catecholamine and serotonin neurotransmitter depletor, is used as a therapeutic drug for HD; however, its clinical application is significantly limited due to the risk of inducing or exacerbating depression (Claassen et al. 2022).

Flavonoids can activate the Nrf2/HO-1 pathway or upregulate the expression of FOXO1, enhance the expression of antioxidant enzyme genes, reduce the levels of ROS and LPO, alleviate neuronal apoptosis, and induce autophagy to clear huntingtin protein, thereby promoting neuronal survival (Gu et al. 2025). Luteolin inhibits mutant huntingtin (Htt) aggregation in the cerebral cortex, hippocampus, and striatum, reduces the level of the neuronal injury biomarker neurofilament light chain (NfL), and maintains neuronal structural integrity. It simultaneously modulates oxidative stress and apoptosis-related pathways, improves proteostasis, and exerts anti-muscle atrophy effects. It improves motor coordination and balance ability, prolongs survival, and prevents weight loss in HD model mice, ultimately achieving neuroprotective effects (Mohammed et al. 2024). Kaempferol inhibits the activation of the NF- κ B pathway, reduces the secretion of pro-inflammatory factors IL-1 α , TNF- α , and complement component C1q, thereby preventing the proteolytic activation of complement C3 and the generation of reactive A1 astrocytes. Additionally, it inhibits the abnormal production of amyloid β -peptide and alleviates 3-nitropropionic acid (NPA)-induced neuronal damage in the striatum and hippocampus of rat models of HD (Lopez-Sanchez et al. 2022). Genistein stimulates the macroautophagy/autophagy process by activating the FOXO3-related pathway. This effect promotes the degradation and reduces the levels of mutant HTT protein in the brains of HD model mice. Meanwhile, genistein ameliorates the inflammatory and oxidative stress status, corrects cognitive, anxiety, and motor-related behavioral abnormalities in model mice, thereby exerting neuroprotective effects against HD (Pierzynowska et al. 2024).

Compared to tetrabenazine, flavonoids not only avoid the risk of inducing depression but also cover core pathological aspects of HD through multi-target actions. Their individual components exhibit distinct and complementary mechanisms of action. These findings provide clear directions and experimental evidence for subsequent research, including optimization of single active compounds, exploration of multi-component synergistic treatment strategies, and facilitating the translation of related basic research into clinical applications.

5.4. Amyotrophic Lateral Sclerosis

Amyotrophic Lateral Sclerosis (ALS), also known as motor neuron disease, is a fatal neurodegenerative disease of the CNS. Its typical clinical feature is combined impairment of upper motor neuron (UMN) and lower motor neuron (LMN) function, which can involve the medulla oblongata, cervical, thoracic, and lumbar segments (Feldman et al. 2022). The intravenous administration regimen of edaravone has been approved for disease-modifying treatment in patients with ALS; however, the evidence for its efficacy is currently limited to the short-term beneficial effects observed in the MCI186-ALS19 study (Witzel et al. 2022).

Natural antioxidants can antagonize oxidative stress and maintain cellular homeostasis; flavonoids such as quercetin and resveratrol have demonstrated clear potential in improving cognitive function and alleviating pathological damage related to neurodegeneration, providing a translational candidate strategy for the prevention and intervention of neurodegenerative diseases (Oyovwi et al. 2025). Quercetin protects motor neurons from damage and delays disease progression in ALS models by activating the Sestrin2/AMPK/SIRT1 signaling axis, alleviating endoplasmic reticulum stress and oxidative stress damage, and inhibiting the activation of inflammation-related pathways such as NF- κ B and mTOR as well as the release of pro-inflammatory factors (Jin, Zhang, et al. 2023). API enhances cellular antioxidant defense capacity to alleviate oxidative stress by upregulating ALDH1A2 expression and activating the Nrf2/ARE

signaling pathway. It simultaneously inhibits the activation of apoptosis-related pathways and the abnormal aggregation of TDP-43 protein, thereby protecting motor neurons in a SOD1*G93A mutation-induced ALS model (Liang et al. 2024a; Liang et al. 2024b). Kaempferol restores mitochondrial calcium uptake capacity and mitochondrial function in the C9ORF72-ALS model by regulating the GRP75-mediated IP3R-VDAC1 pathway, thereby ameliorating intrinsic mitochondrial defects. Additionally, it significantly inhibits the aberrant activation of endoplasmic reticulum stress and enhances cellular resistance to severe endoplasmic reticulum stress. It effectively ameliorates pathological motor dysfunction in model mice, inhibits motor neuron degeneration, and plays a key neuroprotective role in ALS associated with C9ORF72 gene mutations (Pilotto et al. 2025).

In summary, ALS is a fatal neurodegenerative disease of the CNS, whose pathological progression is closely associated with multiple mechanisms, including oxidative stress, inflammatory responses, mitochondrial dysfunction, and apoptosis. Current clinical treatments offer only short-term benefits, while flavonoids, leveraging their natural multi-target advantage, present a more promising translational direction for ALS intervention.

6. Current Research Status in the Field

The mechanisms by which flavonoids synergistically intervene in chronic neuroinflammation through multiple targets and pathways have been further elucidated; however, their low bioavailability and insufficient clinical evidence remain bottlenecks that urgently need to be overcome at the current stage. While the multi-target and synergistic properties of flavonoids bring advantages, they also make it difficult to accurately identify their primary targets of action and specific mechanisms. Their potential depends on effective transport across the blood-brain barrier, bioavailability, and stability in the CNS (Grabska-Kobyłeczka et al. 2023).

6.1. Translation Challenges and Improvement Strategies for Flavonoids

The most striking feature of flavonoids is their “one-stone-multi-bird” mode of action, which enables simultaneous regulation of multiple pathological processes such as ion channels, inflammatory pathways, and oxidative damage. This multi-target and multi-pathway characteristic makes them particularly suitable for intervening in complex diseases like chronic neuroinflammation. However, issues such as low oral bioavailability, rapid intestinal metabolism, insufficient targeting, and complex purification processes severely hinder their approval and application as clinical neuroprotective agents (Liga, Paul, and Péter 2023; Wang, Liu, et al. 2025). High bioavailability is crucial for bioactive compounds to reach sufficient blood concentrations and exert their beneficial health effects. Therefore, bioavailability can be improved through molecular technological and chemical modifications, dosage formulation, combined synergistic effects with other dietary components, and the use of micro/nanoparticle delivery systems (Li, Zeng, et al. 2022; Liu et al. 2026). Sysak et al. demonstrated multiple synthetic possibilities of flavonoid-metal nanoparticle conjugates (e.g., silver nanoparticles and gold nanoparticles) and hybrids (metal oxide nanoparticles), and enhanced their biological effects (Sysak et al. 2023). Li et al. showed that dihydromyricetin-functionalized silver nanoparticles (AgNPs) exhibit strong antioxidant activity, with a free radical scavenging rate of approximately 56-92% at different concentrations (0.01-0.1 mg/mL) (Li, Ali, et al. 2021). However, information on the long-term toxicity of nanoparticles is currently limited. Therefore, the toxicity of the conjugates should be carefully evaluated. Furthermore, site-specific modification of flavonoids through methylation or glycosylation can be used to improve and adapt their biophysical and

pharmacokinetic properties. Jin et al. demonstrated that 3'-O-methyltransferase can modify epigallocatechin gallate (EGCG), enhancing its bioavailability in humans (Jin, Qu, et al. 2023). Nanocrystal technology is an innovative strategy for enhancing the bioavailability of poorly soluble compounds. It has been successfully applied to optimize the bioavailability of dietary flavonoids, with relevant studies confirming that flavonoid nanocrystals can significantly increase plasma drug concentration, shorten time-to-peak, and enhance in vitro bioactivity (Yuan et al. 2024; Maciolek et al. 2025). Flavonoids demonstrate considerable potential in neuroinflammatory intervention due to their multi-target synergistic effects. However, their clinical translation still faces key challenges such as low bioavailability, insufficient targeting, and limited long-term safety data. Future research should focus on multi-dimensional strategies combining structural modification, innovative delivery systems, and systematic toxicity evaluation to collectively overcome existing technical barriers and advance the clinical transformation of flavonoids from natural dietary components into effective and safe neurotherapeutic agents.

6.2. Shortcomings in Clinical Translation Evidence and Model Optimization

Currently, clinical translational evidence for flavonoids in the field of neuroinflammation remains relatively lacking, with most studies being confined to cellular and animal models. Cell models cannot easily replicate the complex intercellular interactions in vivo, while the immune and metabolic pathways in animal models exhibit species differences from humans. Furthermore, most studies employ acute inflammation or young transgenic animal models, which differ considerably from the true pathological process of chronic neuroinflammation in humans. There is currently a lack of large-scale, high-quality human clinical trials to confirm the efficacy and safety of flavonoids. Future efforts should promote clinical translational research, design well-conducted randomized controlled trials, focus on validating their efficacy in specific populations, and pay attention to their long-term safety. Jeziorski used human pluripotent stem cells to construct brain organoids, introduced neuroinflammation-related pathological factors, and created a "humanized" inflammatory microenvironment. This addresses the issue of species-specific brain structure differences in animal models and can simulate the chronic and region-specific characteristics of neuroinflammation in humans (Jeziorski et al. 2023). Pavlou et al. introduced a 3D self-assembled in vitro model of the human neurovascular unit, which combines primary human brain endothelial cells, pericytes, and astrocytes, as well as stem cell-derived neurons and astrocytes carrying familial Alzheimer's disease (FAD) mutations. This model enables visualization of amyloid- β ($A\beta$) accumulation in neuronal and vascular compartments (Pavlou et al. 2025). The use of humanized animal models addresses differences in immune and metabolic pathways (Zhang, Wang, et al. 2025). Humanized rodent models have expanded opportunities for in vivo exploration of human neurodegenerative diseases, other brain disorders, and their treatments, particularly in the study of various CNS diseases such as AD, PD, HD, and ALS. It is necessary to develop models that are more similar to human diseases to provide reliable preclinical evidence for clinical translation and reduce the translation gap from preclinical to clinical research.

7. Conclusion

As a class of natural polyphenols with diverse structures, flavonoids have been widely verified for their value in inflammation intervention. This review systematically summarizes the chemical structures, anti-inflammatory mechanisms, and application potential of flavonoids in neurodegenerative diseases, providing a multi-dimensional

perspective for the research on natural products targeting inflammation.

Flavonoids are widely found in vegetables, fruits, and herbs. Compared with traditional anti-inflammatory drugs, the anti-inflammatory effect of flavonoids relies on a multi-target synergistic mechanism. They can act on multiple key inflammatory signaling pathways, such as NF- κ B and MAPK, simultaneously, reducing the synthesis and release of pro-inflammatory factors, regulating the function of immune cells, and alleviating oxidative stress, thereby achieving comprehensive intervention in the inflammatory cascade reaction. In inflammatory diseases of the nervous system, flavonoids show unique advantages. They not only inhibit the NF- κ B pathway to reduce pro-inflammatory factors such as TNF- α but also inhibit oxidative stress-induced damage to nerve cells by scavenging ROS. This multi-target characteristic makes their anti-inflammatory effect more comprehensive and long-lasting. Originating from plant secondary metabolites and featuring natural low toxicity, flavonoids have great advantages in the treatment of chronic inflammation. Compared with traditional anti-inflammatory drugs such as NSAIDs, long-term use of NSAIDs is prone to cause adverse reactions such as gastrointestinal ulcers and bleeding, and may also affect liver and kidney functions. However, flavonoids are derived from plants, and their long-term use has relatively fewer side effects, making them more suitable for long-term administration in patients with chronic inflammation to maintain stable disease conditions. Moreover, flavonoids have a wide range of sources, existing in large quantities in vegetables, fruits, and herbs in daily diets, and are easily accessible. People can achieve disease prevention through reasonable dietary intake, which has good population accessibility and is of great significance for reducing the incidence of neurodegenerative diseases.

Although flavonoids have significant anti-inflammatory potential, there are still many limitations in their research. Low bioavailability is a core challenge. Most flavonoids have poor oral absorption, insufficient water solubility and stability, and are easily metabolized and degraded by intestinal flora, resulting in insufficient effective concentration in target tissues, making it difficult to fully exert their therapeutic effects. Weak clinical translation evidence also limits their application. Existing studies are mostly based on cell models and animal experiments, and large-scale human clinical trials are scarce. Moreover, there is a lack of unified dosage standards and efficacy evaluation systems, making it difficult to clarify their actual value in human diseases. In addition, the complexity of the mechanism of action has not been fully elucidated. The structure-activity relationship of different flavonoid subclasses still needs to be refined, and the cross-regulatory mechanism of flavonoids on the gut microbiota-immune-neural axis also needs to be further analyzed. Due to insufficient long-term safety data, although flavonoids have low toxicity, they may induce oxidative stress or interfere with drug metabolism at high doses, and the risk assessment of their long-term use still needs to be improved.

Flavonoids have significant advantages in the field of anti-inflammation. Their multi-target, low-toxicity, and wide-source synergistic effects can intervene in the entire chain of inflammatory reactions, especially neurodegenerative diseases. Their natural low toxicity makes them suitable for long-term management of chronic inflammation, and they also have disease-modifying potential and wide source accessibility. However, the limitations of current research restrict its clinical application. Future research can focus on formulation innovations such as nanocarriers and targeted modifications to improve bioavailability; conduct large-sample clinical trials to clarify the medication regimens for specific diseases; combine molecular docking and artificial intelligence to analyze the structure-activity relationship and

design targeted derivatives; explore emerging mechanisms such as the gut-brain axis to discover new regulatory targets; and promote personalized and preventive interventions based on individual characteristics to fully exert their potential in inflammation prevention and treatment.

In summary, flavonoids are expected to play an important role in the prevention and treatment of chronic inflammatory diseases, providing new ideas beyond traditional drugs for the intervention of inflammatory diseases. With the in-depth study of mechanisms and breakthroughs in translation technologies, they are expected to play an important role in the prevention and treatment of chronic inflammatory diseases (especially neurodegenerative diseases), bringing new hope for improving patients' health conditions.

Declaration of competing interest

The authors have nothing to declare.

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