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The Therapeutic Role of Flavonoids for Alzheimer's Disease

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Abstract: Background: Alzheimer's disease (AD) is the most common neurodegenerative disease characterized with mainly cognitive impairments, and the number of elderly having AD is continuously increasing. Objective: To summarize the pathogenesis of AD and the therapeutic effects of flavonoids on related inflammatory processes. Main ideas: Flavonoids have been shown to alleviate effects of AD both in vitro and in vivo. Conclusion: The clinical significance of these research summaries lay a potential groundwork for the development of new drugs targeting AD treatment.

Keywords: Flavonoids, Neurodegenerative Diseases, Alzheimer's Disease, Mitochondrial Dysfunction, Neuroinflammation

1. Introduction

Aging is a gradual, inevitable, and irreversible process leading to significant deterioration in both internal and external anatomical structures [1]. These include tissue degradation and decreased functioning of important organs. Within the nervous system, the effects of aging are most prominently exhibited through the development of dementia and neurodegenerative diseases.

Neurodegenerative diseases include Alzheimer's disease (AD), vascular dementia, Parkinson's disease, amyotrophic lateral sclerosis, Lewy body dementia, and frontotemporal lobe dementia [2, 3]. Progressive degeneration and neuronal death, currently incurable, are the main causes of such diseases and currently incurable, leading to frailty in the elderly. Of these, AD is the most common associated with aging.

Flavonoids, a class of polyphenols, are present in commonly consumed foods such as fruits and vegetables, tea and wine, and grains [4]. They have beneficial effects on the primary cell culture of neurons and glia, as shown in animal models of neurodegenerative diseases. Previous studies have mainly used complexes of multiple bioactive molecules including flavonoids, so the specific mechanism of action of flavonoids has not been thoroughly clarified. Therefore, current research has mainly focused on the biological activity of single compounds of flavonoids in order to help researchers develop new treatment methods for AD in clinical practice [5].

In this review, we will summarize the pathogenesis of Alzheimer's disease, the therapeutic effect of single flavonoids on neuroinflammation, clinical research results, and basic knowledge of the therapeutic potential of flavonoids in AD. We will propose future research directions from the perspectives of in vitro experiments, in vivo experiments, and clinical experiments, in order to promote the theraputic application of flavonoids in clinical practice.

2. Definition and Epidemiology of Alzheimer's Disease

General understanding of dementias commonly encountered in medicine refers to AD, which often occurs in elderly and pre-elderly adults. AD is the most common type of dementia, accounting for 50% to 70% of elderly dementia. Clinical manifestations include but are not limited to memory loss, impairment of abstract thinking, cognitive decline,

impairment of visuospatial ability, and behavioral and personality changes [6, 7].

As of 2018, the overall prevalence of preclinical AD in the general population was 22% [6], and more than 90% of dementias occur after the age of 65. Figure 1 shows the neurological brain health issues that occur at different age stages. At around the age of 30, patients occasionally experience insomnia and anxiety, which can lead to mild damage to brain tissue. At around the age of 40, patients may experience severe insomnia and high anxiety, a repetitive process that can lead to moderate damage to brain tissue. At around the age of 50, patients may experience sleep disorders, depression, decreased cognitive levels, and decreased memory, indicating severe damage to brain tissue. At 60, patients may experience AD, depression, or Parkinson's disease, indicating that brain tissue has deteriorated to the extent of developing severe damage. According to statistics, in 2015, approximately 46.8 million people had developed dementia worldwide, and it is expected that by 2025, the number of people with Alzheimer's disease will reach 131.5 million. By 2050, the number of people with dementia is predicted to double in Europe and triple globally. If only the biological definition of Alzheimer's disease were used, this number would be three times higher [8].

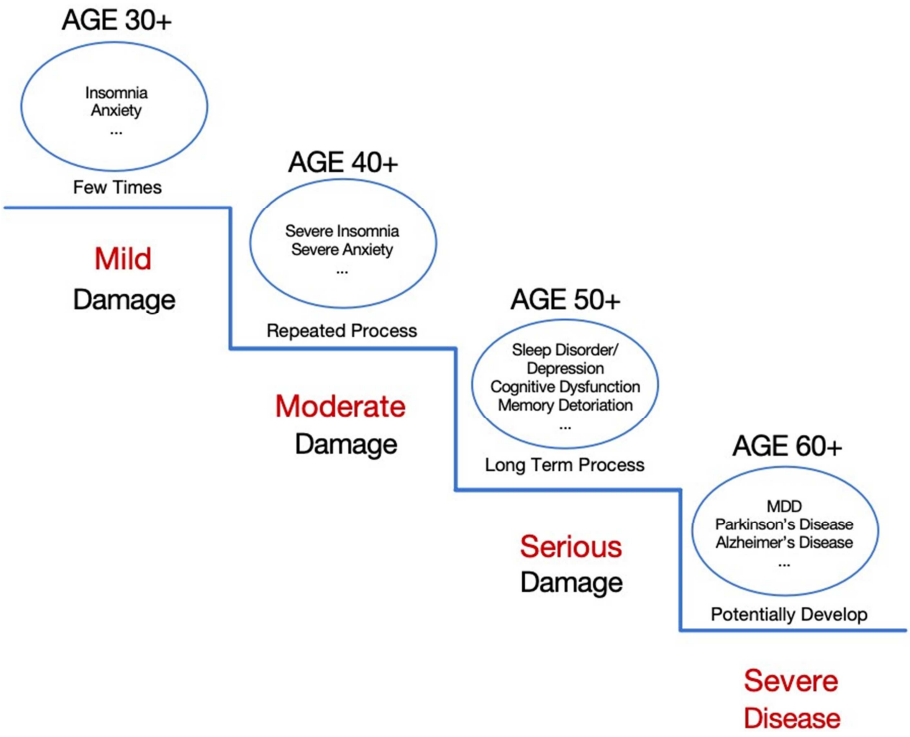

Figure 1. *Health issues can occur at young and old age groups in life.*

3. Early Symptoms and Age of Onset of Alzheimer's Disease

The International Working Group has separated preclinical situations into two at risk states, namely presymptomatic and asymptomatic. People falling in the presymptomatic state category carry an autosomal dominant monogenic mutation related to and directly diagnosable as AD. Symptomatic at risk states refer to patients who do not carry an AD inducing genotype and lack typical and atypical phenotypes, but show at least one key biomarkers of AD, amyloid beta-Aß or Tau. If both amyloid beta-Aß and Tau are present in CSF or PET scans, the patient can be diagnosed with AD [9].

The ϵ4 allele of APOE gene is the main genetic risk factor of AD. A patient carrying two APOE ϵ4 alleles has an increased risk of developing AD, up to 12 times. As a result, patients who carry homozygous APOE ϵ4 alleles often show AD symptoms before the average age of 65. However, having the mutated genotype does not necessarily lead to AD. The development of the disease usually combines both genetic and environmental stimuli; it has also been discovered that the APOE gene and many other suspected genes are related to the innate immune system, showing that the response of microglia toward environmental factors has a therapeutic association with the development of AD [10].

γ-aminobutyric acid, or GABA, is a major neurotransmitter. GABA is expressed throughout the complete human developmental cycle, starting from the embryonic stage and persisting throughout the rest of a person's life. It acts as an excitatory agent during the early developmental stage, and is associated with many key processes of neurogenesis, including but not limited to neuronal migration, differentiation, proliferation, preliminary circuit-building, and the development of critical periods. However, in the mature central nervous system, GABA instead acts as an inhibitor. Its transition is mediated by chloride/cation

transporter expression, and makes it a neurotransmitter of interest in AD-related therapies, as GABA-regulating agents can decrease agitation and inflammation.. GABA also plays a role in the development of oligodendrocyte, as well as interstitial neurons of the white matter, promoting healthy neuronal tissue growth [11, 12].

Sleep disorders are common in AD and are a strongly-correlated risk factor for early hospitalization. The main sleep disorders observed in AD patients include: fragmentation of nocturnal sleep, changes in microstructure of sleep, daytime naps or even reversal of sleep awakening cycles, and shortened duration of nocturnal sleep [13].

Approximately 25-40% of mild to moderate AD patients are affected by sleep disorders. In the years prior to onset of cognitive symptoms, a history of sleep interruption may be a potential risk factor for AD. In many cases, sleep pathology may represent symptoms of potential neurodegenerative diseases.

Sleep disorders in AD patients are more prevalent than in the general population, and also occur during the earlier stages of the disease. In treatment designs that include both non-pharmacological and pharmacological methods, it is essential to comprehensively evaluate the sleep disorders of each patient [14]. Although changes in melatonin and orexin seem to play a major role in the origin of sleep-related disorders, their causes are multifactorial, including behavior, environment, comorbidities and treatment.

Other mechanisms triggered by sleep disorders may also be involved in the development of AD, such as oxidative stress, cerebral hypoxia, blood-brain barrier damage, circadian rhythm disorders, and orexin overexpression. Interruptions in the sleep wake cycle, which are correlated with increased amyloid beta-Aß precipitation, are suspected to be an important related mechanism of sleep disorders which lead to AD development.

4. Alzheimer's Disease - Staging and Clinical Manifestations

AD is generally divided into three stages based on their associated degrees of cognitive impairment. These are mild, moderate, and severe, described as follows [15-16].

Mild Stage: The main manifestation is memory impairment. The first symptom that occurs is a decrease in recent memory, which gradually leads to a decrease in long-term memory as the condition progresses, leading to fatigue, anxiety, and negative emotions. Some patients may experience personality disorders such as irritability, selfishness, and exaggerated suspicions as well as outward changes in physical appearances such as growing more disheveled.

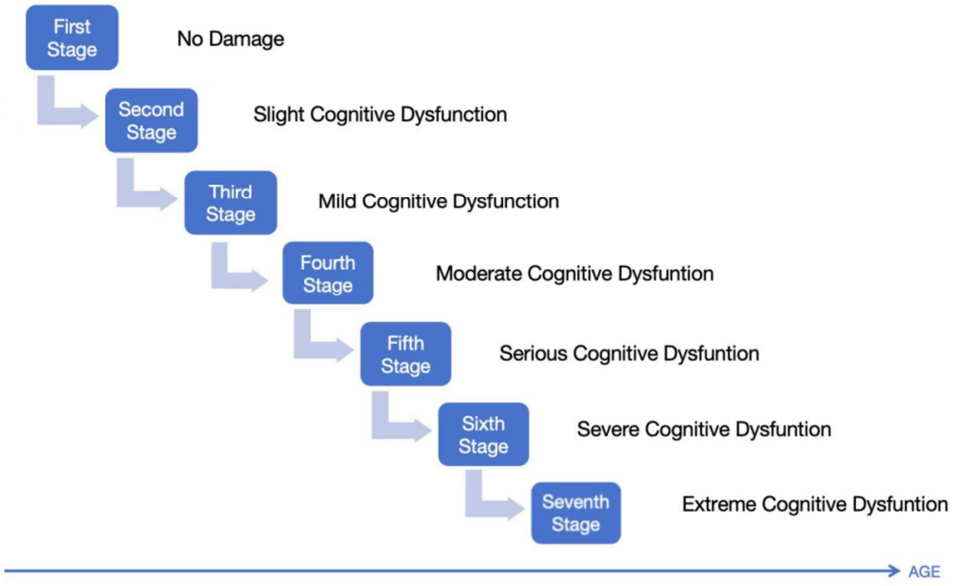

Figure 2. *Seven stages of Alzheimer's disease.*

(1) Moderate Stage: In addition to memory impairment, there may also be a decrease in logical thinking, comprehensive analysis ability, and visuospatial impairment. It manifests as being unable to find one's own room at home, muttering to oneself, and decreasing cognitive ability. During this period, patients often exhibit significant behavioral and mental abnormalities, with personality reversal.

(2) Severe Stage: In addition to the worsening of the aforementioned symptoms, patients are unable to complete simple daily activities such as dressing and eating, exhibit constant crying and laughing, experience gradual loss of speech ability, and ultimately become bedridden. Symptoms also include incontinence, ease of developing pulmonary infections, urinary tract infections, and pressure ulcers, and these usually resulting in death due to complications.

AD is mainly manifested as the following ten major danger signals: (1) Short-term memory loss, which affects self-care ability; (2) Difficulties in language expression or understanding; (3) Difficulty in performing familiar tasks; (4) Feeling confused about identity, time, and location; (5)

Decreased judgment; (6) Difficulties in thinking and calculation; (7) Littering and lack of public awareness; (8) Abnormal emotions and behaviors; (9) personality changes; (10) Loss of initiative in common actions.

In addition to AD, vascular dementia is also a common type of dementia, usually caused by cerebrovascular disease or cardiovascular disease, which can suddenly onset, fluctuate, and progress in a stepwise manner. Small vessel lesions can also cause insidious onset, with a slower progression. Cognitive impairment is often patchy, executive dysfunction is common, personality is relatively preserved, and additionally, degeneration is often accompanied by neurological symptoms and signs. However, Lewy body dementia is characterized by fluctuating cognitive impairment, psychiatric symptoms mainly characterized by visual hallucinations, and Parkinson's disease.

Volatile cognitive impairment refers to the sudden onset of temporary cognitive decline in patients, mainly due to executive and visuospatial impairments, such as getting lost and mild early impairment of short-term memory. The symptoms persist for a few minutes, hours, or days before returning to normal, with a dramatic change. 80% of Lewy body dementia patients experience visual hallucinations, and family members report that patients talk nonsense, can see people and things that others cannot see, and can hear conversations and sounds that others cannot hear. Parkinson's syndrome is generally characterized by slow movement and resting tremors.

Dementia has a variety of clinical manifestations, and memory loss is not necessarily AD. Understanding the symptoms of common dementia as well as early detection and treatment can help elderly people retain their daily living abilities and avoid developing severe dementia (Figure 2). Caring for the elderly is a traditional virtue of Chinese culture, and improving the quality of life for the elderly in a harmonious manner is beneficial from both a societal and health-focused perspective.

5. Four Pathogenic Mechanisms Related to Alzheimer's Disease

Studies have linked AD to specific patterns of protein misfolding and aggregation. There are four AD-related pathogenic mechanisms (Table 1):

Table 1. *Four pathogenesis of Alzheimer's disease.*

The pathogenesis of Alzheimer's disease		Treatment	Effect
Accumulation of Insoluble Forms of Amyloid-β Hypothesis	Mutations in the genes encoding amyloid precursor protein, progerin 1/2, and sortin 1(s) result in aberrant B-amyloid expression.	B-amyloid antibody	No Significant Effect
Acetylcholine hypothesis	Cholinergic neurons are significantly reduced and the release of acetylcholine, glutamate, serotonin and norepinephrine is blocked	Acetylcholinesterase inhibitors Donepezil. Galantamine.	No Significant Effect
Hypothesis of Glutamate Receptor Precursor	Persistent inhibition of N-methyl-D-aspartate receptors results in low-level signaling	NMDA receptor antagonist Memantine	No Significant Effect
Guidance/Support Protein Hypothesis	Reduced expression of inhibitory neuroreceptor support proteins results in reduced inhibitory neuroreceptor expression and impaired nerve signaling.	SmartoOne	Significantly improves patient cognition and memory/learning without toxic side effects

5.1. Accumulation of Insoluble Forms of Amyloid-β Hypothesis of AD

Accumulation of both soluble and insoluble-form β-amyloid proteins in the brain leads to neurotoxicity and is currently the most recognized and popular hypothesis for the pathogenesis of AD [17, 18]. Although it is currently unclear how β-amyloid proteins can cause neurodegenerative diseases, many studies have shown that dysregulation of calcium (2+) homeostasis and insufficient calcium signaling may be a fundamental factor related to pathogenesis. AD's symptoms are strongly correlated with synaptic dysfunction and neuronal loss in the early and later stages of the disease, respectively, suggesting that the impact of β-amyloid protein is a major cause of neuronal dysfunction.

5.2. Acetylcholine Hypothesis of Alzheimer's Disease

Previous studies have demonstrated that the β-amyloid protein causes an increase in the leakage of choline across cell membranes, causing a subsequent decrease in intracellular acetylcholine concentration and thereby reducing the production of acetylcholine. The decrease in acetylcholine production in turn leads to the increase of β-amyloid protein concentrations [19, 20].

5.3. Hypothesis of Glutamate Receptor Precursor of Alzheimer's Disease

The metabolic glutamate receptor 5 (mGluR5) is widely expressed in brain regions responsible for memory and learning. Its affiliate neurotransmitter, glutamate, is an agonist of the N-methyl-d-aspartate receptor and the main excitatory neurotransmitter in the central nervous system. As such, mGluR5 plays a key role in regulating rapid changes in plasticity and overall synaptic transmissions Abnormal mGluR5 signaling and related synaptic failures are considered a new pathophysiological mechanism of AD [21-23].

5.4. Guidance/Support Protein Hypothesis of Alzheimer's Disease

Figure 3 shows the relationship between the GABA receptor system and AD, which suppresses the neural receptor theory. The balance between the "GABA inhibitory nervous system" and the "GABA excitatory nervous system" is crucial for the health of the brain. The specific explanation of the relationship between the excitatory and inhibitory systems of GABA receptors is as follows:

(a) Alzheimer's disease - inhibitory neuroreceptor theory:

Our brain is composed of two interdependent "GABA inhibitory nervous systems" and "excitatory nervous systems". When the two nervous systems are in a balanced state, the brain is in a healthy state. The GABA inhibitory nervous system mainly plays an inhibitory and regulatory role in the brain. When the inhibitory nervous system conduction fails, the excitatory nervous system releases neurotoxins, causing abnormal conduction in the brain.

(b) Hypothesis of "Inhibition of Neuroreceptor Guidance/Support Proteins":

When there is an irregular change in proteins related to neurological guidance and support in the brain, and specifically when the number decreases to half of the normal amount or lower, the brain abnormally suppresses neural receptors, leading to coding disorder in brain conduction.

(c) Discovering the relationship between subcellular level (mitochondria) and neurodegenerative diseases in the brain:

After mitochondrial damage or dysfunction in brain cells, the ATP energy produced by them diminishes, leading to a decrease in the number of guiding support proteins and a decline in the ability to inhibit neural receptor conduction and expression. Subsequently, neurodegenerative diseases can develop, of which AD is a typical symptom.

(d) Neuroimmune deficiency theory:

Microglia (including astrocytes) in the brain that link synapses are the core immune system of the brain, maintaining the structural, nutritional, functional, and defensive properties of the nerves. In order to defend against the negative internal environmental changes caused by decline of neural function, microglia are immediately activated. This activation is often exaggerated and can trigger neuroinflammation.

Dihydromyricetin (DHM) is a plant flavonoid and a positive conformational regulator of GABAARs [28]. In animal experiments, DHM treatment can improve GABAergic transmission and functional synapses, reducing β-amyloid protein, while restoring porphyrin levels and improving symptoms in AD mouse models. Therefore, these studies have demonstrated that DHM has very useful therapeutic effects for AD [24].

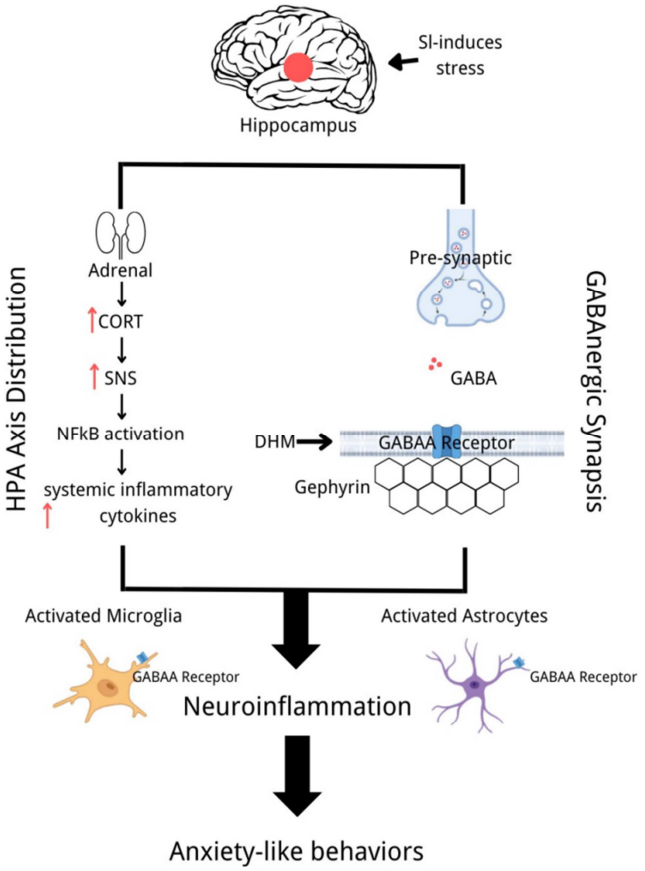

Figure 3. *Mechanism of GABA receptor dysfunction in Alzheimer's disease.*

6. Flavonoids

All vascular plants, in all over 6000 species, contain polyphenols, of which flavonoids are the most commonly found phytochemical. A plant typically contains many different flavonoids [25], and in nature, flavonoids are widely distributed, abundant in many foods and beverages derived from plants. These include commonly consumed articles such as grain roots, cocoa, wine and tea, and fruits and vegetables themselves [26].

Flavonoids include anthocyanins, chalcones, flavones, flavonols, flavanols, also known as catechins, isoflavonoids, flavanonols and flavanones (Figure 4) [26]. Because consumables containing flavonoids exist solely as glycosides, flavonoids are absorbed exclusively through the small intestine after consumption. Most molecules that avoid absorption instead degrade in the rest of the digestive tract, mainly the colon [27]. The few remaining particles are found in blood plasma and urine, primarily as conjugated forms. Therefore, most cells typically experience relatively low levels of flavonoid activity, including from metabolites and their conjugates [28].

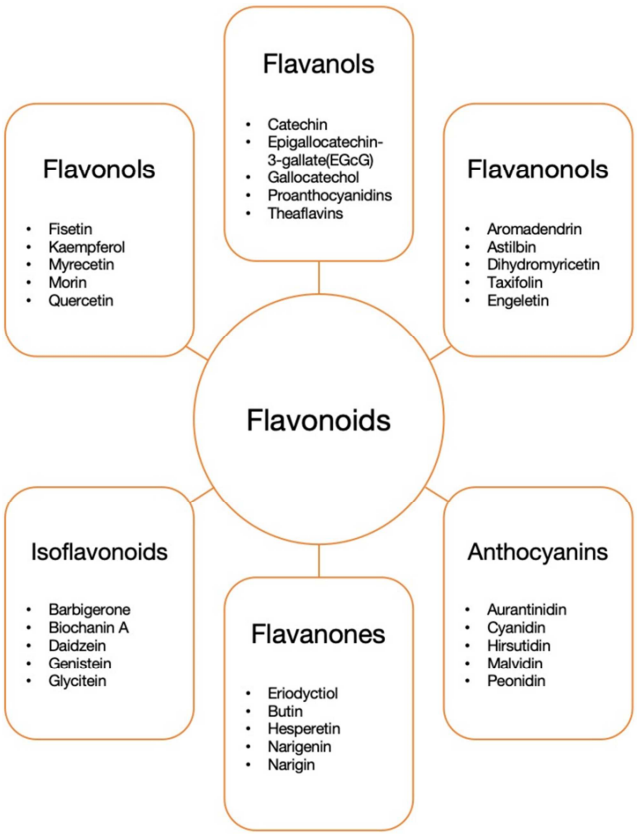

Figure 4. *Different forms of Flavonoids.*

7. Anti-Inflammatory and Anti-Apoptosis Effects of Flavonoids in AD

7.1. In Vitro Studies of Flavonoids

Multiple studies have examined the changes in AD-related protein levels due to certain antagonists. Studies have examined both primary neuronal and SweAPP N2a cells, in which luteolin and diosmetin decrease β-amyloid (1–40 and 1–42) (Table 2) [29]. In cultures of primary hippocampal cells, quercetin was found to markedly decrease β-amyloid (1–42)-induced protein oxidation and liquid peroxidation, as well as cytotoxicity and apoptosis [30]. Additionally, studies have observed myricetin with β-amyloid-mediated fibrillogenesis prevention [31].

There have been a number of in vitro experiments exploring the impact of various flavonoids on β-amyloid oligomers. For example, EGCG has been shown to significantly reduce β-amyloid-mediated fibrillogenesis, transforming fibrils of β-amyloid into smaller nontoxic protein aggregates within mammalian cells [32, 33]. Furthermore, EGCG was observed eliminating oxygen species within hippocampal neuronal cells, offering protection against β-amyloid-induced neuronal apoptosis [34].

In cells with overexpressed APP Swedish mutations (APPswe), both Rutin and Quercetin were capable of preventing new β-amyloid fibrils from forming and destroying existing ones [37]. In studies targeting the human tau protein, Baicalein significantly inhibited aggregation using a variety of biochemical targets [35, 36]. For investigations conducted on neuroblastoma SH-SY5Y cells, Cyanidin 3-*O*-β-glucopyranoside reduced β-amyloid cytotoxicity and aggregation [38]. Lastly, wogonin decreased β-amyloid aggregation and phosphorylated Tau as well [39].

7.2. Animal Model Studies of Flavonoids

Animal models play a vital role in AD research as a analogous testing environment prior to clinical studies. There are three primary types of models: (1) Chemically induced models, in which conditions representative of AD are induced using amyloid protein infusion, streptozotocin, or other compounds; (2) Models where AD naturally occurs, termed spontaneous models, including senescence-accelerated aging mice; and (3) Transgenic models, where animal subjects are genetically modified to express human genes simulating familial and partial idiopathic AD along with associated proteins (neurofibrillary tangles and β-amyloid plaques) [40]. These include 3XTg, 5XFAD, APP/PS1, and TG2576 mice (Table 3). However, though these animals express plaques, tangles, and memory defects, they often lack neurodegeneration, limiting the study of neuroinflammation [41]. As such, these analyses of related models focuses mainly on β-amyloid aggregation and cognitive impairment.

Across all animal models, several flavonoids demonstrated favorable effects on development and expression of AD. Nobiletin was found to reduce soluble β-amyloid (1-40 and 1-42) levels and plaques in hippocampal areas within APP-SL 7-5 transgenic mice [42]. Additionally, it reduced β-amyloid plaques and improved memory deficits, and in 3XTg mice, β-amyloid 1-40 levels were decreased and memory damage reversed [44]. Within natural SAMP8 models sourced from senescence-accelerated mice, nobiletin again reversed hippocampal memory deterioration [45]. Diosmin, along with associated bioactive metabolites also reduced tau hyperphosphorylation and β-amyloid generation in 3XTg mice [43].

Both maringin and rutin improved memory function in a scopolamine-induced chemical model of mouse memory deficits [42]. Isorhamnetin increased both prefrontal cortical and hippocampal levels of brain-derived neurotrophic factor (BDNF), aiding learning and reducing memory impairment.

Kaempferol raised hippocampal neuron density, leading to memory improvement in a streptozotocin-induced chemical model [46]. Luteolin demonstrated memory-enhancing effects [45], and introducing hesperidin within a pretreatment model improved memory while simultaneously reducing levels of inflammatory markers including NF-κB, iNOS, COX-2, and astrogliosis [47]. Quercetin exhibited the capacity to diminish hyperphosphorylated tau and β-amyloid plaques within the hippocampal CA1 region, resulting in memory enhancement in 3XTg mice [48]. Cyanidin 3-*O*-glucoside diminished hippocampal tau phosphorylation

leading to improved memory and learning, reversing deteriorative effects in both rats infused with β-amyloid [49], and the APP(swe)/PS1(ΔE9) mouse model [50].

Hesperidin mitigated astrogliosis as well as microglial activation, resulting in lower cortical and hippocampal levels of β-amyloid plaques. Subsequently, transgenic APP/PS1 mice regained social capabilities [51]. Wogonin enhanced memory in transgenic h-Tau P301L, h-APPswe, and h-PS1 M146V mice [52, 53]. Finally, introduction of dihydromyricetin lowered anxiety levels, reversed β-amyloid accumulation in TG2576 and TG-SwDI transgenic mice, and helped subjects improve localization and movement abilities [54].

7.3. Clinical Studies of Flavonoids

As the most prevalent neurodegenerative condition, AD is characterized by both high rate of incidence and a complex pathogenesis. Currently, all available AD medications focus on alleviating symptoms rather than pursuing a definitive cure.

Inflammation is a common target. among many common diseases, such as myocardial ischemia, hypertension, acute cerebral stroke, cancer, AD, arthritis, diabetes and asthma, inflammation plays an important pathophysiological role during diseases development. Dihydromyricetin (DHM), as a flavonoid compound primarily sourced from Nekemias grossedentata [1], exhibits a range of pharmacological effects of DHM including antioxidant and anti-inflammatory properties which mitigate mitochondrial dysfunction and aid autophagy regulation [24].

Two natural flavonoids, myricetin (MYR) and dihydromyricetin (DMY), are very abundant in vegetables and fruits. Some countries have already approved MYR and DMY as food supplements (Table 4) [58]. They counteract AD development by reducing neuroinflammation and improving β-amyloid imbalance, regulating metal ion homeostasis disorders, improving autophagy disorders, and reducing oxidative stress reactions [58]. However, due to their complicated mechanisms of action, further examination is required for understanding.

In AD patients with only mild impairment of cognition, flavonoids and their respective effects are shown in Table 4 [55]. Additionally, elderly participants showed signs of improved cognitive function after consuming cocoa flavanol [56]. A mixture of mainly epicatechin and catechin flavanols, cocoa flavanol has demonstrated favorable effects aiding AD treatment, though there is currently a lack of clinical research targeting single flavonoid molecules. Another clinical study administered cognitive testing using high-resolution variants of functional magnetic resonance imaging (fMRI) to evaluate the consequences of consuming cocoa flavanols in healthy subjects aged 50-69 over a period of 3 months, finding that flavanols can improve function of the dentate gyrus [57].

Table 2. *Anti-inflammatory effects of flavonoids in AD in-vitro studies.*

Flavonoid	Effect	Model (In Vitro)	References
Luteolin	↓ Aβ (1–40 and 1–42)	Neuronal cells and SweAPP N2a cells	[29]
Diosmetin	↓ Aβ (1–40 and 1-42)	Neuronal cells and SweAPP N2a cells	[30]
Quercetin	↓ Aβ cytotoxicity, lipid peroxidation, protein oxidation, and apoptosis	Hippocampal neuronal cell culture	[31]
Myricetin	Prevents Aβ fibrillogenesis	Cerebral cortices from Tg2576 mouse embryos	[32]
Cyanidin 3-O-β-glucopyranoside	↓ Aβ (25–35) cytotoxicity	SH-SY5Y cells	[33]
Wogonin	↓ Aβ aggregation and phosphorylated Tau	SH-SY5Y cells	[50]
Baicalein	Prevents tau protein aggregation	Several biochemical techniques	[34, 35]
Quercetin	Prevent Aβ aggregation and ↑ disaggregate	Cell system overexpressing APP	[36, 37]
Rutin	Prevent Aβ aggregation and ↑ disaggregate	Cell system overexpressing APP	[38, 39]

↑: significant increase; ↓: significant decrease; Aβ: amyloid-beta.

Table 3. *Anti-inflammatory effects of flavonoids in AD in-vivo studies.*

Flavonoid	Effect	Model (In Vivo)	References
Isorhamnetin	↓ learning and memory deficits and ↑ BDNF in prefrontal cortex and hippocampus	Chemical mouse model	[40]
Naringin	Improve memory	Chemical rat model	[40]
Rutin	Improve memory	Chemical rat model	[41]
kaempferol	Improve memory and ↑ density of neurons in hippocampus	Chemical rat model	[41]
Luteolin	Improve memory	Chemical rat model	[41]
Hesperidin	improves memory and ↓ NF κB, iNOS, COX-2, and astrogliosis	Chemical mouse model	[42]
Nobiletin	↓ soluble Aβ (1–40 and 1–42) and Aβ plaques in the hippocampus	APP-SL 7-5 transgenic mouse	[43]
Diosmin and its bioactive metabolites	↓ tau hyperphosphorylation and Aβ generation	3xTg transgenic mouse	[44]
Hesperidin	↓ Aβ plaque in cortex and hippocampus and ↓ astrocyte and microglial activation	Transgenic APP/PS1 mouse	[45]
Wogonin	Improve memory	Transgenic h-APPswe mouse	[46]
Diosmin	↓ Aβ 1–40 and 1–42	Tg2576 transgenic mouse	[47]
Luteolin	↓ Aβ 1–40 and 1–42	Tg2576 transgenic mouse	[48]

Flavonoid	Effect	Model (In Vivo)	References
EGCG	↓ soluble Aβ (1–40 and 1–42) and Aβ plaques in cortex and hippocampus	APPsw transgenic mouse	[46]
EGCG	↓ Aβ (1–42)	Aβ infusion model, presenilin 2 mutant mouse	[47]
Diosmin	Improve memory	APPsw transgenic mouse	[48]
Nobiletin	↓ Aβ plaques in the hippocampus and ↓ memory deficits	APP-SL 7-5 transgenic mouse	[43]
Nobiletin	↓ memory impairment, ↓ the levels of Aβ 1–40	3XTg transgenic mouse	[49]
Nobiletin	↓ memory impairment	Senescence-accelerated mice SAMP8	[50]
Quercetin	↑ memory and ↓ plaques of Aβ and hyperphosphorylated tau in hippocampus	3XTg transgenic mouse	[51]
Cyanidin 3-O-glucoside	↓ memory impairment, ↓ hyperphosphorylated tau in hippocampus	Aβ infusion rats	[52]
Fisetin	↓ memory and learning problems	APP (swe)/PS1(ΔE9) mouse	[53]
Dihydromyricetin	↑ exploratory and locomotor activity, and memory, ↓ anxiety and Aβ accumulation	TG2576 and TG-SwDI mouse	[54]

↑: significant increase; ↓: significant decrease; TNF-α: tumor necrosis factor α; IL: interleukin; TLR4: Toll-like receptor 4; NF-κB: nuclear factor kappa B; Aβ: amyloid-beta; iNOS: inducible nitric oxide synthase; COX-2: cyclooxygenase 2; fMRI: functional magnetic resonance imaging.

Table 4. *Anti-inflammatory effects of flavonoids in AD clinical studies.*

Flavonoid	Effect	Clinical Studies	References
Cocoa flavanol	Improves cognitive function	Patients with mild cognitive impairment	[55]
Cocoa flavanol	Improved cognitive function in aging subjects	Double-blind study	[56]
Cocoa flavanol	Improves dentate gyrus functions	fMRI in healthy 50–69-year-old subjects	[57]
Myricetin (MYR) Dihydromyricetin (DMY)	anti-AD effects Aβ imbalance Anti-oxidative stress	Review	[58]

↑: significant increase; ↓: significant decrease; Aβ: amyloid-beta; AD: Alzheimer's disease

8. Conclusion

This review article summarizes the therapeutic potential of flavonoids in addressing AD, examining their anti-inflammatory properties, abilities to mitigate the activation of microglia and astrocytes, their influence on the activation of transcription factors such as NF-κB and AP-1, and influences in reducing pro-inflammatory. Consuming foods and beverages rich in flavonoids significantly reduces inflammatory responses and associated molecule levels, such as those of IL-6 and the C-reactive protein [58].

Previous studies include in vitro, in vivo, and clinical researches have demonstrated that flavonoids have pleiotropic effects, primarily through antioxidant and anti-inflammatory mechanisms. Currently, both supplements and dietary changes are widely incorporated in AD prevention through promoting general personal health, and the addition of daily flavonoid intake through diet as well as curated collections has great potential.

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Author Contributions

Conceptualization, J. W. and Z. L.; data curation, J. W. and Z. L.; writing and original draft preparation, J. W. and Z. L.; writing and review and editing, J. W., Z. L. and C. W. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement

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Data Availability Statement

Not applicable.

Conflicts of Interest

The authors declare no conflict of interest.

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